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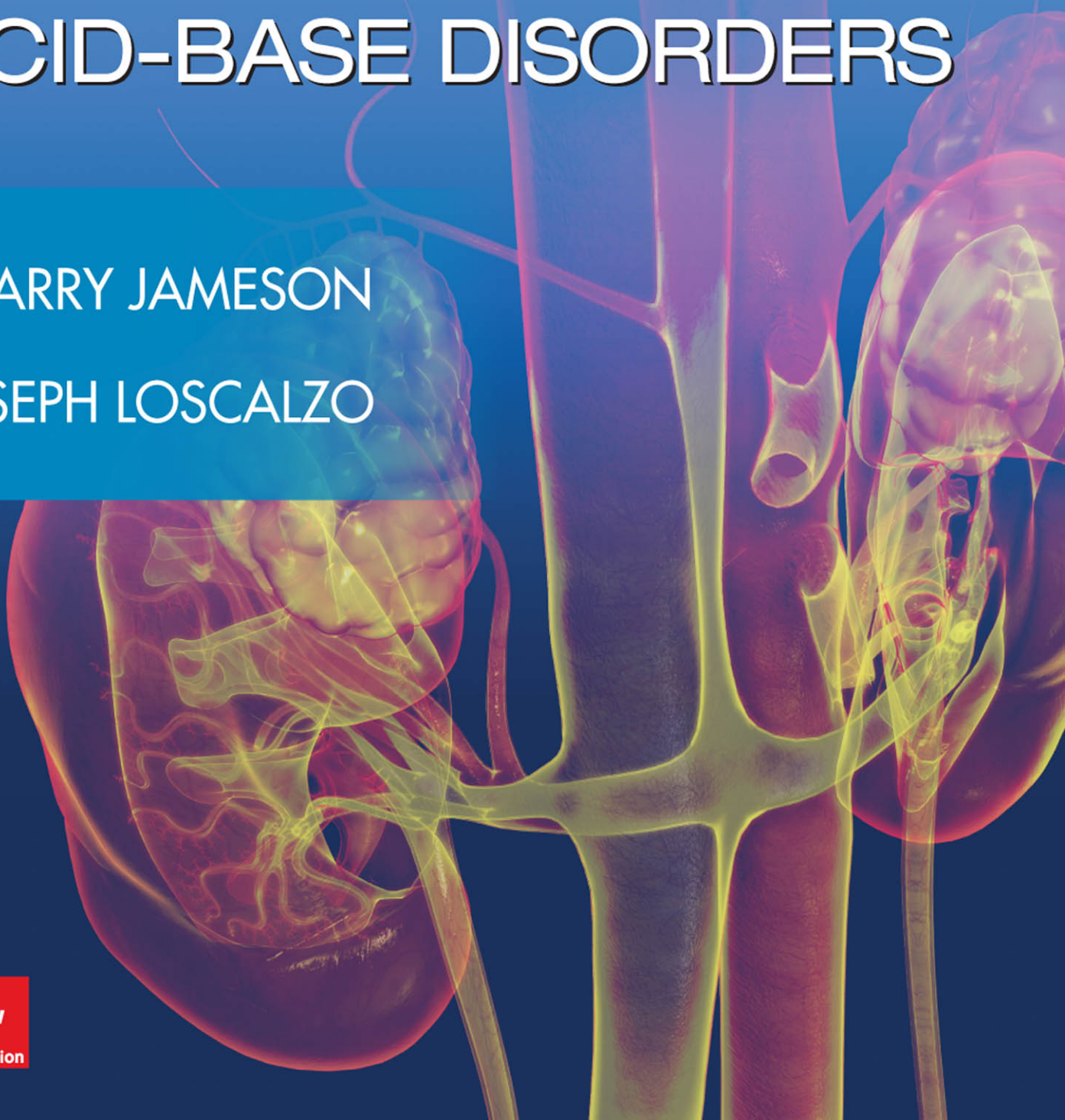
HARRISON'S

NEPHROLOGY AND ACID-BASE DISORDERS

J. LARRY JAMESON

JOSEPH LOSCALZO



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2nd Edition

HARRISON'S™

NEPHROLOGY AND ACID-BASE DISORDERS

Derived from Harrison's Principles of Internal Medicine, 18th Edition

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PREFACE

Harrison's Principles of Internal Medicine has been a respected information source for more than 60 years. Over time, the traditional textbook has evolved to meet the needs of internists, family physicians, nurses, and other health care providers. The growing list of *Harrison's* products now includes *Harrison's* for the iPad, *Harrison's Manual of Medicine*, and *Harrison's Online*. This book, *Harrison's Nephrology and Acid-Base Disorders*, now in its second edition, is a compilation of chapters related to kidney function.

Our readers consistently note the sophistication of the material in the specialty sections of *Harrison's*. Our goal was to bring this information to our audience in a more compact and usable form. Because the topic is more focused, it is possible to enhance the presentation of the material by enlarging the text and the tables. We have also included a review and self-assessment section that includes questions and answers to provoke reflection and to provide additional teaching points.

Renal dysfunction, electrolyte, and acid-base disorders are among the most common problems faced by the clinician. The evaluation of renal function relies heavily on laboratory tests, urinalyses, and characteristics of urinary sediments. Evaluation and management of renal disease also requires a broad knowledge of physiology and pathology since the kidney is involved in many systemic disorders. Thus, this book considers a broad spectrum of topics including acid-base and electrolyte disorders, vascular injury to the kidney, as well as specific diseases of the kidney.

Kidney disorders, such as glomerulonephritis, can be a primary basis for clinical presentation. More commonly, however, the kidney is affected secondary to other medical problems such as diabetes, shock, or complications from dye administration or medications. As such, renal dysfunction may be manifest by azotemia, hypertension, proteinuria, or an abnormal urinary sediment, and it may herald the presence of an underlying medical disorder. Renal insufficiency may also appear late in the course of chronic conditions such as diabetes, lupus, or scleroderma and significantly alter a patient's quality of life. Fortunately, intervention can often reverse or delay renal insufficiency. And, when this is not possible, dialysis and renal transplant provide lifesaving therapies.

Understanding normal and abnormal renal function provides a strong foundation for diagnosis and clinical management. Therefore, topics such as acidosis and alkalosis, fluid and electrolyte disorders, and hypercalcemia are covered here. These basic topics are useful in all fields of medicine and represent a frequent source of renal consultation.

The first section of the book, "Introduction to the Renal System," provides a systems overview, beginning with renal development, function, and physiology, as well as providing an overview of how the kidney responds to injury. The integration of pathophysiology with clinical management is a hallmark of *Harrison's,* and can be found throughout each of the subsequent disease-oriented chapters. The book is divided into seven main sections that reflect the scope of nephrology: (I) Introduction to the Renal System; (II) Alterations of Renal Function and Electrolytes; (III) Acute Kidney Injury and Chronic Renal Failure; (IV) Glomerular and Tubular Disorders; (V) Renal Vascular Disease; (VI) Urinary Tract Infections and Obstruction; and (VII) Cancer of the Kidney and Urinary Tract.

While *Harrison's Nephrology and Acid-Base Disorders* is classic in its organization, readers will sense the impact of the scientific advances as they explore the individual chapters in each section. Genetics and molecular biology are transforming the field of nephrology, whether illuminating the genetic basis of a tubular disorder or explaining the regenerative capacity of the kidney. Recent clinical studies involving common diseases like chronic kidney disease, hypertensive vascular disease, and urinary tract infections provide powerful evidence for medical decision making and treatment. These rapid changes in nephrology are exciting for new students of medicine and underscore the need for practicing physicians to continuously update their knowledge base and clinical skills.

Our access to information through web-based journals and databases is remarkably efficient. Although these sources of information are invaluable, the daunting body of data creates an even greater need for synthesis by experts in the field. Thus, the preparation of these chapters is a special craft that requires the ability to distill core information from the ever-expanding knowledge base. The editors are therefore indebted to our authors, a group of internationally recognized authorities who are masters at providing a comprehensive overview while being able to distill a topic into a concise and interesting chapter. We are indebted to our colleagues at McGraw-Hill. Jim Shanahan is a champion for *Harrison's* and these books were impeccably produced by Kim Davis.

We hope you find this book useful in your effort to achieve continuous learning on behalf of your patients.

J. Larry Jameson, MD, PhD
Joseph Loscalzo, MD, PhD

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

Review and self-assessment questions and answers were taken from Wiener CM, Brown CD, Hemnes AR (eds). *Harrison's Self-Assessment and Board Review*, 18th ed. New York, McGraw-Hill, 2012, ISBN 978-0-07-177195-5.

The global icons call greater attention to key epidemiologic and clinical differences in the practice of medicine throughout the world.

The genetic icons identify a clinical issue with an explicit genetic relationship.

SECTION I

INTRODUCTION TO THE RENAL SYSTEM

CHAPTER 1

CELLULAR AND MOLECULAR BIOLOGY OF THE KIDNEY

Alfred L. George, Jr. ■ Eric G. Neilson

The kidney is one of the most highly differentiated organs in the body. At the conclusion of embryologic development, nearly 30 different cell types form a multitude of filtering capillaries and segmented nephrons enveloped by a dynamic interstitium. This cellular diversity modulates a variety of complex physiologic processes. Endocrine functions, the regulation of blood pressure and intraglomerular hemodynamics, solute and water transport, acid-base balance, and removal of drug metabolites are all accomplished by intricate mechanisms of renal response. This breadth of physiology hinges on the clever ingenuity of nephron architecture that evolved as complex organisms came out of water to live on land.

EMBRYOLOGIC DEVELOPMENT

Kidneys develop from intermediate mesoderm under the timed or sequential control of a growing number of genes, described in **Fig. 1-1**. The transcription of these genes is guided by morphogenic cues that invite two ureteric buds to each penetrate bilateral metanephric blastema, where they induce primary mesenchymal cells to form early nephrons. This induction involves a number of complex signaling pathways mediated by Pax2, Six2, WT-1, Wnt9b, c-Met, fibroblast growth factor, transforming growth factor β, glial cell-derived neurotrophic factor, hepatocyte growth factor, and epidermal growth factor. The two ureteric buds emerge from posterior nephric ducts and mature into separate collecting systems that eventually form a renal pelvis and ureter. Induced mesenchyme undergoes mesenchymal epithelial transitions to form comma-shaped bodies at the proximal end of each ureteric bud, leading to the formation of S-shaped nephrons that cleft and enjoin with penetrating endothelial cells derived from sprouting angioblasts. Under the influence of vascular endothelial growth factor A (VEGF-A), these penetrating cells form capillaries with surrounding mesangial cells that differentiate into a glomerular filter for plasma water and solute. The ureteric buds branch, and each branch produces a new set of nephrons. The number of branching events ultimately determines the total number of nephrons in each kidney. There are approximately 900,000 glomeruli in each kidney in normal birth weight adults and as few as 225,000 in low birth weight adults—producing the latter in numerous comorbid risks.

Glomeruli evolve as complex capillary filters with fenestrated endothelia under the guiding influence of VEGF-A and angiopoietin-1 secreted by adjacently developing podocytes. Epithelial podocytes facing the urinary space envelop the exterior basement membrane supporting these emerging endothelial capillaries. Podocytes are partially polarized and periodically fall off into the urinary space by epithelial-mesenchymal transition, and to a lesser extent apoptosis, only to be replenished by migrating parietal epithelia from Bowman's capsule. Failing replenishment results in heavy proteinuria. Podocytes attach to the basement membrane by special foot processes and share a slit-pore membrane with their neighbor. The slit-pore membrane forms a filter for plasma water and solute by the synthetic interaction of nephrin, annexin-4, CD2AP, FAT, ZO-1, P-cadherin, podocin, TRPC6, PLCE1, and neph 1–3 proteins. Mutations in many of these proteins also result in heavy proteinuria. The glomerular capillaries are embedded in a mesangial matrix shrouded by parietal and proximal tubular epithelia forming Bowman's capsule. Mesangial cells have an embryonic lineage consistent with arteriolar or juxtaglomerular cells and contain contractile actin-myosin fibers. These mesangial cells make contact with glomerular capillary loops, and their local matrix holds them in condensed arrangement.

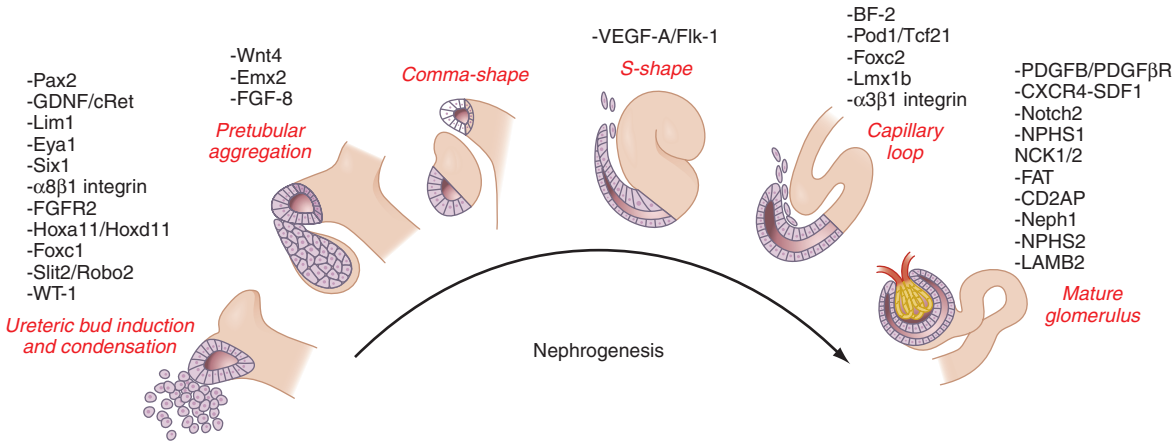

FIGURE 1-1

Genes controlling renal nephrogenesis. A growing number of genes have been identified at various stages of glomerulotubular development in the mammalian kidney. The genes listed have been tested in various genetically modified mice, and their location corresponds to the classical stages of kidney development postulated by Saxen in 1987. GDNF, giant cell line–derived neutrophilic factor; FGFR2, fibroblast growth factor receptor 2; WT-1, Wilms' tumor gene 1; FGF-8, fibroblast growth factor 8; VEGF–A/Flk-1, vascular endothelial growth factor–A/fetal liver kinase-1; PDGFβ, platelet-derived growth factor β; PDGFβR, PDGFβ receptor; SDF-1, stromal-derived factor 1; NPHS1, nephrin; NCK1/2, NCK-adaptor protein; CD2AP, CD2-associated protein; NPHS2, podocin; LAMB2, laminin beta-2.

Between nephrons lies the renal interstitium. This region forms a functional space surrounding glomeruli and their downstream tubules, which are home to resident and trafficking cells such as fibroblasts, dendritic cells, occasional lymphocytes, and lipid-laden macrophages. The cortical and medullary capillaries, which siphon off solute and water following tubular reclamation of glomerular filtrate, are also part of the interstitial fabric as well as a web of connective tissue that supports the kidney's emblematic architecture of folding tubules. The relational precision of these structures determines the unique physiology of the kidney.

Each nephron is partitioned during embryologic development into a proximal tubule, descending and ascending limbs of the loop of Henle, distal tubule, and the collecting duct. These classic tubular segments build from subsegments lined by highly unique epithelia serving regional physiology. All nephrons have the same structural components, but there are two types whose structure depend on their location within the kidney. The majority of nephrons are cortical, with glomeruli located in the mid-to-outer cortex. Fewer nephrons are juxtamedullary, with glomeruli at the boundary of the cortex and outer medulla. Cortical nephrons have short loops of Henle, whereas juxtamedullary nephrons have long loops of Henle. There are critical differences in blood supply as well. The peritubular capillaries surrounding cortical nephrons are shared among adjacent nephrons. By contrast, juxtamedullary nephrons depend on individual capillaries called *vasa recta*. Cortical nephrons perform most of the glomerular filtration because there are more of them and because their afferent arterioles are larger than their respective efferent arterioles. The juxtamedullary nephrons, with longer loops of Henle, create a hyperosmolar gradient for concentrating urine. How developmental instructions specify the differentiation of all these unique epithelia among various tubular segments is still unknown.

DETERMINANTS AND REGULATION OF GLOMERULAR FILTRATION

Renal blood flow normally drains approximately 20% of the cardiac output, or 1000 mL/min. Blood reaches each nephron through the afferent arteriole leading into a glomerular capillary where large amounts of fluid and solutes are filtered to form the tubular fluid. The distal ends of the glomerular capillaries coalesce to form an efferent arteriole leading to the first segment of a second capillary network (cortical peritubular capillaries or medullary vasa recta) surrounding the tubules **(Fig. 1-2*A*)**. Thus, nephrons have two capillary beds arranged in a series separated by the efferent arteriole that regulates the hydrostatic pressure in both capillary beds. The distal capillaries empty into small venous branches that coalesce into larger veins to eventually form the renal vein.

The hydrostatic pressure gradient across the glomerular capillary wall is the primary driving force for glomerular filtration. Oncotic pressure within the capillary lumen, determined by the concentration of unfiltered plasma proteins, partially offsets the hydrostatic pressure gradient and opposes filtration. As the oncotic pressure rises along the length of the glomerular capillary, the driving force for filtration falls to zero on reaching

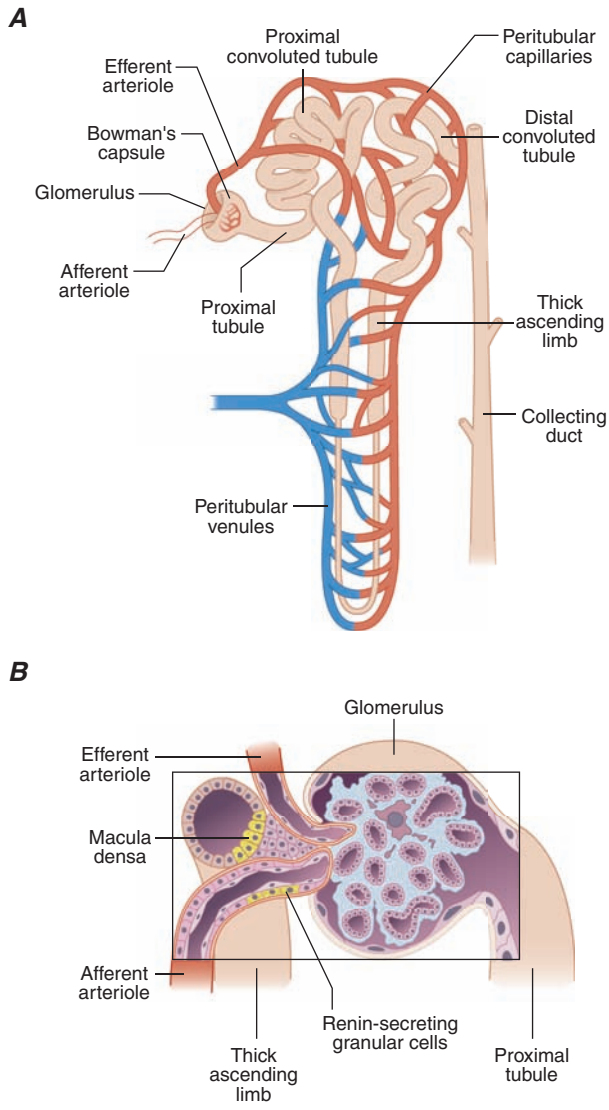

FIGURE 1-2

Renal microcirculation and the renin-angiotensin system. ***A.*** Diagram illustrating relationships of the nephron with glomerular and peritubular capillaries. ***B.*** Expanded view of the glomerulus with its juxtaglomerular apparatus including the macula densa and adjacent afferent arteriole. ***C.*** Proteolytic processing steps in the generation of angiotensins.

the efferent arteriole. Approximately 20% of the renal plasma flow is filtered into Bowman's space, and the ratio of glomerular filtration rate (GFR) to renal plasma flow determines the filtration fraction. Several factors, mostly hemodynamic, contribute to the regulation of filtration under physiologic conditions.

Although glomerular filtration is affected by renal artery pressure, this relationship is not linear across the range of physiologic blood pressures due to autoregulation of GFR. Autoregulation of glomerular filtration is the result of three major factors that modulate either afferent or efferent arteriolar tone: these include an autonomous vasoreactive (myogenic) reflex in the afferent arteriole, *tubuloglomerular feedback*, and angiotensin II–mediated vasoconstriction of the efferent arteriole. The myogenic reflex is a first line of defense against fluctuations in renal blood flow. Acute changes in renal perfusion pressure evoke reflex constriction or dilatation of the afferent arteriole in response to increased or decreased pressure, respectively. This phenomenon helps protect the glomerular capillary from sudden changes in systolic pressure.

Tubuloglomerular feedback changes the rate of filtration and tubular flow by reflex vasoconstriction or dilatation of the afferent arteriole. Tubuloglomerular feedback is mediated by specialized cells in the thick ascending limb of the loop of Henle, called the *macula densa*, that act as sensors of solute concentration and tubular flow rate. With high tubular flow rates, a proxy for an inappropriately high filtration rate, there is increased solute delivery to the macula densa **(Fig. 1-2*B*)** that evokes vasoconstriction of the afferent arteriole causing GFR to return toward normal. One component of the soluble signal from the macula densa is adenosine triphosphate (ATP) released by the cells during increased NaCl reabsorption. ATP is metabolized in the extracellular space to generate adenosine, a potent vasoconstrictor of the afferent arteriole. During conditions associated with a fall in filtration rate, reduced solute delivery to the macula densa attenuates the tubuloglomerular response, allowing afferent arteriolar dilatation and restoring glomerular filtration to normal levels. Angiotensin II and reactive oxygen species enhance, while nitric oxide (NO) blunts, tubuloglomerular feedback.

The third component underlying autoregulation of GFR involves angiotensin II. During states of reduced renal blood flow, renin is released from granular cells within the wall of the afferent arteriole near the macula densa in a region called the juxtaglomerular apparatus (Fig. 1-2*B*). Renin, a proteolytic enzyme, catalyzes the conversion of angiotensinogen to angiotensin I, which is subsequently converted to angiotensin II by angiotensin-converting enzyme (ACE) **(Fig. 1-2*C*)**. Angiotensin II evokes vasoconstriction of the efferent arteriole, and the resulting increased glomerular hydrostatic pressure elevates filtration to normal levels.

MECHANISMS OF RENAL TUBULAR TRANSPORT

The renal tubules are composed of highly differentiated epithelia that vary dramatically in morphology and function along the nephron (Fig. 1-3). The cells lining the various tubular segments form monolayers connected to one another by a specialized region of the adjacent lateral membranes called the *tight junction*. Tight junctions form an occlusive barrier that separates the lumen of the tubule from the interstitial spaces surrounding the tubule and also apportions the cell membrane into discrete domains: the apical membrane facing the tubular lumen and the basolateral membrane facing the interstitium. This regionalization allows cells to allocate membrane proteins and lipids asymmetrically. Owing to this feature, renal epithelial cells are said to be *polarized*. The asymmetric assignment of membrane proteins, especially proteins mediating transport processes, provides the machinery for directional movement of fluid and solutes by the nephron.

EPITHELIAL SOLUTE TRANSPORT

There are two types of epithelial transport. Movement of fluid and solutes sequentially across the apical and basolateral cell membranes (or vice versa) mediated by transporters, channels, or pumps is called *cellular transport*. By contrast, movement of fluid and solutes through the narrow passageway between adjacent cells is called *paracellular transport*. Paracellular transport occurs through tight junctions, indicating that they are not completely "tight." Indeed, some epithelial cell layers allow rather robust paracellular transport to occur

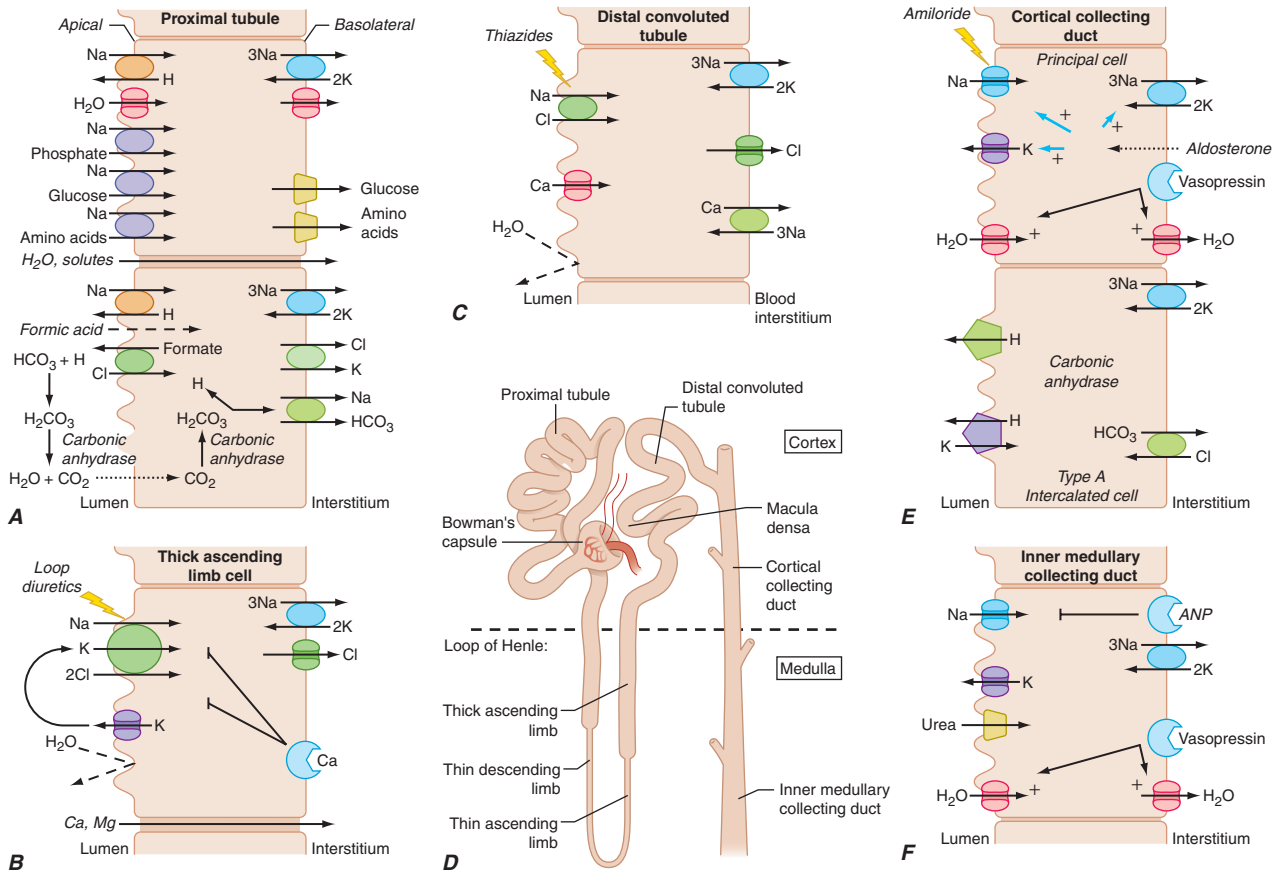

FIGURE 1-3

Transport activities of the major nephron segments. Representative cells from five major tubular segments are illustrated with the lumen side (apical membrane) facing left and interstitial side (basolateral membrane) facing right. ***A.*** Proximal tubular cells. ***B.*** Typical cell in the thick ascending limb of the loop of Henle. ***C.*** Distal convoluted tubular cell. ***D.*** Overview of entire nephron. ***E.*** Cortical collecting duct cells. ***F.*** Typical cell in the inner medullary collecting duct. The major membrane transporters, channels, and pumps are drawn with arrows indicating the direction of solute or water movement. For some events, the stoichiometry of transport is indicated by numerals preceding the solute. Targets for major diuretic agents are labeled. The actions of hormones are illustrated by arrows with plus signs for stimulatory effects and lines with perpendicular ends for inhibitory events. Dotted lines indicate free diffusion across cell membranes. The dashed line indicates water impermeability of cell membranes in the thick ascending limb and distal convoluted tubule.

(*leaky epithelia*), whereas other epithelia have more effective tight junctions (*tight epithelia*). In addition, because the ability of ions to flow through the paracellular pathway determines the electrical resistance across the epithelial monolayer, leaky and tight epithelia are also referred to as low- or high-resistance epithelia, respectively. The proximal tubule contains leaky epithelia, whereas distal nephron segments such as the collecting duct, contain tight epithelia. Leaky epithelia are most well suited for bulk fluid reabsorption, whereas tight epithelia allow for more refined control and regulation of transport.

MEMBRANE TRANSPORT

Cell membranes are composed of hydrophobic lipids that repel water and aqueous solutes. The movement of solutes and water across cell membranes is made possible by discrete classes of integral membrane proteins, including channels, pumps, and transporters. These different mechanisms mediate specific types of transport activities, including *active transport* (pumps), *passive transport* (channels), *facilitated diffusion* (transporters), and *secondary active transport* (cotransporters). Active transport requires metabolic energy generated by the hydrolysis of ATP. Active transport pumps are ion-translocating ATPases, including the ubiquitous Na^+/K^+-ATPase, the H^+-ATPases, and Ca^{2+}-ATPases. Active transport creates asymmetric ion concentrations across a cell membrane and can move ions against a chemical gradient. The potential energy stored in a concentration gradient of an ion such as Na^+ can be utilized to drive transport through other mechanisms (secondary active transport). Pumps are often *electrogenic*, meaning they can create an asymmetric distribution of electrostatic charges across the membrane and establish a voltage or membrane potential. The movement of solutes through a membrane protein by simple diffusion is called passive transport. This activity is mediated by channels created by selectively permeable membrane proteins, and it allows solute or water to move across a membrane driven by favorable *concentration gradients* or *electrochemical potential*. Examples in the kidney include water channels (aquaporins), K^+ channels, epithelial Na^+ channels, and Cl^- channels. Facilitated diffusion is a specialized type of passive transport mediated by simple transporters called *carriers* or *uniporters*. For example, hexose transporters such as GLUT2 mediate glucose transport by tubular cells. These transporters are driven by the concentration gradient for glucose that is highest in extracellular fluids and lowest in the cytoplasm due to rapid metabolism. Many other transporters operate by translocating two or more ions/solutes in concert either in the same direction (*symporters* or *cotransporters*) or in opposite directions (*antiporters* or *exchangers*) across the cell membrane. The movement of two or more ions/solutes may produce no net change in the balance of electrostatic charges across the membrane (*electroneutral*), or a transport event may alter the balance of charges (*electrogenic*). Several inherited disorders of renal tubular solute and water transport occur as a consequence of mutations in genes encoding a variety of channels, transporter proteins, and their regulators **(Table 1-1)**.

SEGMENTAL NEPHRON FUNCTIONS

Each anatomic segment of the nephron has unique characteristics and specialized functions enabling selective transport of solutes and water (Fig. 1-3). Through sequential events of reabsorption and secretion along the nephron, tubular fluid is progressively conditioned into urine. Knowledge of the major tubular mechanisms responsible for solute and water transport is critical for understanding hormonal regulation of kidney function and the pharmacologic manipulation of renal excretion.

PROXIMAL TUBULE

The proximal tubule is responsible for reabsorbing ~60% of filtered NaCl and water, as well as ~90% of filtered bicarbonate and most critical nutrients such as glucose and amino acids. The proximal tubule utilizes both cellular and paracellular transport mechanisms. The apical membrane of proximal tubular cells has an expanded surface area available for reabsorptive work created by a dense array of microvilli called the *brush border*, and leaky tight junctions enable high-capacity fluid reabsorption.

Solute and water pass through these tight junctions to enter the lateral intercellular space where absorption by the peritubular capillaries occurs. Bulk fluid reabsorption by the proximal tubule is driven by high oncotic pressure and low hydrostatic pressure within the peritubular capillaries. Physiologic adjustments in GFR made by changing efferent arteriolar tone cause proportional changes in reabsorption, a phenomenon known as *glomerulotubular balance*. For example, vasoconstriction of the efferent arteriole by angiotensin II will increase glomerular capillary hydrostatic pressure but lower pressure in the peritubular capillaries. At the same time, increased GFR and filtration fraction raise oncotic pressure near the end of the glomerular capillary. These changes, a lowered hydrostatic and increased oncotic pressure, increase the driving force for fluid absorption by the peritubular capillaries.

Cellular transport of most solutes by the proximal tubule is coupled to the Na^+ concentration gradient established by the activity of a basolateral Na^+/K^+-ATPase (Fig. 1-3*A*). This active transport mechanism maintains a steep Na^+ gradient by keeping intracellular Na^+ concentrations low. Solute reabsorption is coupled to the Na^+ gradient by Na^+-dependent transporters such as

TABLE 1-1

INHERITED DISORDERS AFFECTING RENAL TUBULAR ION AND SOLUTE TRANSPORT

DISEASE OR SYNDROME	GENE	OMIM[a]
Disorders Involving the Proximal Tubule		
Proximal renal tubular acidosis	Sodium bicarbonate cotransporter (*SLC4A4,* 4q21)	604278
Fanconi-Bickel syndrome	Glucose transporter, GLUT2 (*SLC2A2,* 3q26.2)	227810
Isolated renal glycosuria	Sodium glucose cotransporter (*SLC5A2,* 16p11.2)	233100
Cystinuria		
Type I	Cystine, dibasic and neutral amino acid transporter (*SLC3A1,* 2p16.3)	220100
Nontype I	Amino acid transporter, light subunit (*SLC7A9,* 19q13.1)	600918
Lysinuric protein intolerance	Amino acid transporter (*SLC7A7,* 4q11.2)	222700
Hartnup disorder	Neutral amino acid transporter (*SLC6A19,* 5p15.33)	34500
Hereditary hypophosphatemic rickets with hypercalcemia	Sodium phosphate cotransporter (*SLC34A3*, 9q34)	241530
Renal hypouricemia		220150
Type 1	Urate-anion exchanger (*SLC22A12,* 11q13)	
Type 2	Urate transporter, GLUT9 (*SLC2A9,* 4p16.1)	612076
Dent's disease	Chloride channel, ClC-5 (*CLCN5,* Xp11.22)	300009
X-linked recessive nephrolithiasis with renal failure	Chloride channel, ClC-5 (*CLCN5,* Xp11.22)	310468
X-linked recessive hypophosphatemic rickets	Chloride channel, ClC-5 (*CLCN5,* Xp11.22)	307800
Disorders Involving the Loop of Henle		
Bartter's syndrome		
Type 1	Sodium, potassium chloride cotransporter (*SLC12A1*, 15q21.1)	241200
Type 2	Potassium channel, ROMK (*KCNJ1,* 11q24)	601678
Type 3	Chloride channel, ClC-Kb (*CLCNKB*, 1p36)	602023
with sensorineural deafness	Chloride channel accessory subunit, Barttin (*BSND*, 1p31)	602522
Autosomal dominant hypocalcemia with Bartter-like syndrome	Calcium-sensing receptor (*CASR*, 3q13.33)	*601199*
Familial hypocalciuric hypercalcemia	Calcium-sensing receptor (*CASR*, 3q13.33)	145980
Primary hypomagnesemia	Claudin-16 or paracellin-1 (*CLDN16* or *PCLN1*, 3q27)	248250
Isolated renal magnesium loss	Sodium potassium ATPase, γ_1-subunit (*ATP1G1*, 11q23)	154020
Disorders Involving the Distal Tubule and Collecting Duct		
Gitelman's syndrome	Sodium chloride cotransporter (*SLC12A3*, 16q13)	263800
Primary hypomagnesemia with secondary hypocalcemia	Melastatin-related transient receptor potential cation channel 6 (*TRPM6*, 9q22)	602014
Pseudoaldosteronism (Liddle's syndrome)	Epithelial sodium channel β and γ subunits (*SCNN1B*, *SCNN1G*, 16p12.1)	177200

(*continued*)

TABLE 1-1

INHERITED DISORDERS AFFECTING RENAL TUBULAR ION AND SOLUTE TRANSPORT (*CONTINUED*)

DISEASE OR SYNDROME	GENE	OMIM[a]
Recessive pseudohypoaldosteronism Type 1	Epithelial sodium channel, α, β, and γ subunits (*SCNN1A*, 12p13; *SCNN1B*, *SCNN1G*, 16pp12.1)	264350
Pseudohypoaldosteronism Type 2 (Gordon's hyperkalemia-hypertension syndrome)	Kinases WNK-1, WNK-4 (*WNK1*, 12p13; *WNK4*, 17q21.31)	145260
X-linked nephrogenic diabetes insipidus	Vasopressin V2 receptor (AVPR2, Xq28)	304800
Nephrogenic diabetes insipidus (autosomal)	Water channel, aquaporin-2 (*AQP2*, 12q13)	125800
Distal renal tubular acidosis		
autosomal dominant	Anion exchanger-1 (*SLC4A1*, 17q21.31)	179800
autosomal recessive	Anion exchanger-1 (*SLC4A1*, 17q21.31)	602722
with neural deafness	Proton ATPase, β1 subunit (*ATP6V1B1*, 2p13.3)	192132
with normal hearing	Proton ATPase, 116-kD subunit (*ATP6V0A4*, 7q34)	602722

[a]Online Mendelian Inheritance in Man database (*http://www.ncbi.nlm.nih.gov/Omim*).

Na^+-glucose and Na^+-phosphate cotransporters. In addition to the paracellular route, water reabsorption also occurs through the cellular pathway enabled by constitutively active water channels (aquaporin-1) present on both apical and basolateral membranes. Small, local *osmotic gradients* close to plasma membranes generated by cellular Na^+ reabsorption are likely responsible for driving directional water movement across proximal tubule cells, but reabsorption along the proximal tubule does not produce a net change in tubular fluid osmolality.

Proximal tubular cells reclaim bicarbonate by a mechanism dependent on carbonic anhydrases. Filtered bicarbonate is first titrated by protons delivered to the lumen by Na^+/H^+ exchange. The resulting carbonic acid (H_2CO_3) is metabolized by brush border carbonic anhydrase to water and carbon dioxide. Dissolved carbon dioxide then diffuses into the cell, where it is enzymatically hydrated by cytoplasmic carbonic anhydrase to re-form carbonic acid. Finally, intracellular carbonic acid dissociates into free protons and bicarbonate anions, and bicarbonate exits the cell through a basolateral Na^+/HCO_3^- cotransporter. This process is saturable, resulting in urinary bicarbonate excretion when plasma levels exceed the physiologically normal range (24–26 meq/L). Carbonic anhydrase inhibitors such as acetazolamide, a class of weak diuretic agents, block proximal tubule reabsorption of bicarbonate and are useful for alkalinizing the urine.

Chloride is poorly reabsorbed throughout the first segment of the proximal tubule, and a rise in Cl^- concentration counterbalances the removal of bicarbonate anion from tubular fluid. In later proximal tubular segments, cellular Cl^- reabsorption is initiated by apical exchange of cellular formate for higher luminal concentrations of Cl^-. Once in the lumen, formate anions are titrated by H^+ (provided by Na^+/H^+ exchange) to generate neutral formic acid, which can diffuse passively across the apical membrane back into the cell where it dissociates a proton and is recycled. Basolateral Cl^- exit is mediated by a K^+/Cl^- cotransporter.

Reabsorption of glucose is nearly complete by the end of the proximal tubule. Cellular transport of glucose is mediated by apical Na^+-glucose cotransport coupled with basolateral, facilitated diffusion by a glucose transporter. This process is also saturable, leading to glycosuria when plasma levels exceed 180–200 mg/dL, as seen in untreated diabetes mellitus.

The proximal tubule possesses specific transporters capable of secreting a variety of organic acids (carboxylate anions) and bases (mostly primary amine cations). Organic anions transported by these systems include urate, ketoacid anions, and several protein-bound drugs not filtered at the glomerulus (penicillins, cephalosporins, and salicylates). Probenecid inhibits renal organic anion secretion and can be clinically useful for raising plasma concentrations of certain drugs like penicillin and oseltamivir. Organic cations secreted by the proximal tubule include various biogenic amine neurotransmitters (dopamine, acetylcholine, epinephrine, norepinephrine, and histamine) and creatinine. The ATP-dependent transporter P-glycoprotein is highly expressed in brush border membranes and secretes several medically important drugs, including cyclosporine, digoxin, tacrolimus, and various cancer chemotherapeutic agents. Certain drugs like cimetidine and trimethoprim compete with endogenous compounds for transport by the organic cation pathways. While these drugs elevate serum creatinine levels, there is no change in the actual GFR.

The proximal tubule, through distinct classes of Na^+-dependent and Na^+-independent transport systems, reabsorbs amino acids efficiently. These transporters are specific for different groups of amino acids. For example, cystine, lysine, arginine, and ornithine are transported by a system comprising two proteins encoded by the *SLC3A1* and *SLC7A9* genes. Mutations in either *SLC3A1* or *SLC7A9* impair reabsorption of these amino acids and cause the disease cystinuria. Peptide hormones such as insulin and growth hormone, β_2-microglobulin, albumin, and other small proteins, are taken up by the proximal tubule through a process of absorptive endocytosis and are degraded in acidified endocytic lysosomes. Acidification of these vesicles depends on a vacuolar H^+-ATPase and Cl^- channel. Impaired acidification of endocytic vesicles because of mutations in a Cl^- channel gene (*CLCN5*) causes low molecular weight proteinuria in Dent's disease. Renal ammoniagenesis from glutamine in the proximal tubule provides a major tubular fluid buffer to ensure excretion of secreted H^+ ion as NH_4^+ by the collecting duct. Cellular K^+ levels inversely modulate ammoniagenesis, and in the setting of high serum K^+ from hypoaldosteronism, reduced ammoniagenesis facilitates the appearance of Type IV renal tubular acidosis.

LOOP OF HENLE

The loop of Henle consists of three major segments: descending thin limb, ascending thin limb, and ascending thick limb. These divisions are based on cellular morphology and anatomic location, but also correlate with specialization of function. Approximately 15–25% of filtered NaCl is reabsorbed in the loop of Henle, mainly by the thick ascending limb. The loop of Henle has an important role in urinary concentration by contributing to the generation of a hypertonic medullary interstitium in a process called *countercurrent multiplication*. The loop of Henle is the site of action for the most potent class of diuretic agents (loop diuretics) and also contributes to reabsorption of calcium and magnesium ions.

The descending thin limb is highly water permeable owing to dense expression of constitutively active aquaporin-1 water channels. By contrast, water permeability is negligible in the ascending limb. In the thick ascending limb, there is a high level of secondary active salt transport enabled by the $Na^+/K^+/2Cl^-$ cotransporter on the apical membrane in series with basolateral Cl^- channels and Na^+/K^+-ATPase (Fig. 1-3*B*). The $Na^+/K^+/2Cl^-$ cotransporter is the primary target for loop diuretics. Tubular fluid K^+ is the limiting substrate for this cotransporter (tubular concentration of K^+ is similar to plasma, about 4 meq/L), but transporter activity is maintained by K^+ recycling through an apical potassium channel. An inherited disorder of the thick ascending limb, Bartter's syndrome, also results in a salt-wasting renal disease associated with hypokalemia and metabolic alkalosis; loss-of-function mutations in one of five distinct genes encoding components of the $Na^+/K^+/2Cl^-$ cotransporter (*NKCC2*), apical K^+ channel (*KCNJ1*), or basolateral Cl^- channel (*CLCNKB*, *BSND*), or calcium-sensing receptor (*CASR*) can cause Bartter's syndrome.

Potassium recycling also contributes to a positive electrostatic charge in the lumen relative to the interstitium that promotes divalent cation (Mg^{2+} and Ca^{2+}) reabsorption through a paracellular pathway. A Ca^{2+}-sensing, G-protein–coupled receptor (CaSR) on basolateral membranes regulates NaCl reabsorption in the thick ascending limb through dual signaling mechanisms utilizing either cyclic AMP or eicosanoids. This receptor enables a steep relationship between plasma Ca^{2+} levels and renal Ca^{2+} excretion. Loss-of-function mutations in CaSR cause familial hypercalcemic hypocalciuria because of a blunted response of the thick ascending limb to extracellular Ca^{2+}. Mutations in *CLDN16* encoding paracellin-1, a transmembrane protein located within the tight junction complex, leads to familial hypomagnesemia with hypercalcuria and nephrocalcinosis, suggesting that the ion conductance of the paracellular pathway in the thick limb is regulated.

The loop of Henle contributes to urine-concentrating ability by establishing a *hypertonic medullary interstitium* that promotes water reabsorption by the downstream inner medullary collecting duct. *Countercurrent multiplication* produces a hypertonic medullary interstitium using two countercurrent systems: the loop of Henle (opposing descending and ascending limbs) and the vasa recta (medullary peritubular capillaries enveloping the loop). The countercurrent flow in these two systems helps maintain the hypertonic environment of the inner medulla, but NaCl reabsorption by the thick ascending limb is the primary initiating event. Reabsorption of NaCl without water dilutes the tubular fluid and adds new osmoles to medullary interstitial fluid. Because the descending thin limb is highly water permeable, osmotic equilibrium occurs between the descending limb tubular fluid and the interstitial space, leading to progressive solute trapping in the inner medulla. Maximum medullary interstitial osmolality also requires partial recycling of urea from the collecting duct.

DISTAL CONVOLUTED TUBULE

The distal convoluted tubule reabsorbs ~5% of the filtered NaCl. This segment is composed of a tight epithelium with little water permeability. The major NaCl-transporting pathway utilizes an apical membrane, electroneutral thiazide-sensitive Na^+/Cl^- cotransporter in tandem with basolateral Na^+/K^+-ATPase and Cl^- channels (Fig. 1-3*C*). Apical Ca^{2+}-selective channels (TRPV5) and basolateral Na^+/Ca^{2+} exchange mediate calcium reabsorption in the distal convoluted tubule.

Ca^{2+} reabsorption is inversely related to Na^+ reabsorption and is stimulated by parathyroid hormone. Blocking apical Na^+/Cl^- cotransport will reduce intracellular Na^+, favoring increased basolateral Na^+/Ca^{2+} exchange and passive apical Ca^{2+} entry. Loss-of-function mutations of *SLC12A3* encoding the apical Na^+/Cl^- cotransporter cause Gitelman's syndrome, a salt-wasting disorder associated with hypokalemic alkalosis and hypocalciuria. Mutations in genes encoding WNK kinases, WNK-1 and WNK-4, cause pseudohypoaldosteronism type II or Gordon's syndrome characterized by familial hypertension with hyperkalemia. WNK kinases influence the activity of several tubular ion transporters. Mutations in this disorder lead to overactivity of the apical Na^+/Cl^- cotransporter in the distal convoluted tubule as the primary stimulus for increased salt reabsorption, extracellular volume expansion, and hypertension. Hyperkalemia may be caused by diminished activity of apical K^+ channels in the collecting duct, a primary route for K^+ secretion. Mutations in *TRPM6* encoding Mg^{2+} permeable ion channels also cause familial hypomagnesemia with hypocalcemia. A molecular complex of TRPM6 and TRPM7 proteins is critical for Mg^{2+} reabsorption in the distal convoluted tubule.

COLLECTING DUCT

The collecting duct modulates the final composition of urine. The two major divisions, the cortical collecting duct and inner medullary collecting duct, contribute to reabsorbing ~4–5% of filtered Na^+ and are important for hormonal regulation of salt and water balance. The cortical collecting duct contains *high-resistance epithelia* with two cell types. Principal cells are the main water, Na^+-reabsorbing, and K^+-secreting cells, and the site of action of aldosterone, K^+-sparing diuretics, and mineralocorticoid receptor antagonists such as spironolactone. The other cells are type A and B intercalated cells. Type A intercalated cells mediate acid secretion and bicarbonate reabsorption also under the influence of aldosterone. Type B intercalated cells mediate bicarbonate secretion and acid reabsorption.

Virtually all transport is mediated through the cellular pathway for both principal cells and intercalated cells. In principal cells, passive apical Na^+ entry occurs through the amiloride-sensitive, epithelial Na^+ channel (ENaC) with basolateral exit via the Na^+/K^+-ATPase (Fig. 1-3*E*). This Na^+ reabsorptive process is tightly regulated by aldosterone and is physiologically activated by a variety of proteolytic enzymes that cleave extracellular domains of ENaC; plasmin in the tubular fluid of nephrotic patients, for example, activates ENaC, leading to sodium retention. Aldosterone enters the cell across the basolateral membrane, binds to a cytoplasmic mineralocorticoid receptor, and then translocates into the nucleus, where it modulates gene transcription, resulting in increased Na^+ reabsorption and K^+ secretion. Activating mutations in ENaC increase Na^+ reclamation and produce hypokalemia, hypertension, and metabolic alkalosis (Liddle's syndrome). The potassium-sparing diuretics amiloride and triamterene block ENaC, causing reduced Na^+ reabsorption.

Principal cells secrete K^+ through an apical membrane potassium channel. Several forces govern the secretion of K^+. Most importantly, the high intracellular K^+ concentration generated by Na^+/K^+-ATPase creates a favorable concentration gradient for K^+ secretion into tubular fluid. With reabsorption of Na^+ without an accompanying anion, the tubular lumen becomes negative relative to the cell interior, creating a favorable electrical gradient for secretion of potassium. When Na^+ reabsorption is blocked, the electrical component of the driving force for K^+ secretion is blunted, and this explains the lack of excess urinary K^+ loss during treatment with potassium-sparing diuretics. K^+ secretion is also promoted by aldosterone actions that increase regional Na^+ transport favoring more electronegativity and by increasing the number and activity of potassium channels. Fast tubular fluid flow rates that occur during volume expansion or diuretics acting "upstream" of the cortical collecting duct also increase K^+ secretion, as does the presence of relatively nonreabsorbable anions (including bicarbonate and semisynthetic penicillins) that contribute to the lumen-negative potential. Off-target effects of certain antibiotics such as trimethoprim and pentamidine, block ENaCs and predispose to hyperkalemia, especially when renal K^+ handling is impaired for other reasons. Principal cells, as described below, also participate in water reabsorption by increased water permeability in response to vasopressin.

Intercalated cells do not participate in Na^+ reabsorption but instead mediate acid-base secretion. These cells perform two types of transport: active H^+ transport mediated by H^+-ATPase (proton pump), and Cl^-/HCO_3^- exchange. Intercalated cells arrange the two transport mechanisms on opposite membranes to enable either acid or base secretion. Type A intercalated cells have an apical proton pump that mediates acid secretion and a basolateral Cl^-/HCO_3^- anion exchanger for bicarbonate reabsorption (Fig. 1-3*E*); aldosterone increases the number of H^+-ATPase pumps, sometimes contributing to the development of metabolic alkalosis. By contrast, type B intercalated cells have the anion exchanger on the apical membrane to mediate bicarbonate secretion while the proton pump resides on the basolateral membrane to enable acid reabsorption. Under conditions of acidemia, the kidney preferentially uses type A intercalated cells to secrete the excess H^+ and generate more HCO_3^-. The opposite is true in states

of bicarbonate excess with alkalemia where the type B intercalated cells predominate. An extracellular protein called *hensin* mediates this adaptation.

Inner medullary collecting duct cells share many similarities with principal cells of the cortical collecting duct. They have apical Na^+ and K^+ channels that mediate Na^+ reabsorption and K^+ secretion, respectively (Fig. 1-3*F*). Inner medullary collecting duct cells also have vasopressin-regulated water channels (aquaporin-2 on the apical membrane, aquaporin-3 and -4 on the basolateral membrane). The antidiuretic hormone vasopressin binds to the V2 receptor on the basolateral membrane and triggers an intracellular signaling cascade through G-protein–mediated activation of adenylyl cyclase, resulting in an increase in the cellular levels of cyclic AMP. This signaling cascade stimulates the insertion of water channels into the apical membrane of the inner medullary collecting duct cells to promote increased water permeability. This increase in permeability enables water reabsorption and production of concentrated urine. In the absence of vasopressin, inner medullary collecting duct cells are water impermeable, and urine remains dilute.

Sodium reabsorption by inner medullary collecting duct cells is also inhibited by the natriuretic peptides called *atrial natriuretic peptide* or *renal natriuretic peptide* (urodilatin); the same gene encodes both peptides but uses different posttranslational processing of a common preprohormone to generate different proteins. Atrial natriuretic peptides are secreted by atrial myocytes in response to volume expansion, whereas urodilatin is secreted by renal tubular epithelia. Natriuretic peptides interact with either apical (urodilatin) or basolateral (atrial natriuretic peptides) receptors on inner medullary collecting duct cells to stimulate guanylyl cyclase and increase levels of cytoplasmic cGMP. This effect in turn reduces the activity of the apical Na^+ channel in these cells and attenuates net Na^+ reabsorption, producing natriuresis.

The inner medullary collecting duct transports urea out of the lumen, returning urea to the interstitium, where it contributes to the hypertonicity of the medullary interstitium. Urea is recycled by diffusing from the interstitium into the descending and ascending limbs of the loop of Henle.

HORMONAL REGULATION OF SODIUM AND WATER BALANCE

The balance of solute and water in the body is determined by the amounts ingested, distributed to various fluid compartments, and excreted by skin, bowel, and kidneys. *Tonicity*, the osmolar state determining the volume behavior of cells in a solution, is regulated by water balance **(Fig. 1-4*A*)**, and *extracellular blood volume* is regulated by Na^+ balance **(Fig. 1-4*B*)**. The kidney is a critical modulator of both physiologic processes.

WATER BALANCE

Tonicity depends on the variable concentration of *effective osmoles* inside and outside the cell causing water to move in either direction across its membrane. Classic effective osmoles, like Na^+, K^+, and their anions, are solutes trapped on either side of a cell membrane, where they collectively partition and obligate water to move and find equilibrium in proportion to retained solute; Na^+/K^+-ATPase keeps most K^+ inside cells and most Na^+ outside. Normal tonicity (~280 mosmol/L) is rigorously defended by osmoregulatory mechanisms that control water balance to protect tissues from inadvertent *dehydration* (cell shrinkage) or *water intoxication* (cell swelling), both of which are deleterious to cell function (Fig. 1-4*A*).

The mechanisms that control osmoregulation are distinct from those governing extracellular volume, although there is some shared physiology in both processes. While cellular concentrations of K^+ have a determinant role in any level of tonicity, the routine surrogate marker for assessing clinical tonicity is the concentration of serum Na^+. Any reduction in total body water, which raises the Na^+ concentration, triggers a brisk sense of thirst and conservation of water by decreasing renal water excretion mediated by release of vasopressin from the posterior pituitary. Conversely, a decrease in plasma Na^+ concentration triggers an increase in renal water excretion by suppressing the secretion of vasopressin. While all cells expressing mechanosensitive TRPV1, 2, or 4 channels, among potentially other sensors, respond to changes in tonicity by altering their volume and Ca^{2+} concentration, only $TRPV^+$ neuronal cells connected to the organum vasculosum of the lamina terminalis are *osmoreceptive*. Only these cells, because of their neural connectivity and adjacency to a minimal blood-brain barrier, modulate the downstream release of vasopressin by the posterior lobe of the pituitary gland. Secretion is stimulated primarily by changing tonicity and secondarily by other nonosmotic signals such as variable blood volume, stress, pain, nausea, and some drugs. The release of vasopressin by the posterior pituitary increases linearly as plasma tonicity rises above normal, although this varies, depending on the perception of extracellular volume (one form of cross-talk between mechanisms that adjudicate blood volume and osmoregulation). Changing the intake or excretion of water provides a means for adjusting plasma tonicity; thus, osmoregulation governs water balance.

The kidneys play a vital role in maintaining water balance through the regulation of renal water excretion.

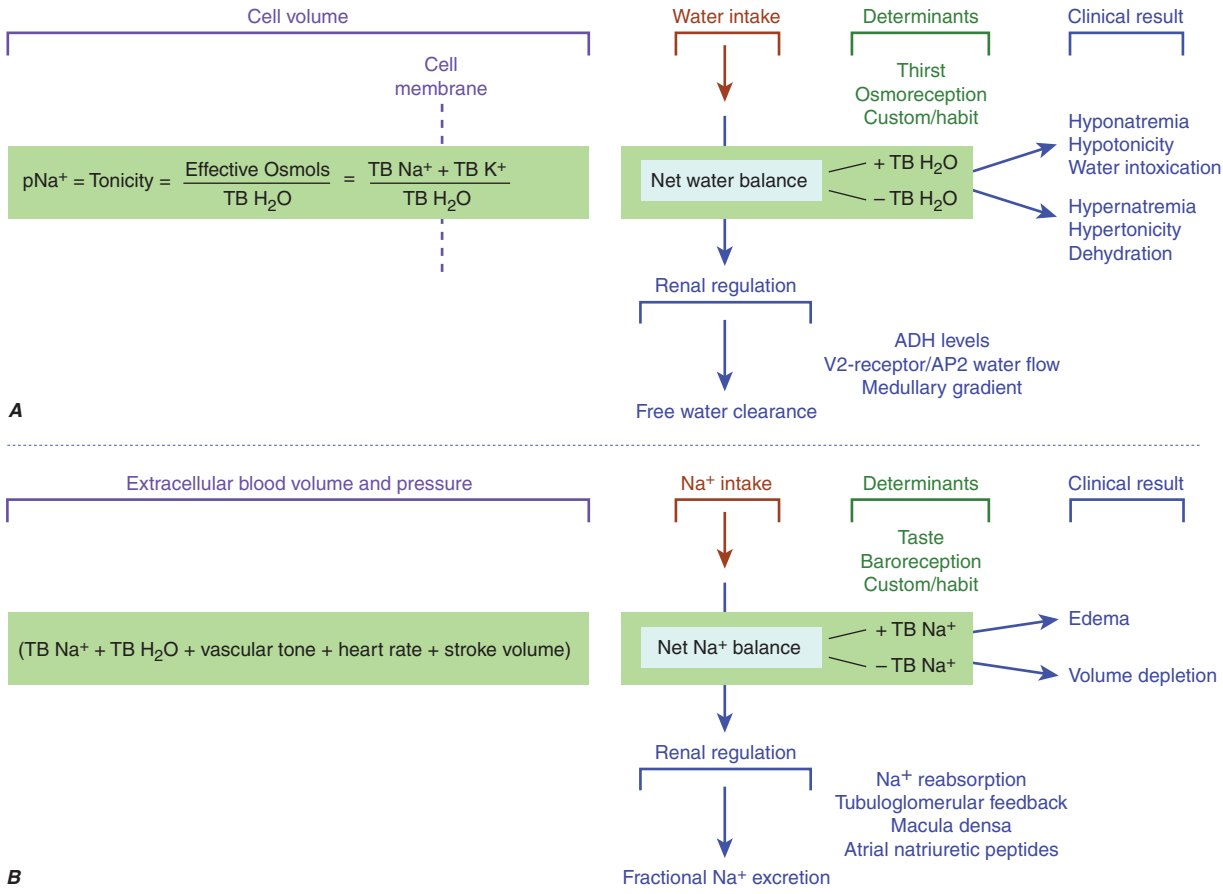

FIGURE 1-4

Determinants of sodium and water balance. ***A.*** Plasma Na^+ concentration is a surrogate marker for plasma tonicity, the volume behavior of cells in a solution. Tonicity is determined by the number of effective osmols in the body divided by the total body H_2O (TB H_2O), which translates simply into the total body Na (TB Na^+) and anions outside the cell separated from the total body K (TB K^+) inside the cell by the cell membrane. Net water balance is determined by the integrated functions of thirst, osmoreception, Na reabsorption, vasopressin release, and the strength of the medullary gradient in the kidney, keeping tonicity within a narrow range of osmolality around 280 mosmol/L. When water metabolism is disturbed and total body water increases, hyponatremia, hypotonicity, and water intoxication occur; when total body water decreases, hypernatremia, hypertonicity, and dehydration occur. ***B.*** Extracellular blood volume and pressure are an integrated function of total body Na^+ (TB Na^+), total body H_2O (TB H_2O), vascular tone, heart rate, and stroke volume that modulates volume and pressure in the vascular tree of the body. This extracellular blood volume is determined by net Na balance under the control of taste, baroreception, habit, Na^+ reabsorption, macula densa/tubuloglomerular feedback, and natriuretic peptides. When Na^+ metabolism is disturbed and total body Na^+ increases, edema occurs; when total body Na^+ is decreased, volume depletion occurs. ADH, antidiuretic hormone; AQP2, aquaporin-2.

The ability to concentrate urine to an osmolality exceeding that of plasma enables water conservation, while the ability to produce urine more dilute than plasma promotes excretion of excess water. For water to enter or exit a cell, the cell membrane must express aquaporins. In the kidney, aquaporin 1 is constitutively active in all water-permeable segments of the proximal and distal tubules, while vasopressin-regulated aquaporins 2, 3, and 4 in the inner medullary collecting duct promote rapid water permeability. Net water reabsorption is ultimately driven by the osmotic gradient between dilute tubular fluid and a hypertonic medullary interstitium.

SODIUM BALANCE

The perception of *extracellular blood volume* is determined, in part, by the integration of arterial tone, cardiac stroke volume, heart rate, and the water and solute content of extracellular fluid. Na^+ and accompanying anions are the most abundant extracellular effective osmols and together support a blood volume around which pressure is generated. Under normal conditions, this volume is regulated by sodium balance (Fig. 1-4*B*), and the balance between daily Na^+ intake and excretion is under the influence of *baroreceptors* in regional blood vessels and vascular hormone sensors modulated by atrial natriuretic

peptides, the renin-angiotensin-aldosterone system, Ca^{2+} signaling, adenosine, vasopressin, and the neural adrenergic axis. If Na^+ intake exceeds Na^+ excretion (positive Na^+ balance), then an increase in blood volume will trigger a proportional increase in urinary Na^+ excretion. Conversely, when Na^+ intake is less than urinary excretion (negative Na^+ balance), blood volume will decrease and trigger enhanced renal Na^+ reabsorption, leading to decreased urinary Na^+ excretion.

The renin-angiotensin-aldosterone system is the best-understood hormonal system modulating renal Na^+ excretion. Renin is synthesized and secreted by granular cells in the wall of the afferent arteriole. Its secretion is controlled by several factors, including β_1-adrenergic stimulation to the afferent arteriole, input from the macula densa, and prostaglandins. Renin and ACE activity eventually produce angiotensin II that directly or indirectly promotes renal Na^+ and water reabsorption. Stimulation of proximal tubular Na^+/H^+ exchange by angiotensin II directly increases Na^+ reabsorption. Angiotensin II also promotes Na^+ reabsorption along the collecting duct by stimulating aldosterone secretion by the adrenal cortex. Constriction of the efferent glomerular arteriole by angiotensin II indirectly increases the filtration fraction and raises peritubular capillary oncotic pressure to promote tubular Na^+ reabsorption. Finally, angiotensin II inhibits renin secretion through a negative feedback loop. Alternative metabolism of angiotensin by ACE2 generates the vasodilatory peptide angiotensin 1-7 that acts through Mas receptors to counterbalance several actions of angiotensin II on blood pressure and renal function (Fig. 1-2*C*).

Aldosterone is synthesized and secreted by granulosa cells in the adrenal cortex. It binds to cytoplasmic mineralocorticoid receptors in the collecting duct principal cells that increase activity of ENaC, apical membrane K^+ channel, and basolateral Na^+/K^+-ATPase. These effects are mediated in part by aldosterone-stimulated transcription of the gene encoding serum/glucocorticoid-induced kinase 1 (SGK1). The activity of ENaC is increased by SGK1-mediated phosphorylation of Nedd4-2, a protein that promotes recycling of the Na^+ channel from the plasma membrane. Phosphorylated Nedd4-2 has impaired interactions with ENaC, leading to increased channel density at the plasma membrane and increased capacity for Na^+ reabsorption by the collecting duct.

Chronic exposure to aldosterone causes a decrease in urinary Na^+ excretion lasting only a few days, after which Na^+ excretion returns to previous levels. This phenomenon, called *aldosterone escape*, is explained by decreased proximal tubular Na^+ reabsorption following blood volume expansion. Excess Na^+ that is not reabsorbed by the proximal tubule overwhelms the reabsorptive capacity of more distal nephron segments. This escape may be facilitated by atrial natriuretic peptides that lose their effectiveness in the clinical settings of heart failure, nephrotic syndrome, and cirrhosis, leading to severe Na^+ retention and volume overload.

CHAPTER 2

ADAPTION OF THE KIDNEY TO RENAL INJURY

Raymond C. Harris ■ Eric G. Neilson

The size of a kidney and the total number of nephrons formed late in embryologic development depend on the degree to which the ureteric bud undergoes branching morphogenesis. Humans have between 225,000 and 900,000 nephrons in each kidney, a number that mathematically hinges on whether ureteric branching goes to completion or is terminated prematurely by one or two cycles. Although the signaling mechanisms regulating cycle number are incompletely understood, these final rounds of branching likely determine how well the kidney will adapt to the physiologic demands of blood pressure and body size, various environmental stresses, or unwanted inflammation leading to chronic renal failure.

One of the intriguing generalities regarding chronic renal failure is that residual nephrons hyperfunction to compensate for the loss of those nephrons succumbing to primary disease. This compensation depends on adaptive changes produced by renal hypertrophy and adjustments in *tubuloglomerular feedback* and *glomerulotubular balance*, as advanced in the *intact nephron hypothesis* by Neal Bricker in 1969. Some physiologic adaptations to nephron loss also produce unintended clinical consequences explained by Bricker's *trade-off hypothesis* in 1972, and eventually some adaptations accelerate the deterioration of residual nephrons, as described by Barry Brenner in his *hyperfiltration hypothesis* in 1982. These three important notions regarding chronic renal failure form a conceptual basis for understanding common pathophysiology leading to uremia.

COMMON MECHANISMS OF PROGRESSIVE RENAL DISEASE

When the initial complement of nephrons is reduced by a sentinel event, such as unilateral nephrectomy, the remaining kidney adapts by enlarging and increasing its glomerular filtration rate. If the kidneys were initially normal, the filtration rate usually returns to 80% of normal for two kidneys. The remaining kidney grows by *compensatory renal hypertrophy* with very little cellular proliferation. This unique event is accomplished by increasing the size of each cell along the nephron, which is accommodated by the elasticity or growth of interstitial spaces under the renal capsule. The mechanism of this *compensatory renal hypertrophy* is only partially understood; studies suggest roles for angiotensin II transactivation of heparin-binding epithelial growth factor, PI3K, and $p27^{kip1}$, a cell cycle protein that prevents tubular cells exposed to angiotensin II from proliferating, and the mammalian target of rapamycin (mTOR), which mediates new protein synthesis.

Hyperfiltration during pregnancy or in humans born with one kidney or who lose one to trauma or transplantation generally produces no ill consequences. By contrast, experimental animals that undergo resection of 80% of their renal mass, or humans who have persistent injury that destroys a comparable amount of renal tissue, progress to end-stage disease **(Fig. 2-1)**. Clearly, there is a critical amount of primary nephron loss that produces maladaptive deterioration in remaining nephrons. This maladaptive response is referred to clinically as *renal progression,* and the pathologic correlate of renal progression is the relentless advance of tubular atrophy and tissue fibrosis. The mechanism for this maladaptive response is the focus of intense investigation. A unified theory of *renal progression* is just starting to emerge, and most importantly, this progression follows a final common pathway regardless of whether renal injury begins in glomeruli or within the tubulointerstitium.

There are six mechanisms that hypothetically unify this final common pathway. If injury begins in glomeruli, these sequential steps build on each other: (1) persistent glomerular injury produces local hypertension in capillary tufts, increases their single-nephron glomerular

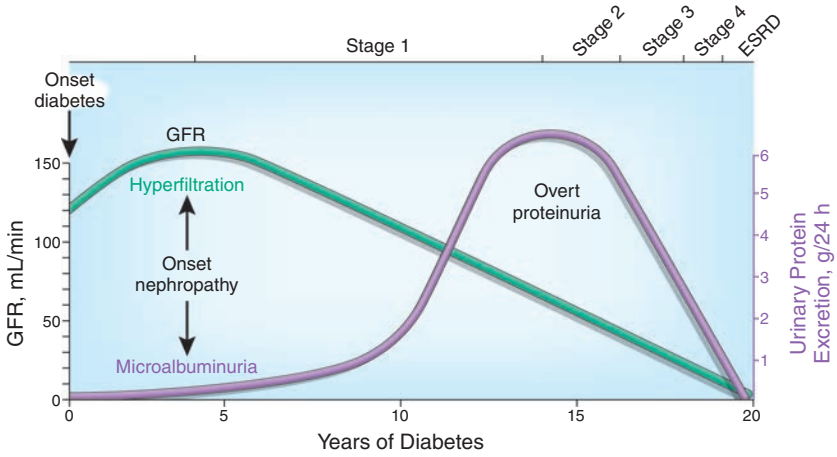

FIGURE 2-1
Progression of chronic renal injury. Although various types of renal injury have their own unique rates of progression, one of the best understood is that associated with type I diabetic nephropathy. Notice the early increase in glomerular filtration rate, followed by inexorable decline associated with increasing proteinuria. Also indicated is the National Kidney Foundation K/DOQI classification of the stages of chronic kidney disease.

filtration rate and engenders protein leak into the tubular fluid; (2) significant glomerular proteinuria, accompanied by increases in the local production of angiotensin II, facilitates a downstream cytokine bath that induces the accumulation of interstitial mononuclear cells; (3) the initial appearance of interstitial neutrophils is quickly replaced by a gathering of macrophages and T lymphocytes, which form a nephritogenic immune response producing interstitial nephritis; (4) some tubular epithelia respond to this inflammation by disaggregating from their basement membrane and adjacent sister cells to undergo *epithelial-mesenchymal transitions* forming new interstitial fibroblasts; and finally (5) surviving fibroblasts lay down a collagenous matrix that disrupts adjacent capillaries and tubular nephrons, eventually leaving an acellular scar. The details of these complex events are outlined in **Fig. 2-2**.

Significant ablation of renal mass results in *hyperfiltration* characterized by an increase in the rate of *single-nephron glomerular filtration*. The remaining nephrons lose their ability to autoregulate, and systemic hypertension is transmitted to the glomerulus. Both the *hyperfiltration* and *intraglomerular* hypertension stimulate the eventual appearance of glomerulosclerosis. Angiotensin II acts as an essential mediator of increased *intraglomerular* capillary pressure by selectively increasing efferent arteriolar vasoconstriction relative to afferent arteriolar tone. Angiotensin II impairs glomerular size selectivity, induces protein ultrafiltration, and increases intracellular Ca^{2+} in podocytes, which alters podocyte function. Diverse vasoconstrictor mechanisms, including blockade of nitric oxide synthase and activation of angiotensin II and thromboxane receptors, can also induce oxidative stress in surrounding renal tissue. Finally, the effects of aldosterone on increasing renal vascular resistance and glomerular capillary pressure, or stimulating plasminogen activator inhibitor-1, facilitate fibrogenesis and may complement the detrimental activity of angiotensin II.

On occasion, inflammation that begins in the renal interstitium disables tubular reclamation of filtered protein, producing mild nonselective proteinuria. Renal inflammation that initially damages glomerular capillaries often spreads to the tubulointerstitium in association with heavier proteinuria. Many clinical observations support the association of worsening *glomerular proteinuria* with *renal progression*. The simplest explanation for this expansion of mononuclear cells is that increasingly severe proteinuria triggers a downstream inflammatory cascade in tubular epithelial cells, producing interstitial nephritis, fibrosis, and tubular atrophy. As albumin is an abundant polyanion in plasma and can bind a variety of cytokines, chemokines, and lipid mediators, it is likely these small albumin-carried molecules initiate the tubular inflammation brought on by proteinuria. Furthermore, glomerular injury either adds activated mediators to the proteinuric filtrate or alters the balance of cytokine inhibitors and activators such that attainment of a critical level of activated cytokines eventually damages downstream tubular nephrons.

Tubular epithelia bathed in these complex mixtures of proteinuric cytokines respond by increasing their secretion of chemokines and relocating NF-κB to the nucleus to induce the proinflammatory release of transforming growth factor β (TGF-β), platelet-derived growth factor–BB (PDGF-BB), and fibroblast growth factor 2 (FGF-2). Inflammatory cells are drawn into the renal interstitium by this cytokine milieu. This interstitial spreading reduces the likelihood that the kidney will survive. The immunologic mechanisms for spreading include loss of tolerance to parenchymal self, immune deposits that share cross-reactive epitopes in either compartment, or glomerular injury that reveals a new interstitial epitope. Drugs, infection, and metabolic defects also induce autoimmunity through toll-like receptors (TLRs) that bind to ligands with an immunologically distinct molecular pattern. Bacterial and viral ligands activate TLRs, but interestingly so do Tamm-Horsfall protein, bacterial CpG repeats, and RNA that is released nonspecifically from injured tubular cells. Dendritic cells and macrophages are subsequently activated, and

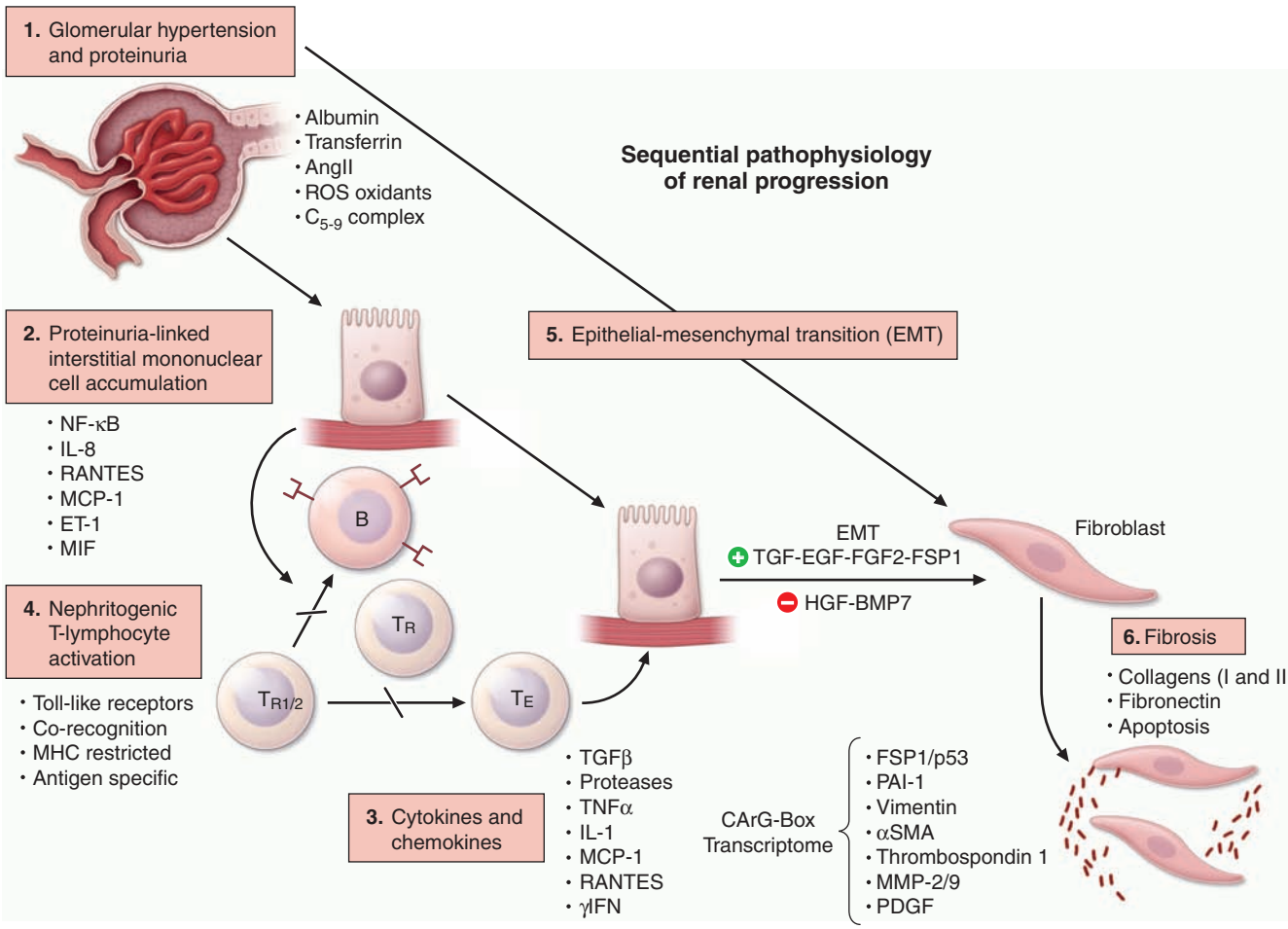

FIGURE 2-2

Mechanisms of renal progression. The general mechanisms of renal progression advance sequentially through six stages that include hyperfiltration, proteinuria, cytokine bath, mononuclear cell infiltration, epithelial-mesenchymal transition, and fibrosis. (*Modified from RC Harris, EG Neilson: Annu Rev Med 57:365, 2006.*)

circulating T cells engage in the formal cellular immunologic response.

Nephritogenic interstitial T cells are a mix of $CD4^+$ helper, $CD17^+$ effector, and $CD8^+$ cytotoxic lymphocytes. Presumptive evidence of antigen-driven T cells found by examining the DNA sequence of T-cell receptors suggests a polyclonal expansion responding to multiple epitopes. Some experimental interstitial lesions are histologically analogous to a cutaneous delayed-type hypersensitivity reaction, and more intense reactions sometimes induce granuloma formation. The cytotoxic activity of antigen-reactive T cells probably accounts for tubular cell destruction and atrophy. Cytotoxic T cells synthesize proteins with serine esterase activity as well as pore-forming proteins, which can effect membrane damage much like the activated membrane attack complex of the complement cascade. Such enzymatic activity provides a structural explanation for target cell lysis.

One long-term consequence of tubular epithelia and adjacent endothelia exposed to cytokines is the profibrotic activation of *epithelial/endothelial-mesenchymal transition* (EMT). Persistent cytokine activity during renal inflammation and disruption of underlying basement membranes by local proteases initiates the process of transition. Rather than collapsing into the tubular lumens and dying, some epithelia become fibroblasts while translocating back into the interstitial space behind deteriorating tubules through holes in the ruptured basement membrane; the contribution of endothelial cells from interstitial vessels may be equally important. Wnt proteins, integrin-linked kinases, insulin-like growth factors, EGF, FGF-2, and TGF-β are among the classic modulators of EMT. Fibroblasts that deposit collagen during fibrogenesis also replicate locally at sites of persistent inflammation. Estimates indicate that more than half of the total fibroblasts found in fibrotic renal tissues are products of the proliferation of newly transitioned or preexisting fibroblasts. Fibroblasts are stimulated to multiply by activation of cognate cell-surface receptors for PDGF and TGF-β.

Tubulointerstitial scars are composed principally of fibronectin, collagen types I and III, and tenascin, but other glycoproteins such as thrombospondin, SPARC, osteopontin, and proteoglycan also may be important.

Although tubular epithelia can synthesize collagens I and III and are modulated by a variety of growth factors, these epithelia disappear through transition and tubular atrophy, leaving fibroblasts as the major contributor to matrix production. After fibroblasts acquire a synthetic phenotype, expand their population, and locally migrate around areas of inflammation, they begin to deposit fibronectin, which provides a scaffold for interstitial collagens. When fibroblasts outdistance their survival factors, they die from apoptosis, leaving an acellular scar.

RESPONSE TO REDUCTION IN NUMBERS OF FUNCTIONING NEPHRONS

As mentioned above, the response to the loss of many functioning nephrons produces an increase in renal blood flow with glomerular *hyperfiltration*, which is the result of increased vasoconstriction in postglomerular efferent arterioles relative to preglomerular afferent arterioles, increasing the *intraglomerular* capillary pressure and filtration fraction. Persistent intraglomerular hypertension is associated with progressive nephron destruction. Although the hormonal and metabolic factors mediating *hyperfiltration* are not fully understood, a number of vasoconstrictive and vasodilatory substances have been implicated, chief among them being angiotensin II. Angiotensin II incrementally vasoconstricts the efferent arteriole, and studies in animals and humans demonstrate that interruption of the renin-angiotensin system with either angiotensin-converting inhibitors or angiotensin II receptor blockers will decrease *intraglomerular* capillary pressure, decrease proteinuria, and slow the rate of nephron destruction. The vasoconstrictive agent endothelin has also been implicated in *hyperfiltration*, and increases in afferent vasodilatation have been attributed, at least in part, to local prostaglandins and release of endothelium-derived nitric oxide. Finally, hyperfiltration may be mediated in part by a resetting of the kidney's intrinsic autoregulatory mechanism of glomerular filtration by a *tubuloglomerular feedback system*. This feedback originates from the macula densa and modulates renal blood flow and glomerular filtration (see Chap. 1).

Even with the loss of functioning nephrons, there is some continued maintenance of *glomerulotubular balance*, by which the residual tubules adapt to increases in *single nephron glomerular filtration* with appropriate alterations in reabsorption or excretion of filtered water and solutes in order to maintain homeostasis. *Glomerulotubular balance* results both from tubular hypertrophy and from regulatory adjustments in tubular oncotic pressure or solute transport along the proximal tubule. Some studies indicate these alterations in tubule size and function may themselves be maladaptive, and as a trade-off, predispose to further tubule injury.

TUBULAR FUNCTION IN CHRONIC RENAL FAILURE

SODIUM

Na^+ ions are reclaimed along many parts of the nephron by various transport mechanisms (see Chap. 2). This transport function and its contribution to maintaining extracellular blood volume usually remains near normal until limitations from advanced renal disease inadequately excrete dietary Na^+ intake. Prior to this point and throughout renal progression, increasing the fractional excretion of Na^+ in final urine at progressively reduced rates of glomerular filtration provides a mechanism of early adaptation. Na^+ excretion increases predominantly by decreasing Na^+ reabsorption in the loop of Henle and distal nephron. An increase in the osmotic obligation of residual nephrons increases tubular water and lowers the concentration of Na^+ in tubular fluid, reducing efficient Na^+ reclamation; increased excretion of inorganic and organic anions also obligates more Na^+ excretion. In addition, hormonal influences, notably increased expression of atrial natriuretic peptides that increase distal Na^+ excretion, play an important role in maintaining net Na^+ excretion. Although many details of these adjustments are only understood conceptually, it is an example of a trade-off by which initial adjustments following the loss of functioning nephrons leads to compensatory responses that maintain homeostasis. Eventually, with advancing nephron loss, the atrial natriuretic peptides lose their effectiveness, and Na^+ retention results in intravascular volume expansion, edema, and worsening hypertension.

URINARY DILUTION AND CONCENTRATION

Patients with progressive renal injury gradually lose the capacity either to dilute or concentrate their urine, and urine osmolality becomes relatively fixed about 350 mosmol/L (specific gravity ~1.010). Although the absolute ability of a single nephron to excrete water free of solute may not be impaired, the reduced number of functioning nephrons obligates increased fractional solute excretion by residual nephrons, and this greater obligation impairs the ability to dilute tubular fluid maximally. Similarly, urinary concentrating ability falls as more water is needed to hydrate an increasing solute load. Tubulointerstitial damage also creates insensitivity to the antidiuretic effects of vasopressin along the collecting duct or loss of the medullary gradient that eventually disturbs control of variation in urine osmolality. Patients with moderate degrees of chronic renal failure often complain of *nocturia* as a manifestation of this fixed urine osmolality, and they are prone to extracellular volume depletion if they do not keep up with the persistent loss of Na^+ or to hypotonicity if they drink too much water.

POTASSIUM

Renal excretion is the major pathway for reducing excess total body K^+. Normally, the kidney excretes 90% of dietary K^+, while 10% is excreted in the stool with a trivial amount lost to sweat. Although the colon possesses some capacity to increase K^+ excretion—up to 30% of ingested K^+ may be excreted in the stool of patients with worsening renal failure—the majority of the K^+ load continues to be excreted by the kidneys due to elevation in levels of serum K^+ that increase filtered load. Aldosterone also regulates collecting duct Na^+ reabsorption and K^+ secretion. Aldosterone is released from the adrenal cortex not only in response to the renin-angiotensin system, but also in direct response to elevated levels of serum K^+ and, for a while, a compensatory increase in the capacity of the collecting duct to secrete K^+ keeps up with *renal progression*. As serum K^+ levels rise with renal failure, circulating levels of aldosterone also increase over what is required to maintain normal levels of blood volume.

ACID-BASE REGULATION

The kidneys excrete 1 meq/kg/day of noncarbonic H^+ ion on a normal diet. To do this, all of the filtered HCO_3^{2-} needs to be reabsorbed proximally so that H^+ pumps in the intercalated cells of the collecting duct can secrete H^+ ions that are subsequently trapped by urinary buffers, particularly phosphates and ammonia (see Chap. 1). While remaining nephrons increase their solute load with loss of renal mass, the ability to maintain total body H^+ excretion is often impaired by the gradual loss of H^+ pumps or with reductions in ammoniagenesis, leading to development of a nondelta acidosis. Although hypertrophy of the proximal tubules initially increases their ability to reabsorb filtered HCO_3^{2-} and increases ammoniagenesis, with progressive loss of nephrons this compensation is eventually overwhelmed. In addition, with advancing renal failure, ammoniagenesis is further inhibited by elevation in levels of serum K^+, producing type IV renal tubular acidosis. Once the glomerular filtration rate falls below 25 mL/min, noncarbonic organic acids accumulate, producing a delta metabolic acidosis. Hyperkalemia can also inhibit tubular HCO_3^{2-} reabsorption, as can extracellular volume expansion and elevated levels of parathyroid hormone. Eventually, as the kidneys fail, the level of serum HCO_3^{2-} falls severely, reflecting the exhaustion of all body buffer systems, including bone.

CALCIUM AND PHOSPHATE

The kidney and gut play an important role in the regulation of serum levels of Ca^{2+} and PO_4^{2-}. With decreasing renal function and the appearance of tubulointerstitial nephritis, the expression of 1α-hydroxylase by the proximal tubule is reduced, lowering levels of calcitriol and Ca^{2+} absorption by the gut. Loss of nephron mass with progressive renal failure also gradually reduces the excretion of PO_4^{2-} and Ca^{2+}, and elevations in serum PO_4^{2-} further lower serum levels of Ca^{2+}, causing sustained secretion of parathyroid hormone. Unregulated increases in levels of parathyroid hormone cause Ca^{2+} mobilization from bone, Ca^{2+}/PO_4^{2-} precipitation in vascular tissues, abnormal bone remodeling, decreases in tubular bicarbonate reabsorption, and increases in renal PO_4^{2-} excretion. While elevated serum levels of parathyroid hormone initially maintain serum PO_4^{2-} near normal, with progressive nephron destruction, the capacity for renal PO_4^{2-} excretion is overwhelmed, the serum PO_4^{2-} elevates, and bone is progressively demineralized from secondary hyperparathyroidism. These adaptations evoke another classic functional trade-off **(Fig. 2-3)**.

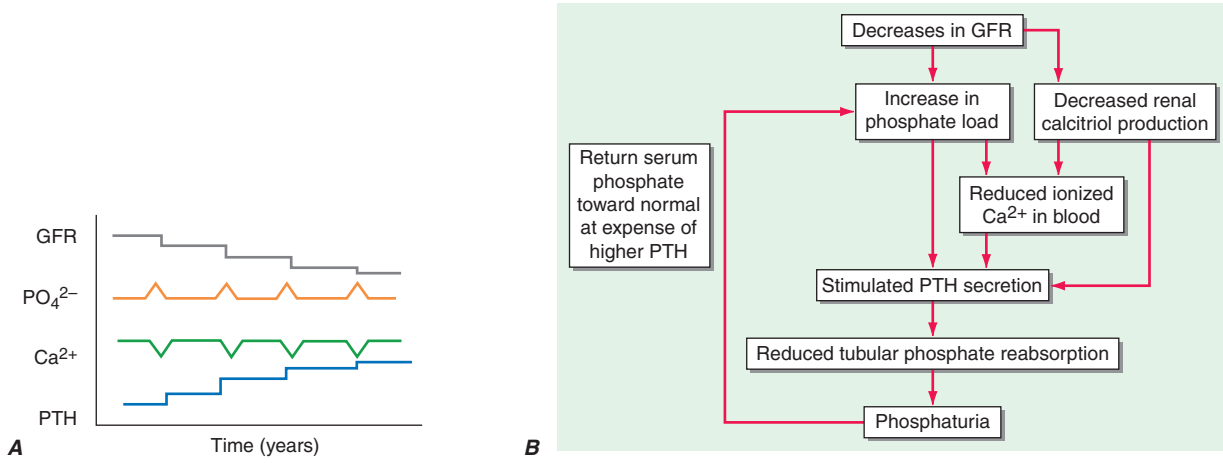

FIGURE 2-3

The "Trade-off Hypothesis" for Ca^{2+}/PO_4^{2-} homeostasis with progressively declining renal function. ***A.*** How adaptation to maintain Ca^{2+}/PO_4^{2-} homeostasis leads to increasing levels of parathyroid hormone *("classic" presentation from E Slatopolsky et al: Kidney Int 4:141, 1973)*. ***B.*** current understanding of the underlying mechanisms for this Ca^{2+}/PO_4^{2-} trade-off.

MODIFIERS INFLUENCING THE PROGRESSION OF RENAL DISEASE

Well-described risk factors for the progressive loss of renal function include systemic hypertension, diabetes, and activation of the renin-angiotensin-aldosterone system **(Table 2-1)**. Poor glucose control will aggravate *renal progression* in both diabetic and nondiabetic renal disease. Angiotensin II produces *intraglomerular* hypertension and stimulates fibrogenesis. Aldosterone also serves as an independent fibrogenic mediator of progressive nephron loss apart from its role in modulating Na^+ and K^+ homeostasis. Genetic factors also play a role. There is recent, exciting evidence that risk alleles for *APOL1* underlie the increased susceptibility of African Americans to development of progressive kidney injury.

Lifestyle choices also affect the progression of renal disease. Cigarette smoking either predisposes or accelerates the progression of nephron loss. Whether the effect of cigarettes is related to systemic hemodynamic alterations or specific damage to the renal microvasculature and/or tubules is unclear. Increases in fetuin-A, decreases in adiponectin, and increases in lipid oxidation associated with obesity also accelerate cardiovascular disease and progressive renal damage. Recent epidemiologic studies also confirm an association between high protein diets and progression of renal disease. Progressive nephron loss in experimental animals, and possibly in humans, is slowed by adherence to a low protein diet. Although a large multicenter trial, the Modification of Diet in Renal Disease, did not provide conclusive evidence that dietary protein restriction could retard progression to renal failure in humans, secondary analyses and a number of meta-analyses suggest a renoprotective effect from supervised low-protein diets in the range of 0.6–0.75 g/kg/day. Repair of chronic low serum bicarbonate levels during renal progression increases kidney survival. Abnormal Ca^{2+} and PO_4^{2-} metabolism in chronic kidney disease also plays a role in renal progression, and administration of calcitriol or its analogues can attenuate progression in a variety of models of chronic kidney disease.

TABLE 2-1

POTENTIAL MODIFIERS OF RENAL DISEASE PROGRESSION	
Hypertension	Hyperlipidemia
Renin-angiotensin system activation	Abnormal calcium/phosphorus homeostasis
Angiotensin II	Cigarette smoking
Aldosterone	Intrinsic paucity in nephron number
Diabetes	Prematurity/low birth weight
Obesity	Genetic predisposition
Excessive dietary protein	Genetic factors

An intrinsic paucity in the number of functioning nephrons predisposes to the development of renal disease. A reduced number of nephrons leads to permanent hypertension, either through direct renal damage or *hyperfiltration* producing glomerulosclerosis, or by primary induction of systemic hypertension that further exacerbates glomerular barotrauma. Younger individuals with hypertension who die suddenly as a result of trauma have 47% fewer glomeruli per kidney than age-matched controls.

A consequence of low birth weight is a relative deficit in the number of total nephrons, and low birth weight associates in adulthood with more hypertension and renal failure, among other abnormalities. In this regard, in addition or instead of a genetic predisposition to development of a specific disease or condition such as low birth weight, different epigenetic phenomena may produce varying clinical phenotypes from a single genotype depending on maternal exposure to different environmental stimuli during gestation, a phenomenon known as *developmental plasticity*. A specific clinical phenotype can also be selected in response to an adverse environmental exposure during critical periods of intrauterine development, also known as *fetal programming*. In the United States, there is at least a twofold increased incidence of low birth weight among blacks compared with whites, much but not all of which can be attributed to maternal age, health, or socioeconomic status.

As in other conditions producing nephron loss, the glomeruli of low-birth-weight individuals enlarge and associate with early *hyperfiltration* to maintain normal levels of renal function. With time, the resulting *intraglomerular* hypertension initiates a progressive decline in residual hyperfunctioning nephrons, ultimately accelerating renal failure. In African Americans as well as other populations at increased risk for kidney failure, such as Pima Indians and Australian aborigines, large glomeruli are seen at early stages of kidney disease. An association between low birth weight and the development of albuminuria and nephropathy is reported for both diabetic and nondiabetic renal disease.

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SECTION II

ALTERATIONS OF RENAL FUNCTION AND ELECTROLYTES

CHAPTER 3

AZOTEMIA AND URINARY ABNORMALITIES

Julie Lin ■ Bradley M. Denker

Normal kidney functions occur through numerous cellular processes to maintain body homeostasis. Disturbances in any of those functions can lead to a constellation of abnormalities that may be detrimental to survival. The clinical manifestations of those disorders depend on the pathophysiology of the renal injury and often are identified initially as a complex of symptoms, abnormal physical findings, and laboratory changes that together make possible the identification of specific syndromes. These renal syndromes **(Table 3-1)** may arise as a consequence of a systemic illness or can occur as a primary renal disease. Nephrologic syndromes usually consist of several elements that reflect the underlying pathologic processes. The duration and severity of the disease affect those findings and typically include one or more of the following: (1) reduction in glomerular filtration rate (GFR) (azotemia), (2) abnormalities of urine sediment [red blood cells (RBCs), white blood cells, casts, and crystals], (3) abnormal excretion of serum proteins (proteinuria), (4) disturbances in urine volume (oliguria, anuria, polyuria), (5) presence of hypertension and/or expanded total body fluid volume (edema), (6) electrolyte abnormalities, (7) in some syndromes, fever/pain. The combination of these findings should permit identification of one of the major nephrologic syndromes (Table 3-1) and will allow differential diagnoses to be narrowed and the appropriate diagnostic evaluation and therapeutic course to be determined. All these syndromes and their associated diseases are discussed in more detail in subsequent chapters. This chapter focuses on several aspects of renal abnormalities that are critically important for distinguishing among those processes: (1) reduction in GFR leading to azotemia, (2) alterations of the urinary sediment and/or protein excretion, and (3) abnormalities of urinary volume.

AZOTEMIA

ASSESSMENT OF GLOMERULAR FILTRATION RATE

Monitoring the GFR is important in both the hospital and outpatient settings, and several different methodologies are available. GFR is the primary metric for kidney "function," and its direct measurement involves administration of a radioactive isotope (such as inulin or iothalamate) that is filtered at the glomerulus but neither reabsorbed nor secreted throughout the tubule. Clearance of inulin or iothalamate in milliliters per minute equals the GFR and is calculated from the rate of removal from the blood and appearance in the urine over several hours. Direct GFR measurements are frequently available through nuclear radiology departments. In most clinical circumstances direct measurement of GFR is not available, and the serum creatinine level is used as a surrogate to estimate GFR. Serum creatinine is the most widely used marker for GFR, and the GFR is related directly to the urine creatinine excretion and inversely to the serum creatinine (U_{Cr}/P_{Cr}). Based on this relationship and some important caveats (discussed below), the GFR will fall in roughly inverse proportion to the rise in P_{Cr}. Failure to account for GFR reductions in drug dosing can lead to significant morbidity and mortality from drug toxicities (e.g., digoxin, aminoglycosides). In the outpatient setting, the serum creatinine serves as an estimate for GFR (although much less accurate; see below). In patients with chronic progressive renal disease, there is an approximately linear relationship between $1/P_{Cr}$ (y axis) and time (x axis). The slope of that line will remain constant for an individual patient, and when values are obtained that do not fall on the line, an investigation

TABLE 3-1

INITIAL CLINICAL AND LABORATORY DATABASE FOR DEFINING MAJOR SYNDROMES IN NEPHROLOGY

SYNDROMES	IMPORTANT CLUES TO DIAGNOSIS	COMMON FINDINGS	LOCATION OF DISCUSSION OF DISEASE-CAUSING SYNDROME
Acute or rapidly progressive renal failure	Anuria Oliguria Documented recent decline in GFR	Hypertension, hematuria Proteinuria, pyuria Casts, edema	Chaps. 10, 15, 17, 21
Acute nephritis	Hematuria, RBC casts Azotemia, oliguria Edema, hypertension	Proteinuria Pyuria Circulatory congestion	Chap. 15
Chronic renal failure	Azotemia for >3 months Prolonged symptoms or signs of uremia Symptoms or signs of renal osteodystrophy Kidneys reduced in size bilaterally Broad casts in urinary sediment	Proteinuria Casts Polyuria, nocturia Edema, hypertension Electrolyte disorders	Chaps. 2, 11
Nephrotic syndrome	Proteinuria >3.5 g per 1.73 m^2 per 24 h Hypoalbuminemia Edema Hyperlipidemia	Casts Lipiduria	Chap. 15
Asymptomatic urinary abnormalities	Hematuria Proteinuria (below nephrotic range) Sterile pyuria, casts		Chap. 15
Urinary tract infection/ pyelonephritis	Bacteriuria >10^5 colonies per milliliter Other infectious agent documented in urine Pyuria, leukocyte casts Frequency, urgency Bladder tenderness, flank tenderness	Hematuria Mild azotemia Mild proteinuria Fever	Chap. 20
Renal tubule defects	Electrolyte disorders Polyuria, nocturia Renal calcification Large kidneys Renal transport defects	Hematuria "Tubular" proteinuria (<1 g/24 h) Enuresis	Chaps. 16, 17
Hypertension	Systolic/diastolic hypertension	Proteinuria Casts Azotemia	Chaps. 18, 19
Nephrolithiasis	Previous history of stone passage or removal Previous history of stone seen by x-ray Renal colic	Hematuria Pyuria Frequency, urgency	Chap. 9
Urinary tract obstruction	Azotemia, oliguria, anuria Polyuria, nocturia, urinary retention Slowing of urinary stream Large prostate, large kidneys Flank tenderness, full bladder after voiding	Hematuria Pyuria Enuresis, dysuria	Chap. 21

Abbreviations: GFR; glomerular filtration rate; RBC, red blood cell.

for a superimposed acute process (e.g., volume depletion, drug reaction) should be initiated. Signs and symptoms of uremia develop at significantly different levels of serum creatinine, depending on the patient (size, age, and sex), the underlying renal disease, the existence of concurrent diseases, and true GFR. In general, patients do not develop symptomatic uremia until renal insufficiency is quite severe (GFR <15 mL/min).

A significantly reduced GFR (either acute or chronic) usually is reflected in a rise in serum creatinine and leads to retention of nitrogenous waste products (azotemia) such as urea. Azotemia may result from reduced renal perfusion, intrinsic renal disease, or postrenal processes (ureteral obstruction; see below and **Fig. 3-1**). Precise determination of GFR is problematic as both commonly measured indices (urea and creatinine) have characteristics that affect their accuracy as markers of clearance. Urea clearance may underestimate GFR significantly because of urea reabsorption by the tubule. In contrast, creatinine is derived from muscle metabolism of creatine, and its generation varies little from day to day.

Creatinine clearance, an approximation of GFR, is measured from plasma and urinary creatinine excretion rates for a defined time period (usually 24 h) and is expressed in milliliters per minute: $CrCl = (U_{vol} \times U_{Cr})/(PCr \times T_{min})$. Creatinine is useful for estimating GFR because it is a small, freely filtered solute that is not reabsorbed by the tubules. Serum creatinine levels can increase acutely from dietary ingestion of cooked meat, however, and creatinine can be secreted into the proximal tubule through an organic cation pathway (especially in advanced progressive chronic kidney disease), leading to overestimation of GFR. When a timed collection for creatinine clearance is not available, decisions

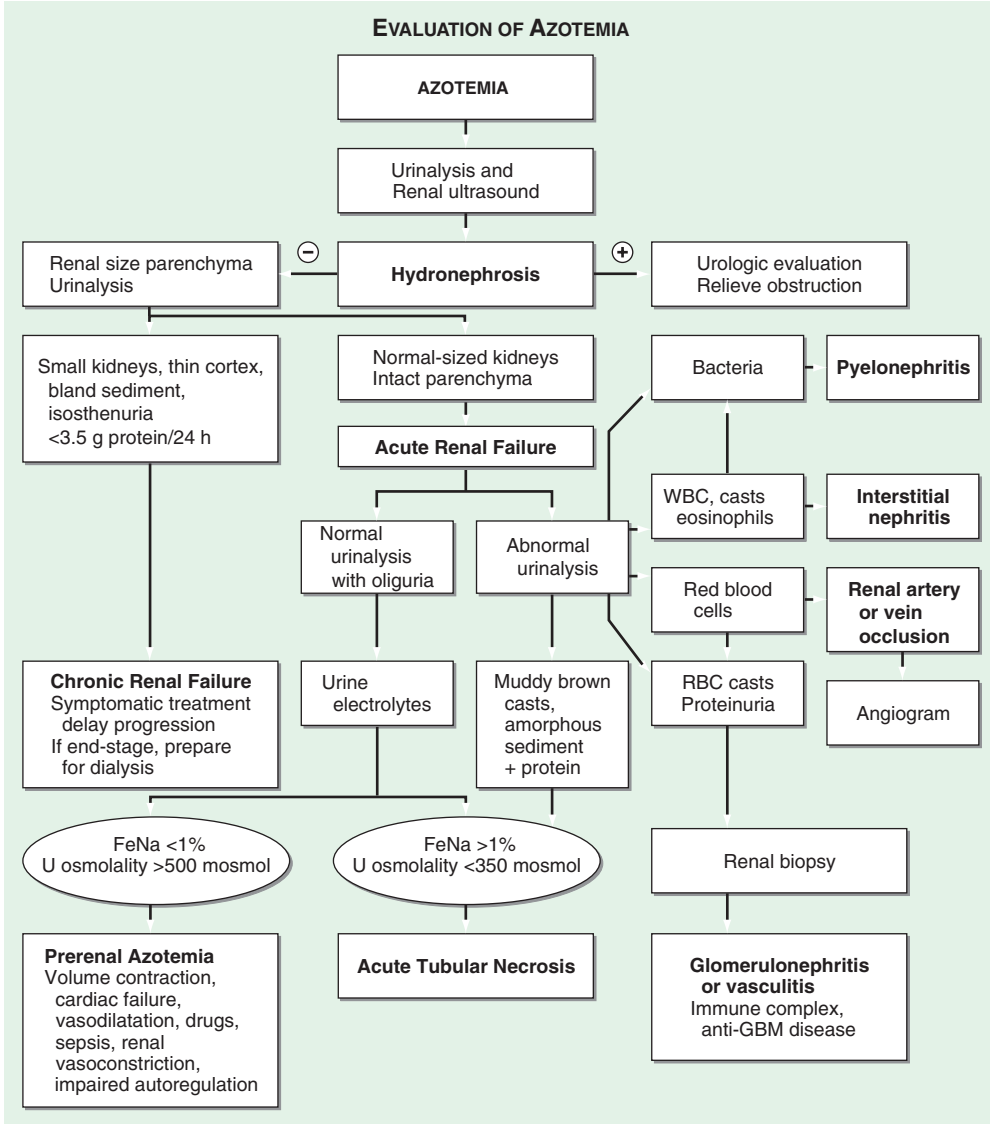


FIGURE 3-1

Approach to the patient with azotemia. FeNa, fractional excretion of sodium; GBM, glomerular basement membrane; RBC, red blood cell; WBC, white blood cell.

about drug dosing must be based on serum creatinine alone. Two formulas are used widely to estimate kidney function from serum creatinine: (1) Cockcroft-Gault and (2) four-variable MDRD (Modification of Diet in Renal Disease).

$$\text{Cockcroft-Gault: CrCl (mL/min)} = (140 - \text{age [years]} \times \text{weight [kg]} \times [0.85 \text{ if female}])/(72 \times \text{sCr [mg/dL]})$$

$$\text{MDRD: eGFR (mL/min per 1.73 m}^2) = 186.3 \times P_{Cr}\,(e^{-1.154}) \times \text{age}\,(e^{-0.203}) \times (0.742 \text{ if female}) \times (1.21 \text{ if black}).$$

Numerous websites are available for making these calculations (*www.kidney.org/professionals/kdoqi/gfr_calculator.cfm*). A newer CKD-EPI eGFR was developed by pooling several cohorts with and without kidney disease who had data on directly measured GFR and appears to be more accurate:

$$\text{CKD-EPI: eGFR} = 141 \times \min(\text{Scr}/k, 1)^{a} \times \max(\text{Scr}/k, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ (if female)} \times 1.159 \text{ (if black)}$$

where Scr is serum creatinine, k is 0.7 for females and 0.9 for males, a is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1 (*http://www.qxmd.com/renal/Calculate-CKD-EPI-GFR.php*).

Several limitations of using serum creatinine–based estimating equations must be acknowledged. Each equation, along with the 24-h urine collection for measurement of creatinine clearance, is based on the assumption that the patient is in steady state, without daily increases or decreases in serum creatinine levels as a result of rapidly changing GFR. The MDRD equation has poorer accuracy when GFR >60 mL/min per 1.73 m^2. The gradual loss of muscle from chronic illness, chronic use of glucocorticoids, or malnutrition can mask significant changes in GFR with small or imperceptible changes in serum creatinine concentration. Cystatin C is a member of the cystatin superfamily of cysteine protease inhibitors and is produced at a relatively constant rate from all nucleated cells. Serum cystatin C has been proposed to be a more sensitive marker of early GFR decline than is plasma creatinine; however, like serum creatinine, cystatin C is influenced by age, race, and sex and additionally is associated with diabetes, smoking, and markers of inflammation.

APPROACH TO THE PATIENT: Azotemia

Once it has been established that GFR is reduced, the physician must decide if this represents acute or chronic renal injury. The clinical situation, history, and laboratory data often make this an easy distinction. However, the laboratory abnormalities characteristic of chronic renal failure, including anemia, hypocalcemia, and hyperphosphatemia, often are also present in patients presenting with acute renal failure. Radiographic evidence of renal osteodystrophy (Chap. 11) can be seen only in chronic renal failure but is a very late finding, and these patients are usually on dialysis. The urinalysis and renal ultrasound occasionally can facilitate distinguishing acute from chronic renal failure. An approach to the evaluation of azotemic patients is shown in Fig. 3-1. Patients with advanced chronic renal insufficiency often have some proteinuria, nonconcentrated urine (isosthenuria; isoosmotic with plasma), and small kidneys on ultrasound, characterized by increased echogenicity and cortical thinning. Treatment should be directed toward slowing the progression of renal disease and providing symptomatic relief for edema, acidosis, anemia, and hyperphosphatemia, as discussed in Chap. 11. Acute renal failure (Chap. 10) can result from processes that affect renal blood flow (prerenal azotemia), intrinsic renal diseases (affecting small vessels, glomeruli, or tubules), or postrenal processes (obstruction to urine flow in ureters, bladder, or urethra) (Chap. 21).

Prerenal Failure Decreased renal perfusion accounts for 40–80% of acute renal failure and, if appropriately treated, is readily reversible. The etiologies of prerenal azotemia include any cause of decreased circulating blood volume (gastrointestinal hemorrhage, burns, diarrhea, diuretics), volume sequestration (pancreatitis, peritonitis, rhabdomyolysis), or decreased effective arterial volume (cardiogenic shock, sepsis). Renal perfusion also can be affected by reductions in cardiac output from peripheral vasodilation (sepsis, drugs) or profound renal vasoconstriction [severe heart failure, hepatorenal syndrome, drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs)]. True or "effective" arterial hypovolemia leads to a fall in mean arterial pressure, which in turn triggers a series of neural and humoral responses that include activation of the sympathetic nervous and renin-angiotensin-aldosterone systems and antidiuretic hormone (ADH) release. GFR is maintained by prostaglandin-mediated relaxation of afferent arterioles and angiotensin II–mediated constriction of efferent arterioles. Once the mean arterial pressure falls below 80 mmHg, there is a steep decline in GFR.

Blockade of prostaglandin production by NSAIDs can result in severe vasoconstriction and acute renal failure. Blocking angiotensin action with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) decreases efferent arteriolar tone and in turn decreases glomerular capillary perfusion pressure.

Patients on NSAIDs and/or ACE inhibitors/ARBs are most susceptible to hemodynamically mediated acute renal failure when blood volume is reduced for any reason. Patients with bilateral renal artery stenosis (or stenosis in a solitary kidney) are dependent on efferent arteriolar vasoconstriction for maintenance of glomerular filtration pressure and are particularly susceptible to a precipitous decline in GFR when given ACE inhibitors or ARBs.

Prolonged renal hypoperfusion may lead to acute tubular necrosis (ATN), an intrinsic renal disease that is discussed below. The urinalysis and urinary electrolytes can be useful in distinguishing prerenal azotemia from ATN (Table 3-2). The urine of patients with prerenal azotemia can be predicted from the stimulatory actions of norepinephrine, angiotensin II, ADH, and low tubule fluid flow rate on salt and water reabsorption. In prerenal conditions, the tubules are intact, leading to a concentrated urine (>500 mosmol), avid Na retention (urine Na concentration <20 m*M*/L, fractional excretion of Na <1%), and U_{Cr}/P_{Cr} >40 (Table 3-2). The prerenal urine sediment is usually normal or has occasional hyaline and granular casts, whereas the sediment of ATN usually is filled with cellular debris and dark (muddy brown) granular casts.

Postrenal Azotemia Urinary tract obstruction accounts for <5% of cases of acute renal failure, but it is usually reversible and must be ruled out early in the evaluation (Fig. 3-1). Since a single kidney is capable of adequate clearance, obstructive acute renal failure requires obstruction at the urethra or bladder outlet, bilateral ureteral obstruction, or unilateral obstruction in a patient with a single functioning kidney. Obstruction usually is diagnosed by the presence of ureteral and renal pelvic dilation on renal ultrasound. However, early in the course of obstruction or if the ureters are unable to dilate (e.g., encasement by pelvic tumors or periureteral), the ultrasound examination may be negative. The specific urologic conditions that cause obstruction are discussed in Chap. 21.

Intrinsic Renal Disease When prerenal and postrenal azotemia have been excluded as etiologies of renal failure, an intrinsic parenchymal renal disease is present. Intrinsic renal disease can arise from processes involving large renal vessels, intrarenal microvasculature and glomeruli, or the tubulointerstitium. Ischemic and toxic ATN account for ~90% of cases of acute intrinsic renal failure. As outlined in Fig. 3-1, the clinical setting and urinalysis are helpful in separating the possible etiologies of acute intrinsic renal failure. Prerenal azotemia and ATN are part of a spectrum of renal hypoperfusion; evidence of structural tubule injury is present in ATN, whereas prompt reversibility occurs with prerenal azotemia upon restoration of adequate renal perfusion. Thus, ATN often can be distinguished from prerenal azotemia by urinalysis and urine electrolyte composition (Table 3-2 and Fig. 3-1). Ischemic ATN is observed most frequently in patients who have undergone major surgery, trauma, severe hypovolemia, overwhelming sepsis, or extensive burns. Nephrotoxic ATN complicates the administration of many common medications, usually by inducing a combination of intrarenal vasoconstriction, direct tubule toxicity, and/or tubule obstruction. The kidney is vulnerable to toxic injury by virtue of its rich blood supply (25% of cardiac output) and its ability to concentrate and metabolize toxins. A diligent search for hypotension and nephrotoxins usually will uncover the specific etiology of ATN. Discontinuation of nephrotoxins and stabilization of blood pressure often will suffice without the need for dialysis while the tubules recover. An extensive list of potential drugs and toxins implicated in ATN can be found in Chap. 10.

Processes that involve the tubules and interstitium can lead to acute kidney injury (AKI), a subtype of acute renal failure. These processes include drug-induced interstitial nephritis (especially antibiotics, NSAIDs, and diuretics), severe infections (both bacterial and viral), systemic diseases (e.g., systemic lupus erythematosus), and infiltrative disorders (e.g., sarcoid, lymphoma, or leukemia). A list of drugs associated with allergic interstitial nephritis can be found in Chap. 17. The urinalysis usually shows mild to moderate proteinuria, hematuria, and pyuria (~75% of cases) and occasionally shows white blood cell casts. The finding of RBC casts in interstitial nephritis has been reported but should prompt a search for glomerular diseases (Fig. 3-1). Occasionally, renal biopsy will be needed to distinguish among these possibilities. The finding of eosinophils in the urine is

TABLE 3-2

LABORATORY FINDINGS IN ACUTE RENAL FAILURE

INDEX	PRERENAL AZOTEMIA	OLIGURIC ACUTE RENAL FAILURE
BUN/P_{Cr} ratio	>20:1	10–15:1
Urine sodium (U_{Na}), meq/L	<20	>40
Urine osmolality, mosmol/L H_2O	>500	<350
Fractional excretion of sodium	<1%	>2%
$FE_{Na} = \frac{U_{Na} \quad P_{Cr} \quad 100}{P_{Na} \quad U_{Cr}}$		
Urine/plasma creatinine (U_{Cr}/P_{Cr})	>40	<20

Abbreviations: BUN, blood urea nitrogen; P_{Cr}, plasma creatinine; P_{Na}, plasma sodium concentration; U_{Cr}, urine creatinine concentration; U_{Na}, urine sodium concentration.

suggestive of allergic interstitial nephritis or atheroembolic renal disease and is optimally observed by using a Hansel stain. The absence of eosinophiluria, however, does not exclude these etiologies.

Occlusion of large renal vessels including arteries and veins is an uncommon cause of acute renal failure. A significant reduction in GFR by this mechanism suggests bilateral processes or a unilateral process in a patient with a single functioning kidney. Renal arteries can be occluded with atheroemboli, thromboemboli, in situ thrombosis, aortic dissection, or vasculitis. Atheroembolic renal failure can occur spontaneously but most often is associated with recent aortic instrumentation. The emboli are cholesterol rich and lodge in medium and small renal arteries, leading to an eosinophil-rich inflammatory reaction. Patients with atheroembolic acute renal failure often have a normal urinalysis, but the urine may contain eosinophils and casts. The diagnosis can be confirmed by renal biopsy, but this is often unnecessary when other stigmata of atheroemboli are present (livedo reticularis, distal peripheral infarcts, eosinophilia). Renal artery thrombosis may lead to mild proteinuria and hematuria, whereas renal vein thrombosis typically induces heavy proteinuria and hematuria. These vascular complications often require angiography for confirmation and are discussed in Chap. 18.

Diseases of the glomeruli (glomerulonephritis and vasculitis) and the renal microvasculature (hemolytic-uremic syndromes, thrombotic thrombocytopenic purpura, and malignant hypertension) usually present with various combinations of glomerular injury: proteinuria, hematuria, reduced GFR, and alterations of sodium excretion that lead to hypertension, edema, and circulatory congestion (acute nephritic syndrome). These findings may occur as primary renal diseases or as renal manifestations of systemic diseases. The clinical setting and other laboratory data help distinguish primary renal diseases from systemic diseases. The finding of RBC casts in the urine is an indication for early renal biopsy (Fig. 3-1) as the pathologic pattern has important implications for diagnosis, prognosis, and treatment. Hematuria without RBC casts also can be an indication of glomerular disease; this evaluation is summarized in Fig. 3-2. A detailed discussion of glomerulonephritis and diseases of the microvasculature can be found in Chap. 17.

Oliguria and Anuria *Oliguria* refers to a 24-h urine output <400 mL, and *anuria* is the complete absence of urine formation (<100 mL). Anuria can be caused by total urinary tract obstruction, total renal artery or vein occlusion, and shock (manifested by severe hypotension and intense renal vasoconstriction). Cortical necrosis, ATN, and rapidly progressive glomerulonephritis occasionally cause anuria. Oliguria can accompany any cause of acute renal failure and carries a more serious prognosis for renal recovery in all conditions except prerenal azotemia. *Nonoliguria* refers to urine output >400 mL/d in patients with acute or chronic azotemia. With nonoliguric ATN, disturbances of potassium and hydrogen balance are less severe than in oliguric patients, and recovery to normal renal function is usually more rapid.

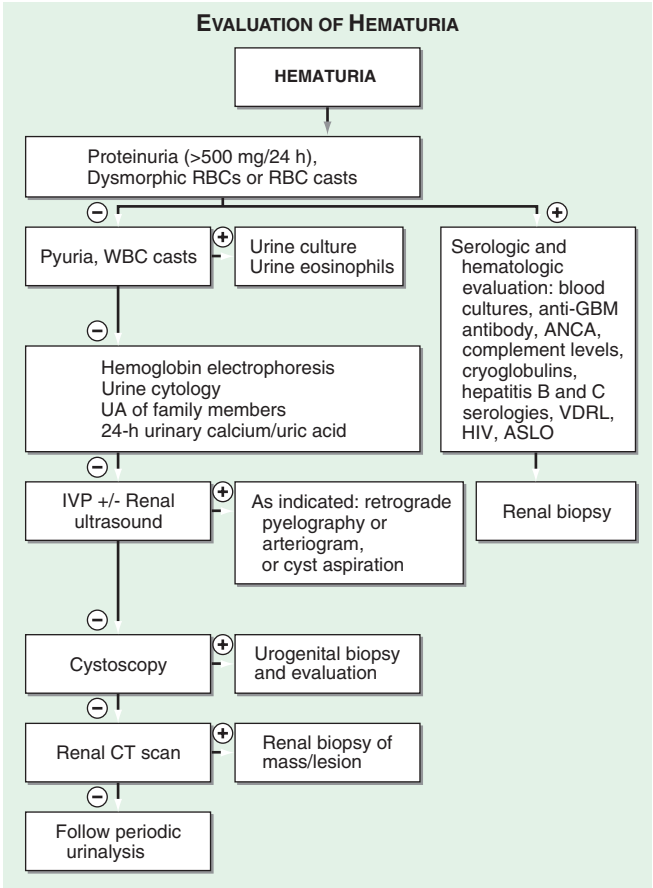


FIGURE 3-2
Approach to the patient with hematuria. ANCA, antineutrophil cytoplasmic antibody; ASLO, antistreptolysin O; CT, computed tomography; GBM, glomerular basement membrane; IVP, intravenous pyelography; RBC, red blood cell; UA, urinalysis; VDRL, Venereal Disease Research Laboratory; WBC, white blood cell.

ABNORMALITIES OF THE URINE

PROTEINURIA

The evaluation of proteinuria is shown schematically in Fig. 3-3 and typically is initiated after detection of proteinuria by dipstick examination. The dipstick measurement detects only albumin and gives false-positive results when pH >7.0 and the urine is very concentrated or contaminated with blood. Because the dipstick relies on urinary albumin concentration, a very dilute urine may obscure significant proteinuria on dipstick

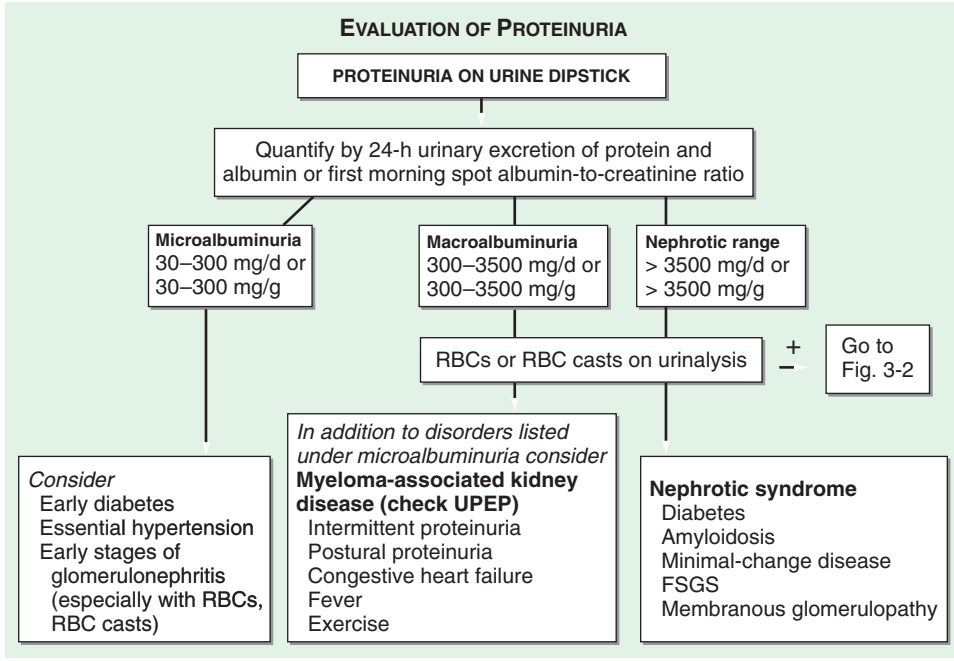


FIGURE 3-3

Approach to the patient with proteinuria. Investigation of proteinuria is often initiated by a positive dipstick on routine urinalysis. Conventional dipsticks detect predominantly albumin and provide a semiquantitative assessment (trace, 1+, 2+, or 3+), which is influenced by urinary concentration as reflected by urine specific gravity (minimum <1.005, maximum 1.030). However, more exact determination of proteinuria should employ a spot morning protein/creatinine ratio (mg/g) or a 24-h urine collection (mg/24 h). FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; RBC, red blood cell.

examination. Quantification of urinary albumin on a spot urine sample (ideally from a first morning void) by measuring an albumin-to-creatinine ratio (ACR) is helpful in approximating a 24-h albumin excretion rate (AER) where ACR (mg/g) ≈AER (mg/24 h). Furthermore, proteinuria that is not predominantly albumin will be missed by dipstick screening. This is particularly important for the detection of Bence Jones proteins in the urine of patients with multiple myeloma. Tests to measure total urine protein concentration accurately rely on precipitation with sulfosalicylic or trichloracetic acid (Fig. 3-3).

The magnitude of proteinuria and the protein composition of the urine depend on the mechanism of renal injury that leads to protein losses. Both charge and size selectivity normally prevent virtually all plasma albumin, globulins, and other high-molecular-weight proteins from crossing the glomerular wall; however, if this barrier is disrupted, plasma proteins may leak into the urine (glomerular proteinuria; Fig. 3-3). Smaller proteins (<20 kDa) are freely filtered but are readily reabsorbed by the proximal tubule. Traditionally, healthy individuals excrete <150 mg/d of total protein and <30 mg/d of albumin. However, even at albuminuria levels <30 mg/d, risk for progression to overt nephropathy or subsequent cardiovascular disease is increased. The remainder of the protein in the urine is secreted by the tubules (Tamm-Horsfall, IgA, and urokinase) or represents small amounts of filtered β_2-microglobulin, apoproteins, enzymes, and peptide hormones. Another mechanism of proteinuria occurs when there is excessive production of an abnormal protein that exceeds the capacity of the tubule for reabsorption. This most commonly occurs with plasma cell dyscrasias, such as multiple myeloma, amyloidosis, and lymphomas that are associated with monoclonal production of immunoglobulin light chains.

The normal glomerular endothelial cell forms a barrier composed of pores of ~100 nm that retain blood cells but offer little impediment to passage of most proteins. The glomerular basement membrane traps most large proteins (>100 kDa), and the foot processes of epithelial cells (podocytes) cover the urinary side of the glomerular basement membrane and produce a series of narrow channels (slit diaphragms) to allow molecular passage of small solutes and water but not proteins. Some glomerular diseases, such as minimal-change disease, cause fusiown of glomerular epithelial cell foot processes, resulting in predominantly "selective" (Fig. 3-3) loss of albumin. Other glomerular diseases can present with disruption of the basement membrane and slit diaphragms (e.g., by immune complex deposition),

resulting in losses of albumin and other plasma proteins. The fusion of foot processes causes increased pressure across the capillary basement membrane, resulting in areas with larger pore sizes. The combination of increased pressure and larger pores results in significant proteinuria ("nonselective"; Fig. 3-3).

When the total daily excretion of protein is >3.5 g, hypoalbuminemia, hyperlipidemia, and edema (nephrotic syndrome; Fig. 3-3) are often present as well. However, total daily urinary protein excretion >3.5 g can occur without the other features of the nephrotic syndrome in a variety of other renal diseases (Fig. 3-3). Plasma cell dyscrasias (multiple myeloma) can be associated with large amounts of excreted light chains in the urine, which may not be detected by dipstick. The light chains produced from these disorders are filtered by the glomerulus and overwhelm the reabsorptive capacity of the proximal tubule. Renal failure from these disorders occurs through a variety of mechanisms, including tubule obstruction (cast nephropathy) and light chain deposition.

Hypoalbuminemia in nephrotic syndrome occurs through excessive urinary losses and increased proximal tubule catabolism of filtered albumin. Edema forms from renal sodium retention and reduced plasma oncotic pressure, which favors fluid movement from capillaries to interstitium. To compensate for the perceived decrease in effective intravascular volume, activation of the renin-angiotensin system, stimulation of ADH, and activation of the sympathetic nervous system occur that promote continued renal salt and water reabsorption and progressive edema. The urinary loss of regulatory proteins and changes in hepatic synthesis contribute to the other manifestations of the nephrotic syndrome. A hypercoagulable state may arise from urinary losses of antithrombin III, reduced serum levels of proteins S and C, hyperfibrinogenemia, and enhanced platelet aggregation. Hypercholesterolemia may be severe and results from increased hepatic lipoprotein synthesis. Loss of immunoglobulins contributes to an increased risk of infection. Many diseases (some listed in Fig. 3-3) and drugs can cause the nephrotic syndrome; a complete list can be found in Chap. 15.

HEMATURIA, PYURIA, AND CASTS

Isolated hematuria without proteinuria, other cells, or casts is often indicative of bleeding from the urinary tract. Hematuria is defined as two to five RBCs per high-power field (HPF) and can be detected by dipstick. A false-positive dipstick for hematuria (where no RBCs are seen on urine microscopy) may occur when myoglobinuria is present, often in the setting of rhabdomyolysis. Common causes of isolated hematuria include stones, neoplasms, tuberculosis, trauma, and prostatitis. Gross hematuria with blood clots is usually not an intrinsic renal process; rather, it suggests a postrenal source in the urinary collecting system. Evaluation of patients presenting with microscopic hematuria is outlined in Fig. 3-2. A single urinalysis with hematuria is common and can result from menstruation, viral illness, allergy, exercise, or mild trauma. Persistent or significant hematuria (>3 RBCs/HPF on three urinalyses, a single urinalysis with >100 RBCs, or gross hematuria) is associated with significant renal or urologic lesions in 9.1% of cases. Even patients who are chronically anticoagulated should be investigated as outlined in Fig. 3-2. The suspicion for urogenital neoplasms in patients with isolated painless hematuria and nondysmorphic RBCs increases with age. Neoplasms are rare in the pediatric population, and isolated hematuria is more likely to be "idiopathic" or associated with a congenital anomaly. Hematuria with pyuria and bacteriuria is typical of infection and should be treated with antibiotics after appropriate cultures. Acute cystitis or urethritis in women can cause gross hematuria. Hypercalciuria and hyperuricosuria are also risk factors for unexplained isolated hematuria in both children and adults. In some of these patients (50–60%), reducing calcium and uric acid excretion through dietary interventions can eliminate the microscopic hematuria.

Isolated microscopic hematuria can be a manifestation of glomerular diseases. The RBCs of glomerular origin are often dysmorphic when examined by phase-contrast microscopy. Irregular shapes of RBCs may also result from pH and osmolarity changes produced along the distal nephron. Observer variability in detecting dysmorphic RBCs is common. The most common etiologies of isolated glomerular hematuria are IgA nephropathy, hereditary nephritis, and thin basement membrane disease. IgA nephropathy and hereditary nephritis can lead to episodic gross hematuria. A family history of renal failure is often present in patients with hereditary nephritis, and patients with thin basement membrane disease often have other family members with microscopic hematuria. A renal biopsy is needed for the definitive diagnosis of these disorders, which are discussed in more detail in Chap. 15. Hematuria with dysmorphic RBCs, RBC casts, and protein excretion >500 mg/d is virtually diagnostic of glomerulonephritis. RBC casts form as RBCs that enter the tubule fluid become trapped in a cylindrical mold of gelled Tamm-Horsfall protein. Even in the absence of azotemia, these patients should undergo serologic evaluation and renal biopsy as outlined in Fig. 3-2.

Isolated pyuria is unusual since inflammatory reactions in the kidney or collecting system also are associated with hematuria. The presence of bacteria suggests infection, and white blood cell casts with bacteria are indicative of pyelonephritis. White blood cells and/or white blood cell casts also may be seen in acute glomerulonephritis as well as in tubulointerstitial processes

such as interstitial nephritis and transplant rejection. In chronic renal diseases, degenerated cellular casts called *waxy casts* can be seen in the urine. *Broad casts* are thought to arise in the dilated tubules of enlarged nephrons that have undergone compensatory hypertrophy in response to reduced renal mass (i.e., chronic renal failure). A mixture of broad casts typically seen with chronic renal failure together with cellular casts and RBCs may be seen in smoldering processes such as chronic glomerulonephritis.

ABNORMALITIES OF URINE VOLUME

The volume of urine produced varies with the fluid intake, renal function, and physiologic demands of the individual. See "Azotemia," above, for discussion of decreased (oliguria) or absent urine production (anuria). The physiology of water formation and renal water conservation are discussed in Chap. 2.

POLYURIA

By history, it is often difficult for patients to distinguish urinary frequency (often of small volumes) from true polyuria (>3 L/d), and a quantification of volume by 24-h urine collection may be needed **(Fig. 3-4)**. Polyuria results from two potential mechanisms: (1) excretion of nonabsorbable solutes (such as glucose) or (2) excretion of water (usually from a defect in ADH production or renal responsiveness). To distinguish a solute diuresis from a water diuresis and to determine if the diuresis is appropriate for the clinical circumstances, a urine osmolality is measured. The average person excretes between 600 and 800 mosmol of solutes per day, primarily as urea and electrolytes. If the urine output is >3 L/d and the urine is dilute (<250 mosmol/L), total mosmol excretion is normal and a water diuresis is present. This circumstance could arise from polydipsia, inadequate secretion of vasopressin (central diabetes insipidus), or failure of renal tubules to respond to vasopressin (nephrogenic diabetes insipidus). If the urine volume is >3 L/d and urine osmolality is >300 mosmol/L, a solute diuresis is clearly present and a search for the responsible solute(s) is mandatory.

Excessive filtration of a poorly reabsorbed solute such as glucose, mannitol, or urea can depress reabsorption of NaCl and water in the proximal tubule and lead to enhanced excretion in the urine. Poorly controlled diabetes mellitus with glucosuria is the most common cause of a solute diuresis, leading to volume depletion and serum hypertonicity. Since the urine sodium concentration is less than that of blood, more water than sodium is lost, causing hypernatremia and hypertonicity.

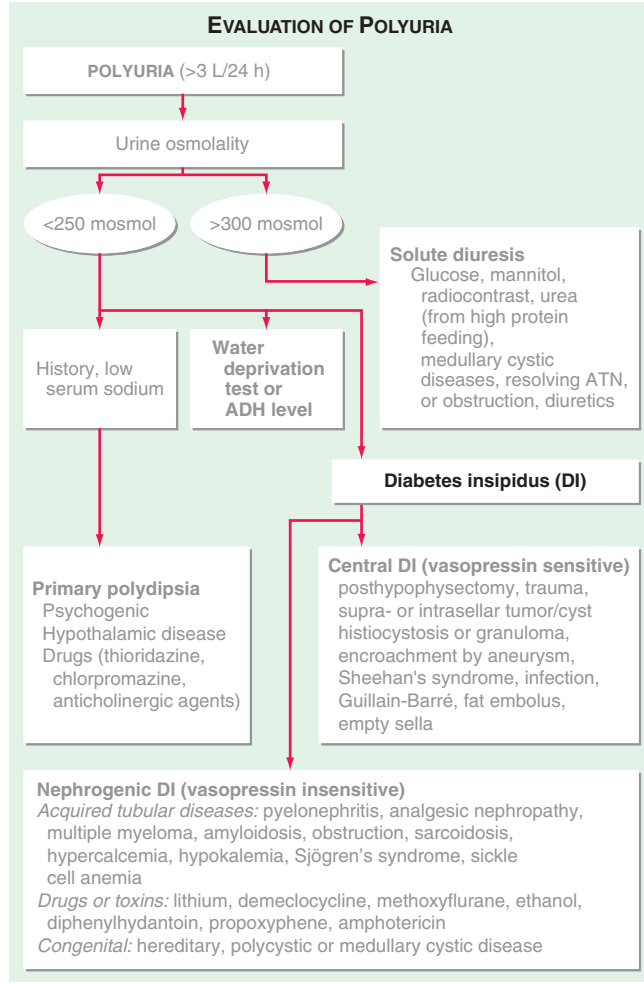


FIGURE 3-4
Approach to the patient with polyuria. ADH, antidiuretic hormone; ATN, acute tubular necrosis.

Common iatrogenic solute diuresis occurs from mannitol administration, radiocontrast media, and high-protein feedings (enterally or parenterally), leading to increased urea production and excretion. Less commonly, excessive sodium loss may result from cystic renal diseases or Bartter's syndrome or during the course of a tubulointerstitial process (such as resolving ATN). In these so-called salt-wasting disorders, the tubule damage results in direct impairment of sodium reabsorption and indirectly reduces the responsiveness of the tubule to aldosterone. Usually, the sodium losses are mild, and the obligatory urine output is <2 L/d (resolving ATN and postobstructive diuresis are exceptions and may be associated with significant natriuresis and polyuria).

Formation of large volumes of dilute urine is usually due to polydipsic states or diabetes insipidus. Primary polydipsia can result from habit, psychiatric disorders, neurologic lesions, or medications. During deliberate polydipsia, extracellular fluid volume is normal or expanded and plasma vasopressin levels are reduced

because serum osmolality tends to be near the lower limits of normal. Urine osmolality should also be maximally dilute at 50 mosmol/L.

Central diabetes insipidus may be idiopathic in origin or secondary to a variety of hypothalamic conditions, including posthypophysectomy or trauma or neoplastic, inflammatory, vascular, or infectious hypothalamic diseases. Idiopathic central diabetes insipidus is associated with selective destruction of the vasopressin-secreting neurons in the supraoptic and paraventricular nuclei and can be inherited as an autosomal dominant trait or occur spontaneously. Nephrogenic diabetes insipidus can occur in a variety of clinical situations, as summarized in Fig. 3-4.

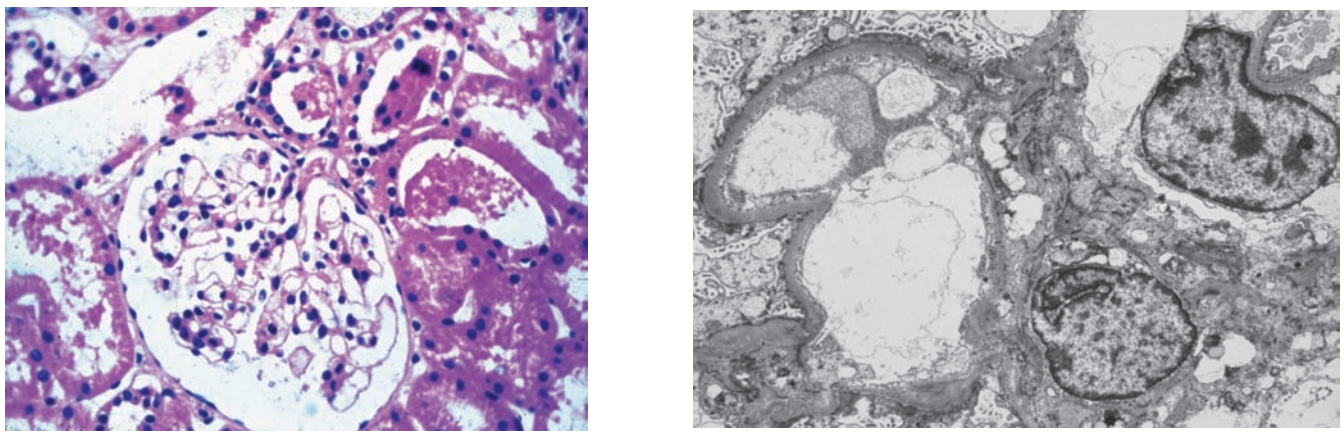
A plasma vasopressin level is recommended as the best method for distinguishing between central and nephrogenic diabetes insipidus. Alternatively, a water deprivation test plus exogenous vasopressin may distinguish primary polydipsia from central and nephrogenic diabetes insipidus.

CHAPTER 4

ATLAS OF URINARY SEDIMENTS AND RENAL BIOPSIES

Agnes B. Fogo ■ Eric G. Neilson

Key diagnostic features of selected diseases in renal biopsy are illustrated, with light, immunofluorescence, and electron microscopic images. Common urinalysis findings are also documented.



A *B*

FIGURE 4-1

Minimal-change disease. In minimal-change disease, light microscopy is unremarkable (***A***), while electron microscopy (***B***) reveals podocyte injury evidenced by complete foot process effacement. (*ABF/Vanderbilt Collection.*)

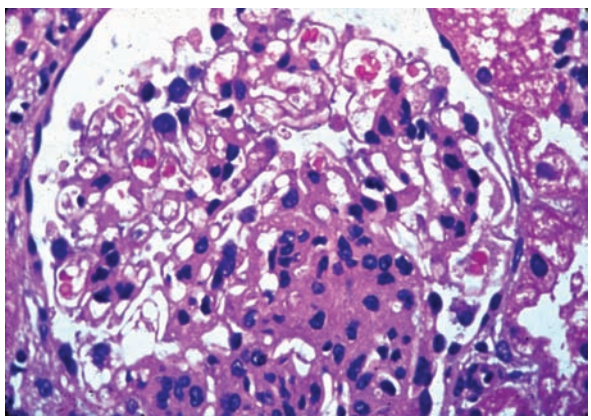


FIGURE 4-2

Focal segmental glomerulosclerosis (FSGS). There is a well-defined segmental increase in matrix and obliteration of capillary loops, the sine qua non of segmental sclerosis not otherwise specified (nos) type. (*EGN/UPenn Collection.*)

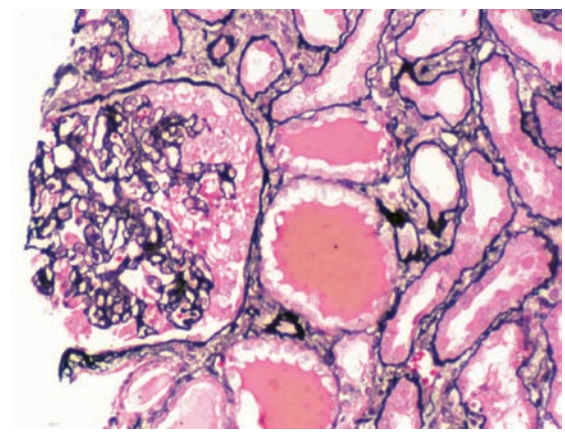


FIGURE 4-3

Collapsing glomerulopathy. There is segmental collapse of the glomerular capillary loops and overlying podocyte hyperplasia. This lesion may be idiopathic or associated with HIV infection and has a particularly poor prognosis. (*ABF/Vanderbilt Collection.*)

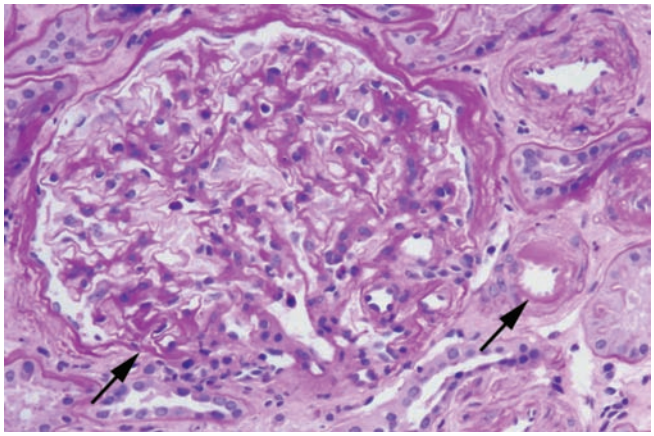


FIGURE 4-4
Hilar variant of FSGS. There is segmental sclerosis of the glomerular tuft at the vascular pole with associated hyalinosis, also present in the afferent arteriole (*arrows*). This lesion often occurs as a secondary response when nephron mass is lost due to, e.g., scarring from other conditions. Patients usually have less proteinuria and less steroid response than FSGS, nos type. (*ABF/Vanderbilt Collection.*)

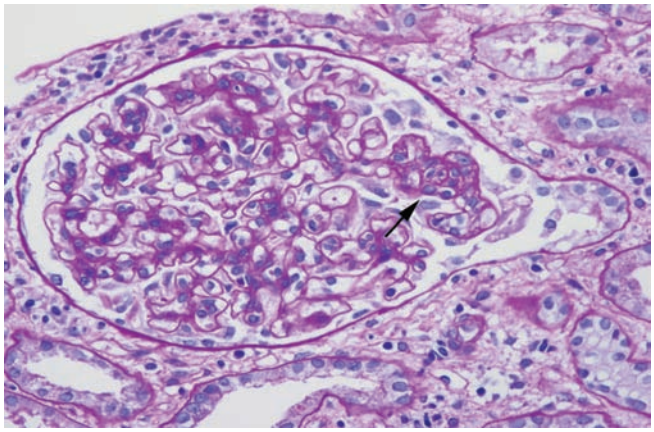
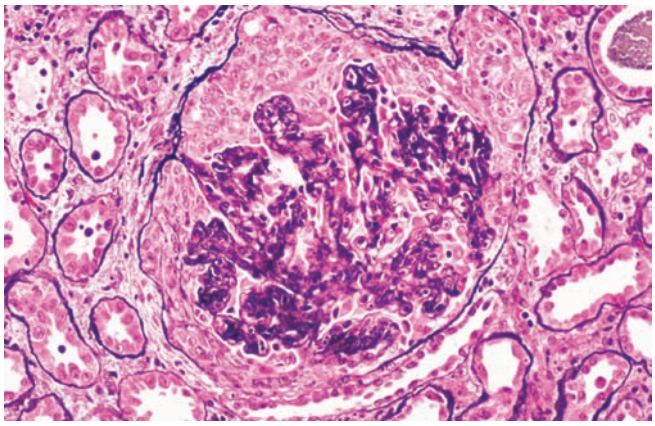
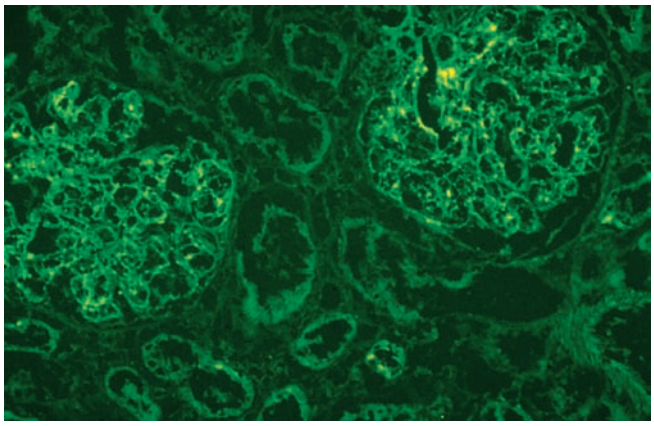


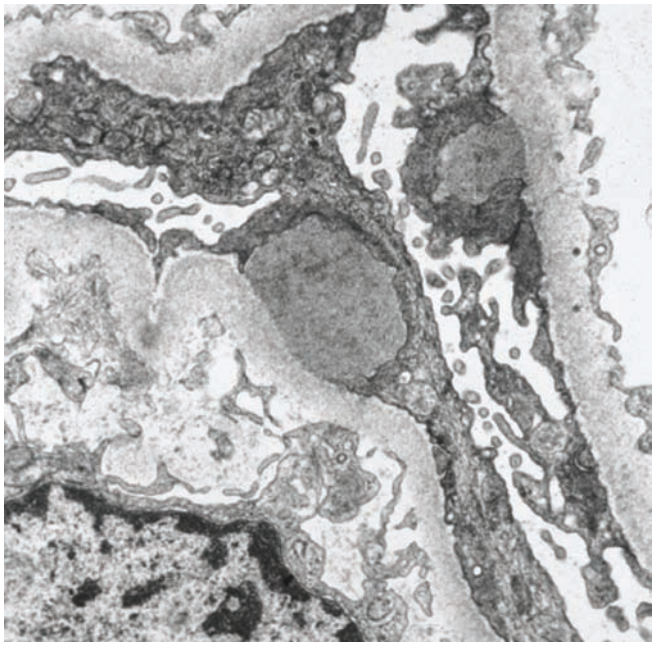
FIGURE 4-5
Tip lesion variant of FSGS. There is segmental sclerosis of the glomerular capillary loops at the proximal tubular outlet (*arrow*). This lesion has a better prognosis than other types of FSGS. (*ABF/Vanderbilt Collection.*)



A

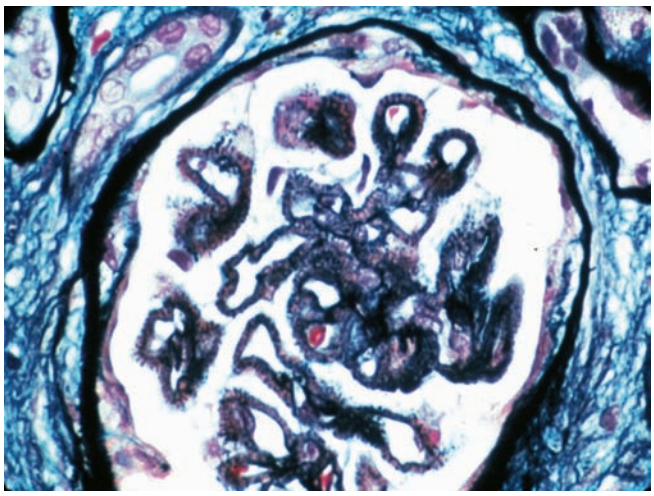


B

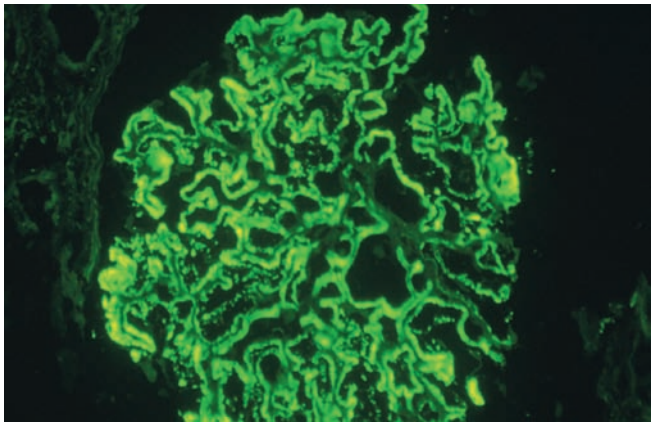


C

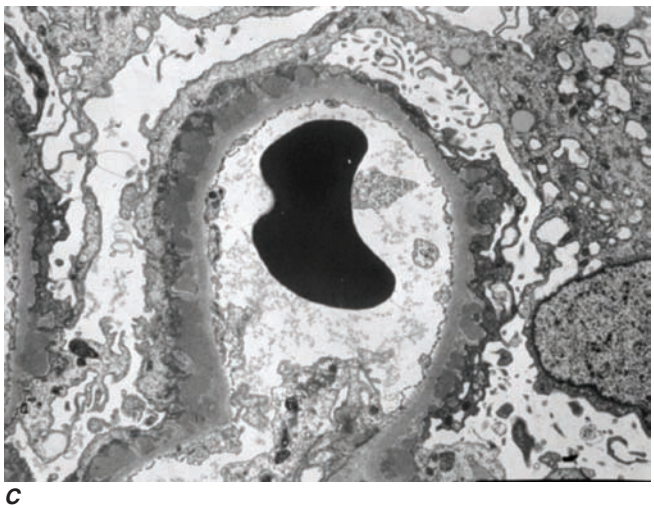
FIGURE 4-6
Postinfectious (poststreptococcal) glomerulonephritis. The glomerular tuft shows proliferative changes with numerous PMNs, with a crescentic reaction in severe cases (***A***). These deposits localize in the mesangium and along the capillary wall in a subepithelial pattern and stain dominantly for C3 and to a lesser extent for IgG (***B***). Subepithelial hump-shaped deposits are seen by electron microscopy (***C***). (*ABF/Vanderbilt Collection.*)



A



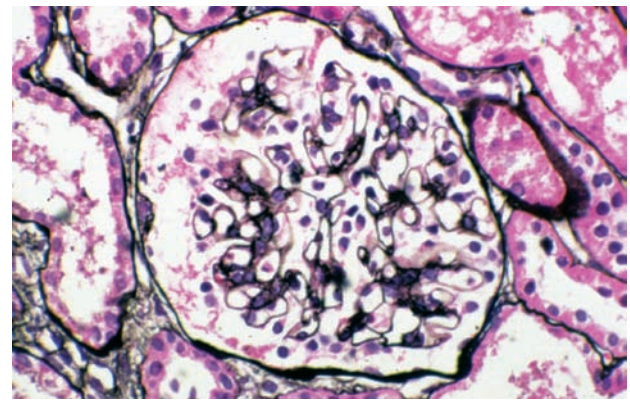
B



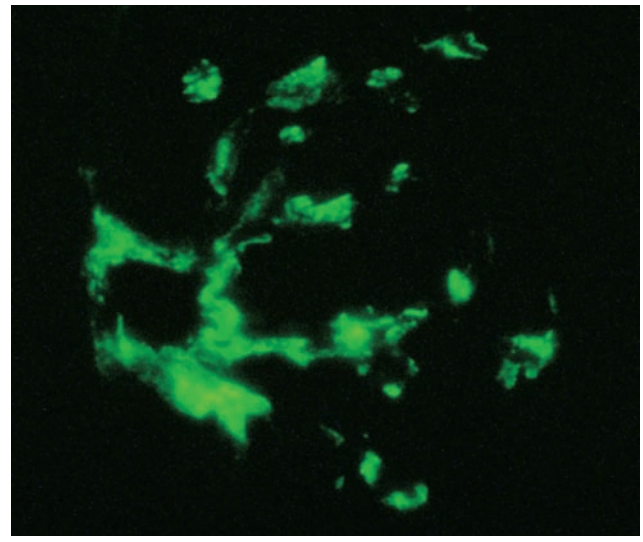
C

FIGURE 4-7

Membranous glomerulopathy. Membranous glomerulopathy is due to subepithelial deposits, with resulting basement membrane reaction, resulting in the appearance of spike-like projections on silver stain (***A***). The deposits are directly visualized by fluorescent anti-IgG, revealing diffuse granular capillary loop staining (***B***). By electron microscopy, the subepithelial location of the deposits and early surrounding basement membrane reaction is evident, with overlying foot process effacement (***C***). (*ABF/Vanderbilt Collection.*)



A



B

FIGURE 4-8

IgA nephropathy. There is variable mesangial expansion due to mesangial deposits, with some cases also showing endocapillary proliferation or segmental sclerosis (***A***). By immunofluorescence, mesangial IgA deposits are evident (***B***). (*ABF/Vanderbilt Collection.*)

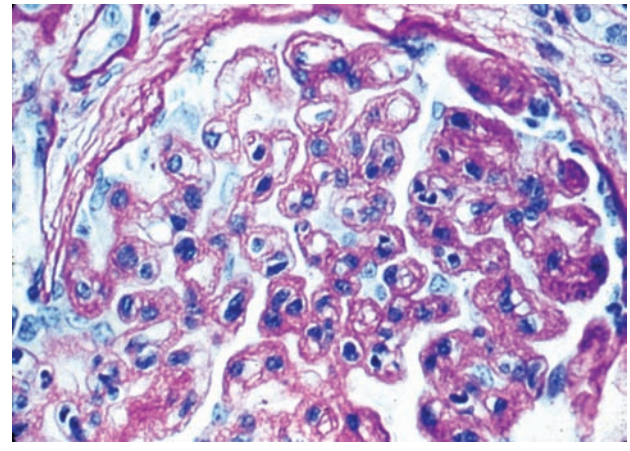


FIGURE 4-9

Membranoproliferative glomerulonephritis. There is mesangial expansion and endocapillary proliferation with cellular interposition in response to subendothelial deposits, resulting in the "tram-track" of duplication of glomerular basement membrane. (*EGN/UPenn Collection.*)

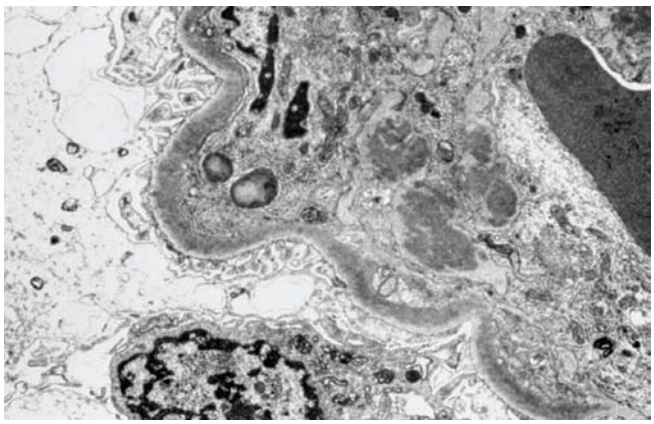


FIGURE 4-10

Dense deposit disease (membranoproliferative glomerulonephritis type II). By light microscopy, there is a membranoproliferative pattern. By electron microscopy, there is a dense transformation of the glomerular basement membrane with round, globular deposits within the mesangium. By immunofluorescence, only C3 staining is usually present. (*ABF/Vanderbilt Collection.*)

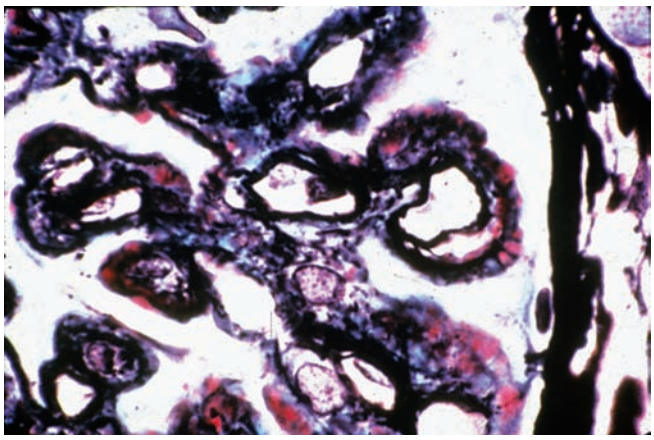
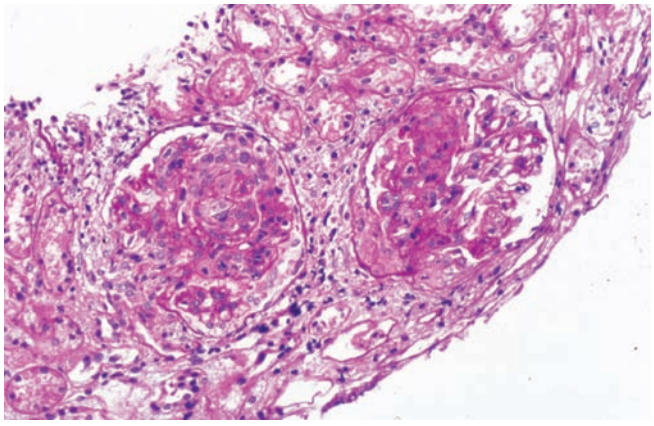
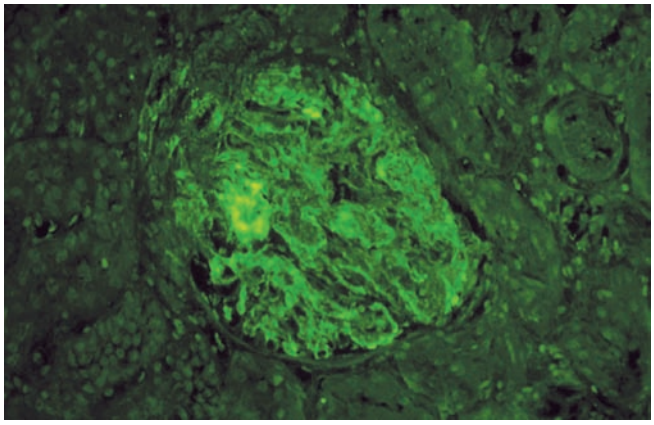


FIGURE 4-11

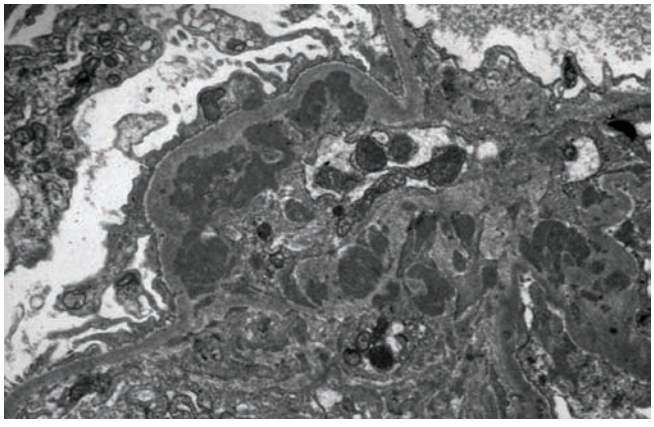
Mixed proliferative and membranous glomerulonephritis. This specimen shows pink subepithelial deposits with spike reaction, and the "tram-track" sign of reduplication of glomerular basement membrane, resulting from subendothelial deposits, as may be seen in mixed membranous and proliferative lupus nephritis (ISN/RPS classes V and IV). (*EGN/UPenn Collection.*)



A



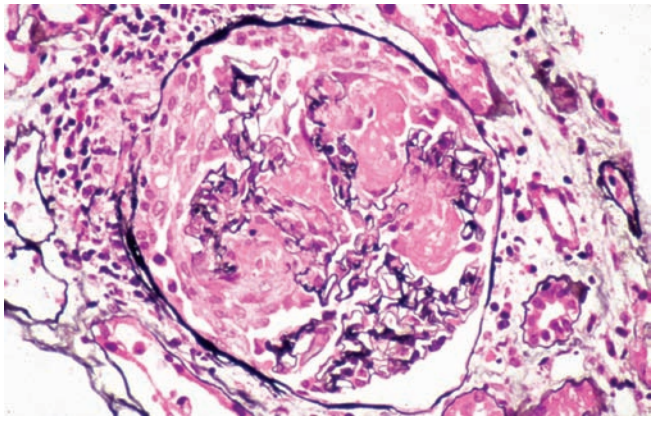
B

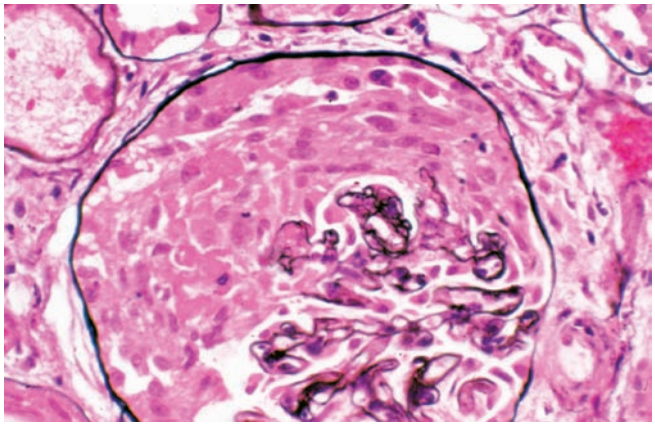


C

FIGURE 4-12

Lupus nephritis. Proliferative lupus nephritis, ISN/RPS class III (focal) or IV (diffuse), manifests as endocapillary proliferation, which may result in segmental necrosis due to deposits, particularly in the subendothelial area (***A***). By immunofluorescence, chunky irregular mesangial and capillary loop deposits are evident, with some of the peripheral loop deposits having a smooth, molded outer contour due to their subendothelial location. These deposits typically stain for all three immunoglobulins (IgG, IgA, IgM) and both C3 and C1q (***B***). By electron microscopy, subendothelial, mesangial, and rare subepithelial dense immune complex deposits are evident, along with extensive foot process effacement (***C***). (*ABF/Vanderbilt Collection.*)

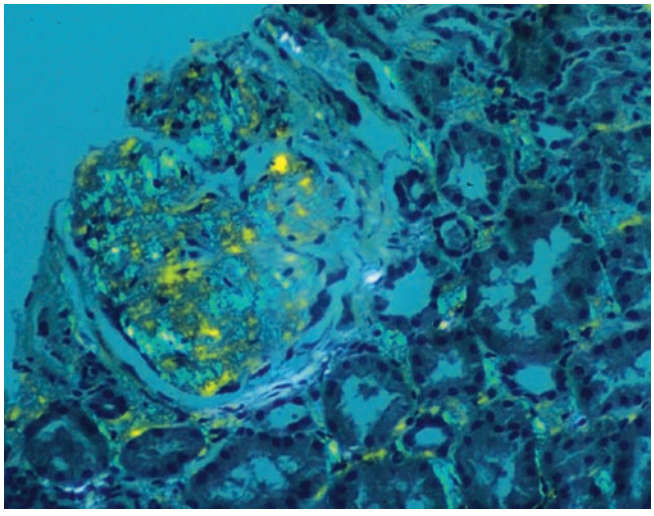




A

FIGURE 4-14

Anti-GBM antibody-mediated glomerulonephritis. There is segmental necrosis with a break of the glomerular basement membrane and a cellular crescent (***A***), and immunofluorescence for IgG shows linear staining of the glomerular basement membrane with a small crescent at ~1 o'clock (***B***). (*ABF/Vanderbilt Collection.*)



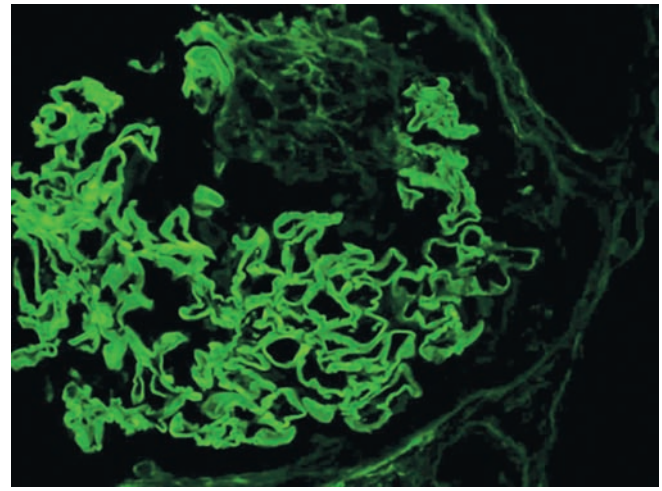
A

FIGURE 4-15

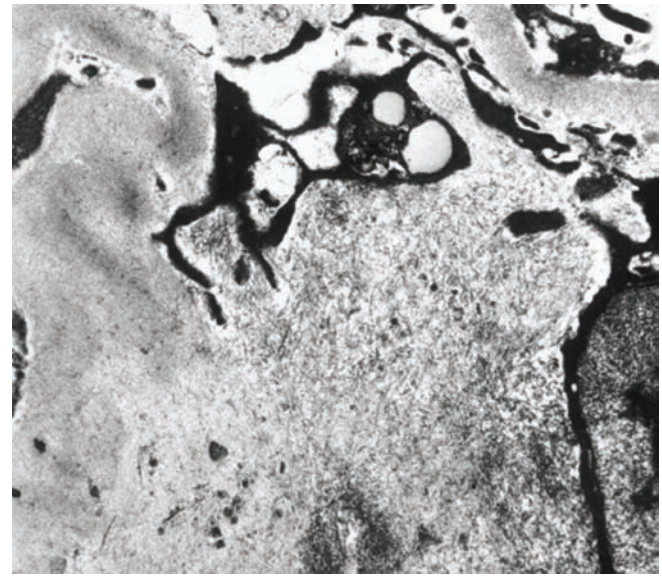
Amyloidosis. Amyloidosis shows amorphous, acellular expansion of the mesangium, with material often also infiltrating glomerular basement membranes, vessels, and in the interstitium, with apple-green birefringence by polarized Congo red stain (***A***). The deposits are composed of randomly organized 9- to 11-nm fibrils by electron microscopy (***B***). (*ABF/Vanderbilt Collection.*)

FIGURE 4-13

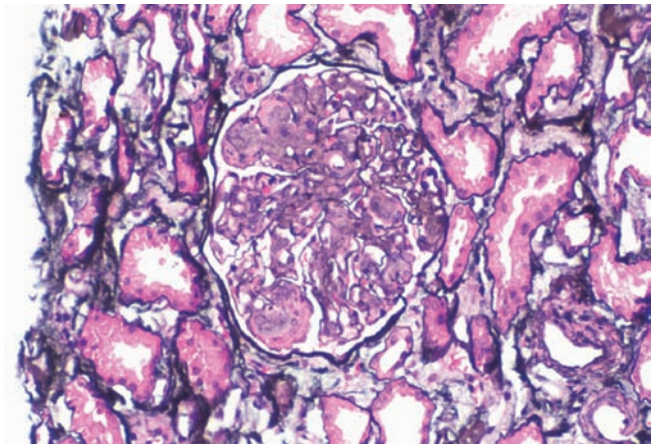
Granulomatosis with polyangiitis (Wegener's). This pauci-immune necrotizing crescentic glomerulonephritis shows numerous breaks in the glomerular basement membrane with associated segmental fibrinoid necrosis, and a crescent formed by proliferation of the parietal epithelium. Note that the uninvolved segment of the glomerulus (at ~5 o'clock) shows no evidence of proliferation or immune complexes. (*ABF/Vanderbilt Collection.*)



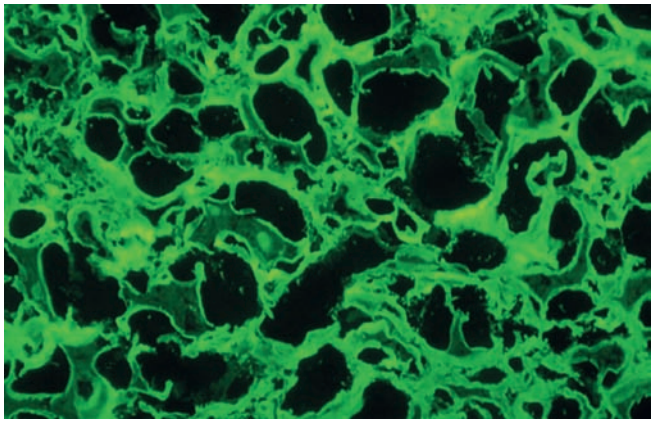
B



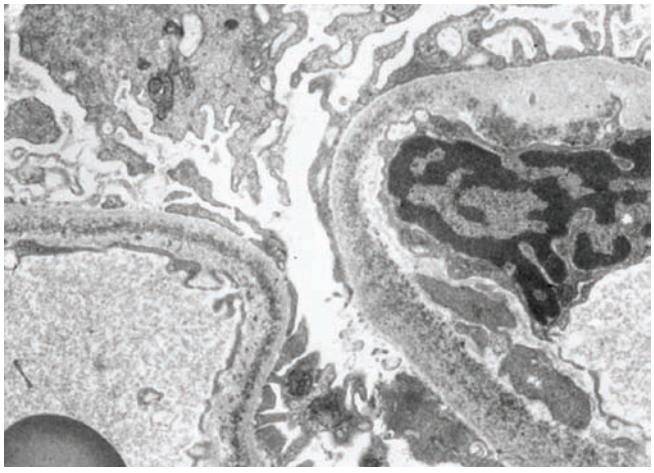
B



A



B



C

FIGURE 4-16

Light chain deposition disease. There is mesangial expansion, often nodular by light microscopy (***A***), with immunofluorescence showing monoclonal staining, more commonly with kappa than lambda light chain, of tubules (***B***) and glomerular tufts. By electron microscopy (***C***), the deposits show an amorphous granular appearance and line the inside of the glomerular basement membrane and are also found along the tubular basement membranes. (*ABF/Vanderbilt Collection.*)

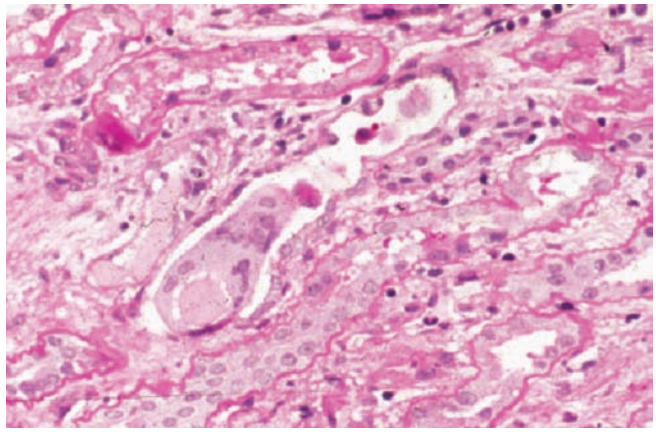
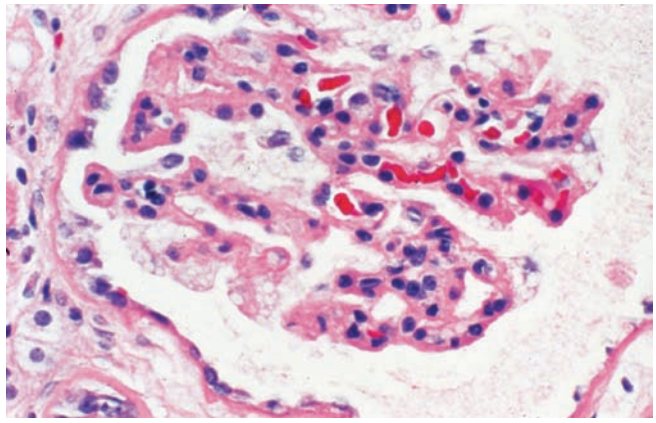
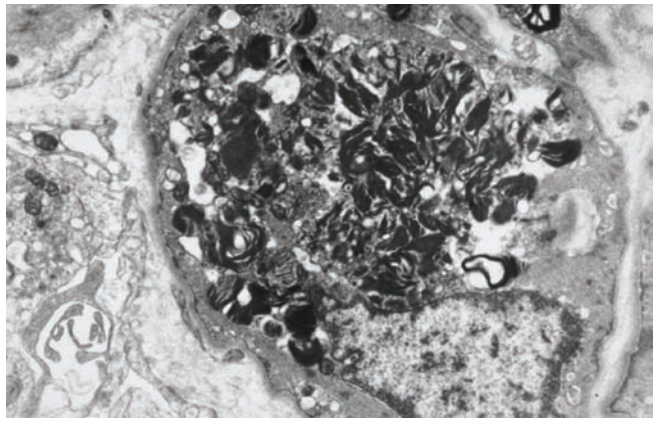


FIGURE 4-17

Light chain cast nephropathy (myeloma kidney). Monoclonal light chains precipitate in tubules and result in a syncytial giant cell reaction surrounding the casts, and a surrounding chronic interstitial nephritis with tubulointerstitial fibrosis. (*ABF/Vanderbilt Collection.*)



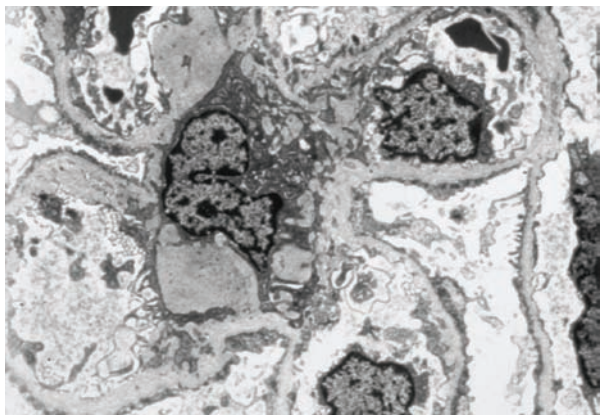
A



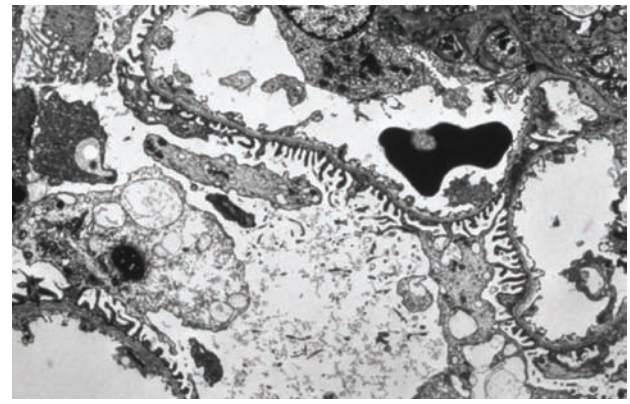
B

FIGURE 4-18

Fabry's disease. Due to deficiency of α-galactosidase, there is abnormal accumulation of glycolipids, resulting in foamy podocytes by light microscopy (***A***). These deposits can be directly visualized by electron microscopy (***B***), where the glycosphingolipid appears as whorled so-called myeloid bodies, particularly in the podocytes. (*ABF/Vanderbilt Collection.*)



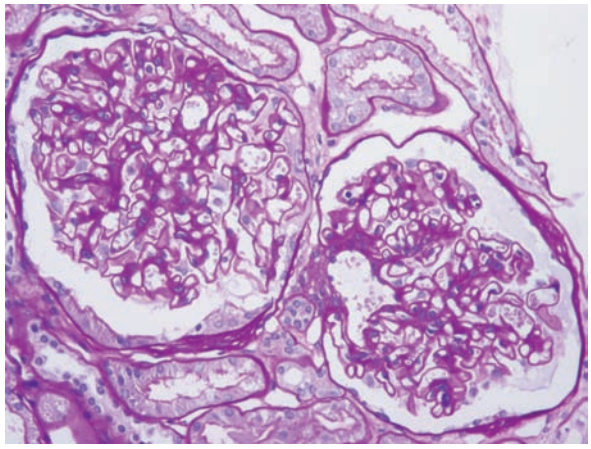
A



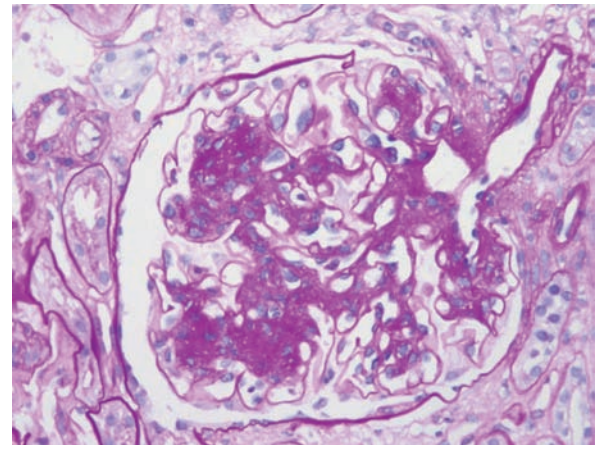
B

FIGURE 4-19

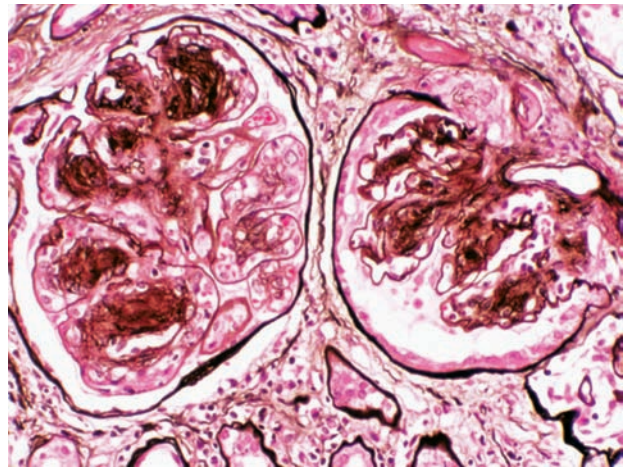
Alport's syndrome and thin glomerular basement membrane lesion. In Alport's syndrome, there is irregular thinning alternating with thickened so-called basket-weaving abnormal organization of the glomerular basement membrane (GBM) (***A***). In benign familial hematuria, or in early cases of Alport's syndrome or female carriers, only extensive thinning of the GBM is seen by electron microscopy (***B***). (*ABF/Vanderbilt Collection.*)



A



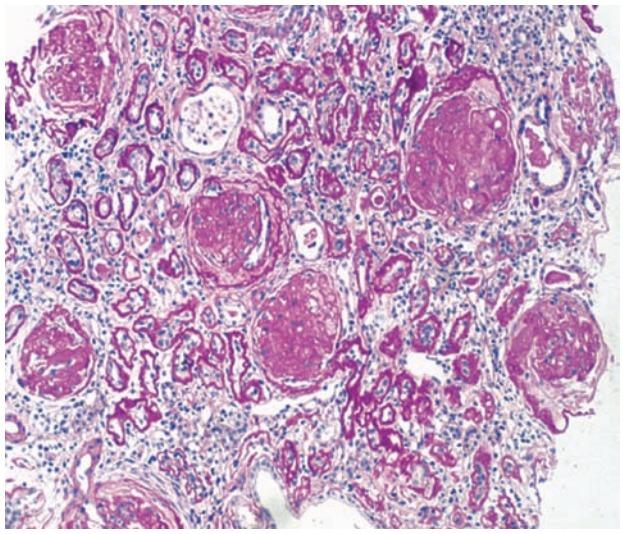
B



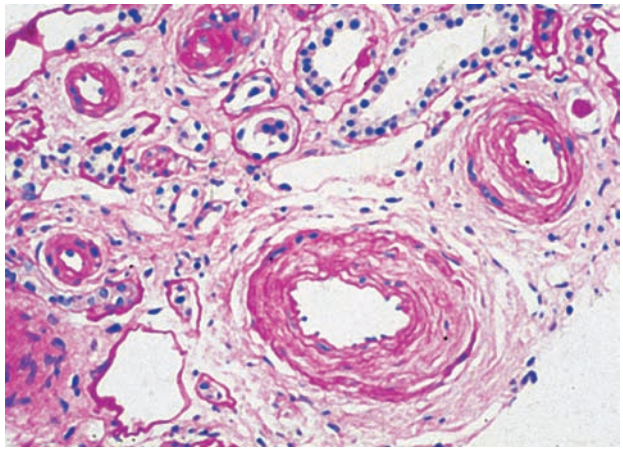
C

FIGURE 4-20

Diabetic nephropathy. In the earliest stage of diabetic nephropathy, only mild mesangial increase and prominent glomerular basement membranes (confirmed to be thickened by electron microscopy) are present (***A***). In slightly more advanced stages, more marked mesangial expansion with early nodule formation develops, with evident arteriolar hyaline (***B***). In established diabetic nephropathy, there is nodular mesangial expansion, so-called Kimmelstiel-Wilson nodules, with increased mesangial matrix and cellularity, microaneurysm formation in the glomerulus on the left, and prominent glomerular basement membranes without evidence of immune deposits and arteriolar hyalinosis of both afferent and efferent arterioles (***C***). (*ABF/Vanderbilt Collection.*)



A



B

FIGURE 4-21

Arterionephrosclerosis. Hypertension-associated injury often manifests extensive global sclerosis of glomeruli, with accompanying and proportional tubulointerstitial fibrosis and pericapsular fibrosis, and there may be segmental sclerosis (***A***). The vessels show disproportionately severe changes of intimal fibrosis, medial hypertrophy, and arteriolar hyaline deposits (***B***). (*ABF/Vanderbilt Collection.*)

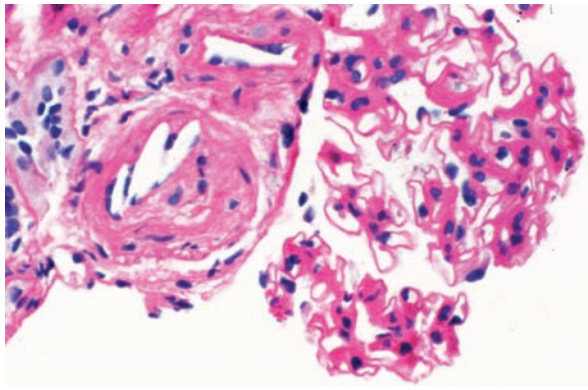


FIGURE 4-22

Cholesterol emboli. Cholesterol emboli cause cleft-like spaces where the lipid has been extracted during processing, with smooth outer contours, and surrounding fibrotic and mononuclear cell reaction in these arterioles. (*ABF/Vanderbilt Collection.*)

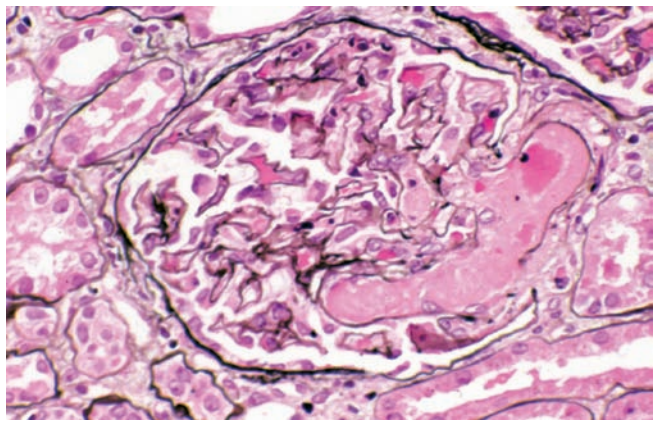
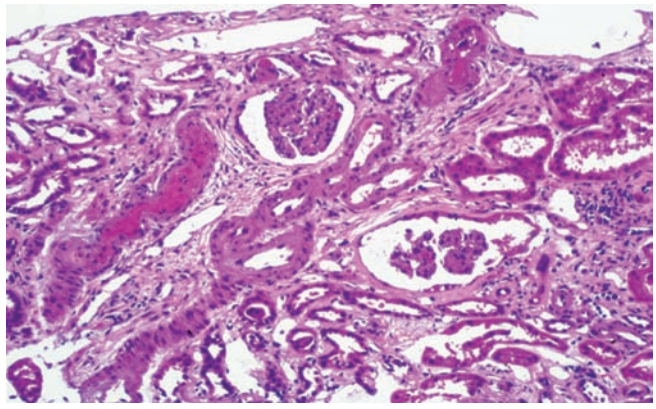
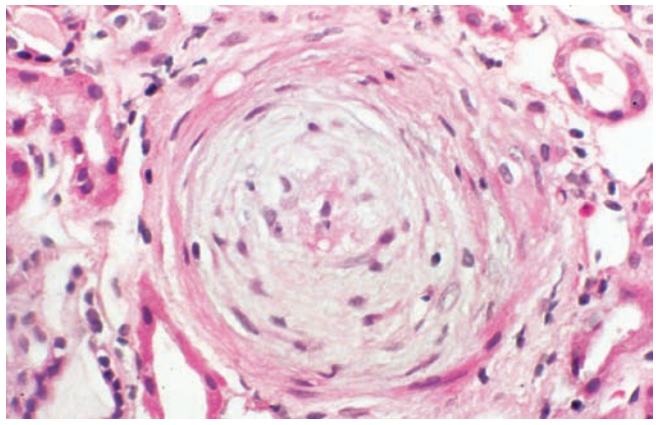


FIGURE 4-23

Hemolytic uremic syndrome. There are characteristic intraglomerular fibrin thrombi, with a chunky pink appearance (thrombotic microangiopathy). The remaining portion of the capillary tuft shows corrugation of the glomerular basement membrane due to ischemia. (*ABF/Vanderbilt Collection.*)



A



B

FIGURE 4-24

Progressive systemic sclerosis. Acutely, there is fibrinoid necrosis of interlobular and larger vessels, with intervening normal vessels and ischemic change in the glomeruli (***A***). Chronically, this injury leads to intimal proliferation, the so-called onion-skinning appearance (***B***). (*ABF/Vanderbilt Collection.*)

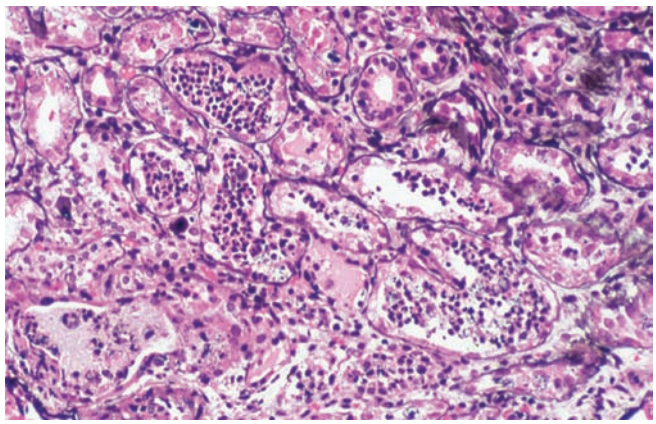


FIGURE 4-25

Acute pyelonephritis. There are characteristic intratubular plugs and casts of PMNs with inflammation extending into the surrounding interstitium, and accompanying tubular injury. (*ABF/Vanderbilt Collection.*)

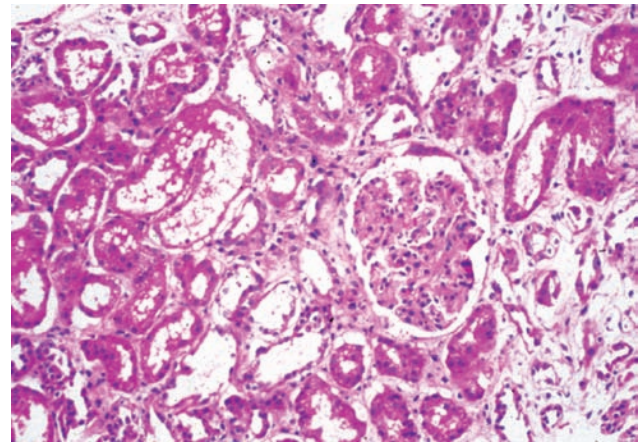
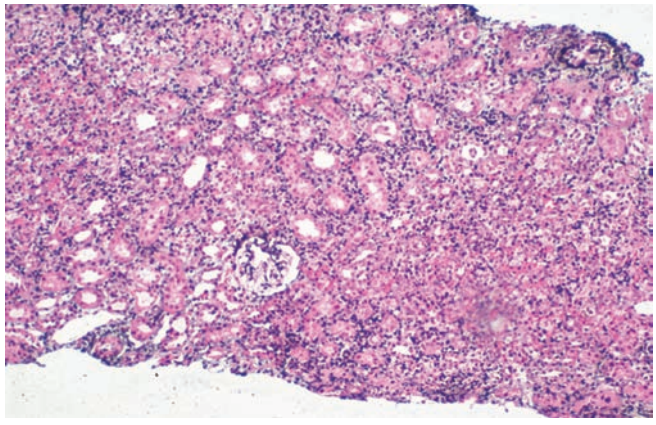
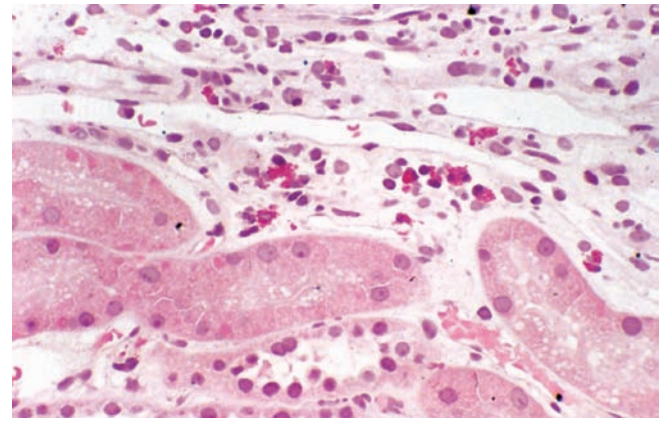


FIGURE 4-26

Acute tubular injury. There is extensive flattening of the tubular epithelium and loss of the brush border, with mild interstitial edema, characteristic of acute tubular injury due to ischemia. (*ABF/Vanderbilt Collection.*)



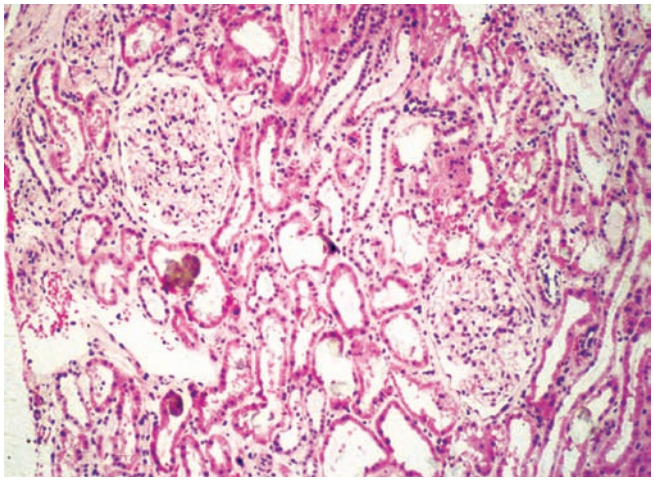
A



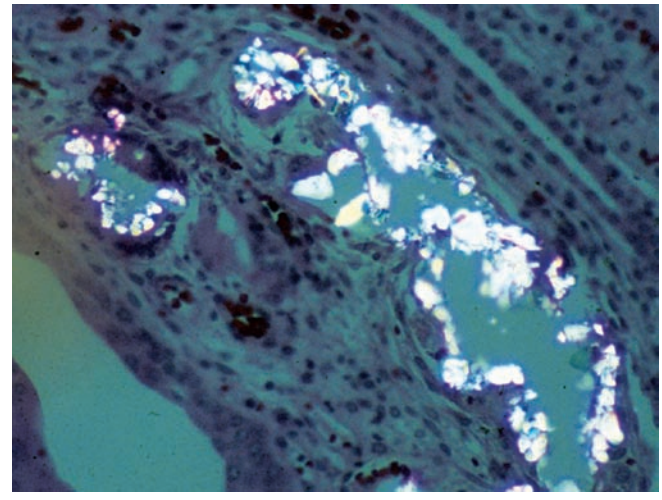
B

FIGURE 4-27

Acute interstitial nephritis. There is extensive interstitial lymphoplasmocytic infiltrate with mild edema and associated tubular injury (***A***), which is frequently associated with interstitial eosinophils (***B***) when caused by a drug hypersensitivity reaction. (*ABF/Vanderbilt Collection.*)



A



B

FIGURE 4-28

Oxalosis. Calcium oxalate crystals have caused extensive tubular injury, with flattening and regeneration of tubular epithelium (***A***). Crystals are well visualized as sheaves when viewed under polarized light (***B***). (*ABF/Vanderbilt Collection.*)

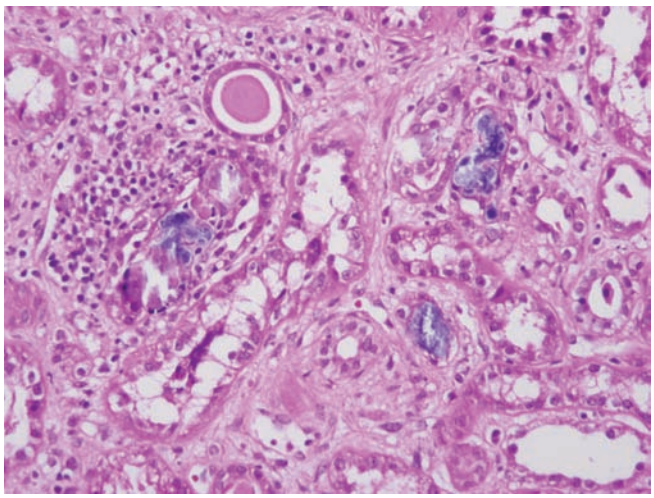


FIGURE 4-29

Acute phosphate nephropathy. There is extensive acute tubular injury with intratubular nonpolarizable calcium phosphate crystals. (*ABF/Vanderbilt Collection.*)

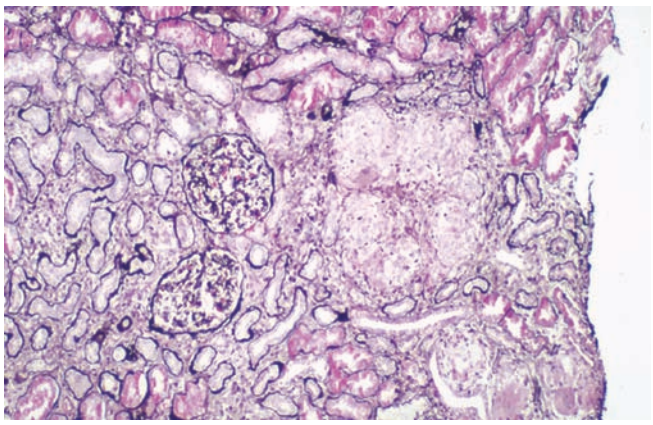


FIGURE 4-30

Sarcoidosis. There is chronic interstitial nephritis with numerous, confluent, non-necrotizing granulomas. The glomeruli are unremarkable, but there is moderate tubular atrophy and interstitial fibrosis. (*ABF/Vanderbilt Collection.*)

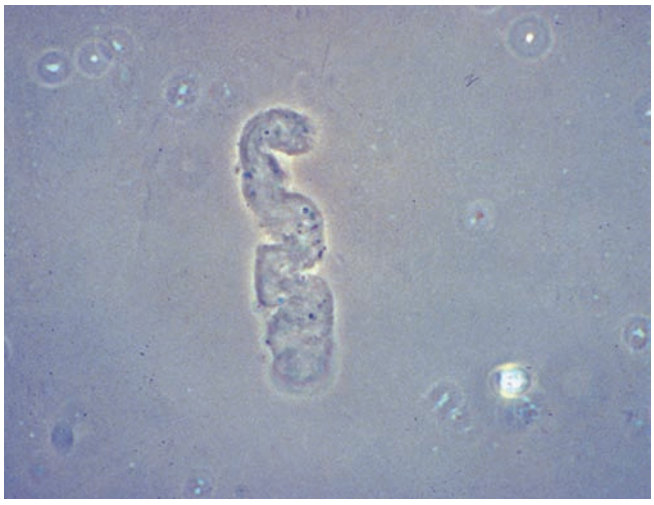


FIGURE 4-31

Hyaline cast. (*ABF/Vanderbilt Collection.*)

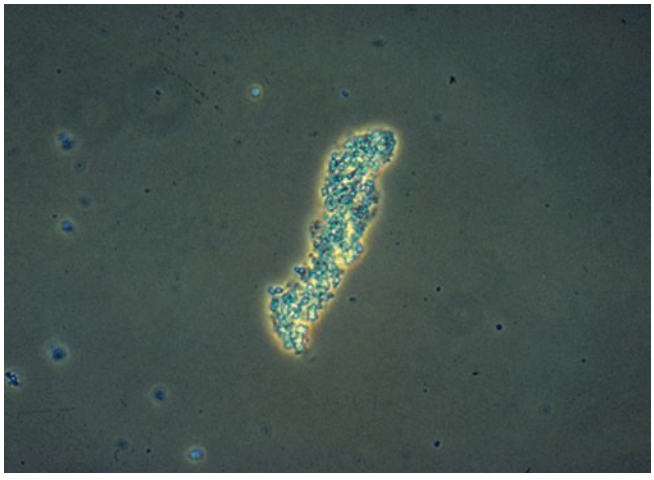


FIGURE 4-32

Coarse granular cast. (*ABF/Vanderbilt Collection.*)

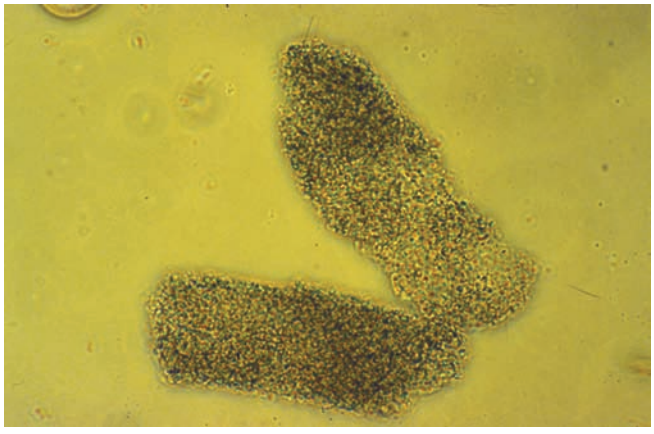


FIGURE 4-33

Fine granular casts. (*ABF/Vanderbilt Collection.*)

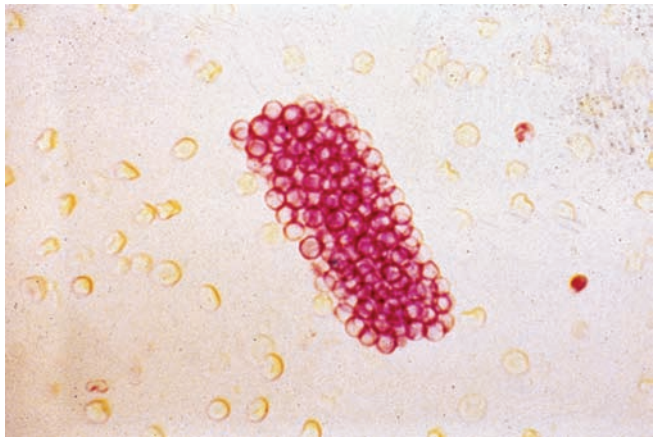


FIGURE 4-34

Red blood cell cast. (*ABF/Vanderbilt Collection.*)

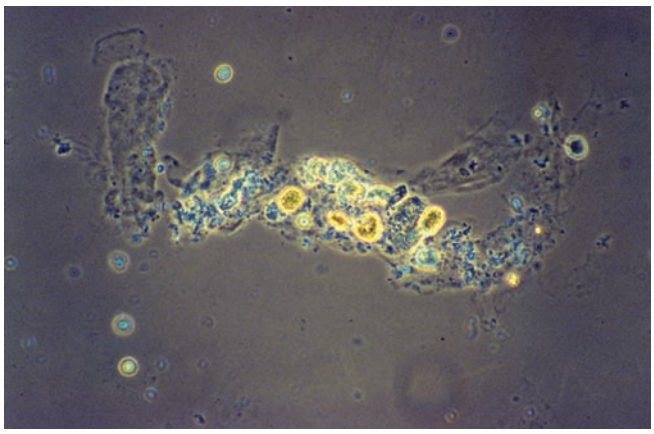


FIGURE 4-35
WBC cast. (*ABF/Vanderbilt Collection.*)

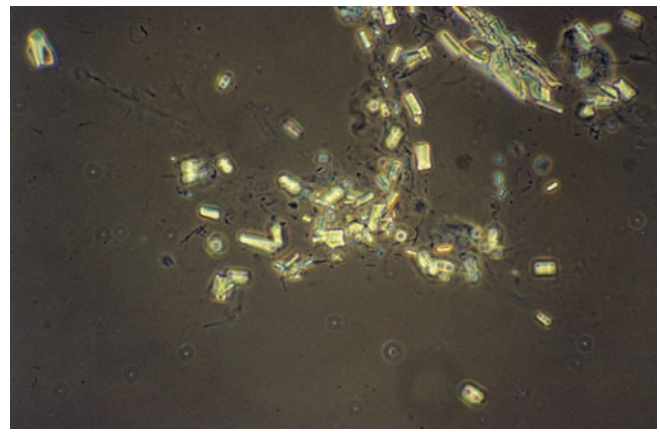


FIGURE 4-36
Triple phosphate crystals. (*ABF/Vanderbilt Collection.*)

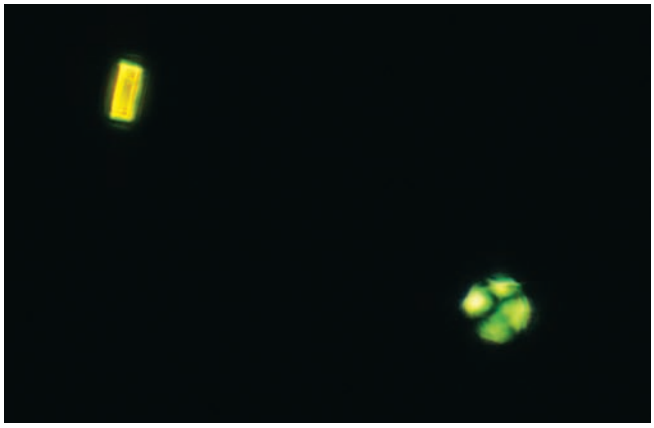


FIGURE 4-37
"Maltese cross" formation in an oval fat body. (*ABF/Vanderbilt Collection.*)

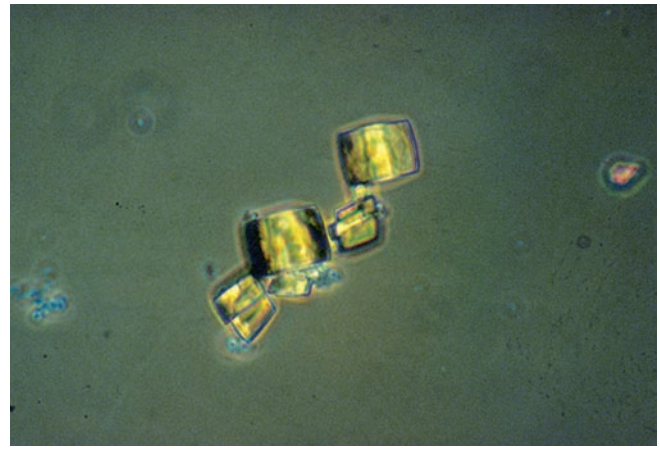


FIGURE 4-38
Uric acid crystals. (*ABF/Vanderbilt Collection.*)

CHAPTER 5

ACIDOSIS AND ALKALOSIS

Thomas D. DuBose, Jr.

NORMAL ACID-BASE HOMEOSTASIS

Systemic arterial pH is maintained between 7.35 and 7.45 by extracellular and intracellular chemical buffering together with respiratory and renal regulatory mechanisms. The control of arterial CO_2 tension (Pa_{co_2}) by the central nervous system (CNS) and respiratory systems and the control of the plasma bicarbonate by the kidneys stabilize the arterial pH by excretion or retention of acid or alkali. The metabolic and respiratory components that regulate systemic pH are described by the Henderson-Hasselbalch equation:

$$pH = 6.1 + \log \frac{HCO_3^-}{Pa_{co_2} \times 0.0301}$$

Under most circumstances, CO_2 production and excretion are matched, and the usual steady-state Pa_{co_2} is maintained at 40 mmHg. Underexcretion of CO_2 produces hypercapnia, and overexcretion causes hypocapnia. Nevertheless, production and excretion are again matched at a new steady-state Pa_{co_2}. Therefore, the Pa_{co_2} is regulated primarily by neural respiratory factors and is not subject to regulation by the rate of CO_2 production. Hypercapnia is usually the result of hypoventilation rather than of increased CO_2 production. Increases or decreases in Pa_{co_2} represent derangements of neural respiratory control or are due to compensatory changes in response to a primary alteration in the plasma [HCO_3^-].

The kidneys regulate plasma [HCO_3^-] through three main processes: (1) "reabsorption" of filtered HCO_3^-, (2) formation of titratable acid, and (3) excretion of NH_4^+ in the urine. The kidney filters ~4000 mmol of HCO_3^- per day. To reabsorb the filtered load of HCO_3^-, the renal tubules must therefore secrete 4000 mmol of hydrogen ions. Between 80 and 90% of HCO_3^- is reabsorbed in the proximal tubule. The distal nephron reabsorbs the remainder and secretes H^+ to defend systemic pH. While this quantity of protons, 40–60 mmol/d, is small, it must be secreted to prevent chronic positive H^+ balance and metabolic acidosis. This quantity of secreted protons is represented in the urine as titratable acid and NH_4^+. Metabolic acidosis in the face of normal renal function increases NH_4^+ production and excretion. NH_4^+ production and excretion are impaired in chronic renal failure, hyperkalemia, and renal tubular acidosis.

DIAGNOSIS OF GENERAL TYPES OF DISTURBANCES

The most common clinical disturbances are simple acid-base disorders, i.e., metabolic acidosis or alkalosis or respiratory acidosis or alkalosis. Because compensation is not complete, the pH is abnormal in simple disturbances. More complicated clinical situations can give rise to mixed acid-base disturbances.

SIMPLE ACID-BASE DISORDERS

Primary respiratory disturbances (primary changes in Pa_{co_2}) invoke compensatory metabolic responses (secondary changes in [HCO_3^-]), and primary metabolic disturbances elicit predictable compensatory respiratory responses (secondary changes in Pa_{co_2}). Physiologic compensation can be predicted from the relationships displayed in **Table 5-1**. Metabolic acidosis due to an increase in endogenous acids (e.g., ketoacidosis) lowers extracellular fluid [HCO_3^-] and decreases extracellular pH. This stimulates the medullary chemoreceptors to increase ventilation and to return the ratio of [HCO_3^-] to Pa_{co_2}, and thus pH, toward, but not to, normal.

TABLE 5-1

PREDICTION OF COMPENSATORY RESPONSES ON SIMPLE ACID-BASE DISTURBANCES AND PATTERN OF CHANGES

DISORDER	PREDICTION OF COMPENSATION	RANGE OF VALUES		
		pH	HCO_3^-	Pa_{CO_2}
Metabolic acidosis	$Pa_{CO_2} = (1.5 \times HCO_3^-) + 8 \pm 2$ *or* Pa_{CO_2} will ↓ 1.25 mmHg per mmol/L ↓ in $[HCO_3^-]$ *or* $Pa_{CO_2} = [HCO_3^-] + 15$	Low	Low	Low
Metabolic alkalosis	Pa_{CO_2} will ↑ 0.75 mmHg per mmol/L ↑ in $[HCO_3^-]$ *or* Pa_{CO_2} will ↑ 6 mmHg per 10 mmol/L ↑ in $[HCO_3^-]$ *or* $Pa_{CO_2} = [HCO_3^-] + 15$	High	High	High
Respiratory alkalosis		High	Low	Low
Acute	$[HCO_3^-]$ will ↓ 0.2 mmol/L per mmHg ↓ in Pa_{CO_2}			
Chronic	$[HCO_3^-]$ will ↓ 0.4 mmol/L per mmHg ↓ in Pa_{CO_2}			
Respiratory acidosis		Low	High	High
Acute	$[HCO_3^-]$ will ↑ 0.1 mmol/L per mmHg ↑ in Pa_{CO_2}			
Chronic	$[HCO_3^-]$ will ↑ 0.4 mmol/L per mmHg ↑ in Pa_{CO_2}			

The degree of respiratory compensation expected in a simple form of metabolic acidosis can be predicted from the relationship $Pa_{CO_2} = (1.5 \times [HCO_3^-]) + 8 \pm 2$. Thus, a patient with metabolic acidosis and $[HCO_3^-]$ of 12 mmol/L would be expected to have a Pa_{CO_2} between 24 and 28 mmHg. Values for Pa_{CO_2} <24 or >28 mmHg define a mixed disturbance (metabolic acidosis and respiratory alkalosis or metabolic alkalosis and respiratory acidosis, respectively). Another way to judge the appropriateness of the response in $[HCO_3^-]$ or Pa_{CO_2} is to use an acid-base nomogram **(Fig. 5-1)**. While the shaded areas of the nomogram show the 95% confidence limits for normal compensation in simple disturbances, finding acid-base values within the shaded area does not necessarily rule out a mixed disturbance. Imposition of one disorder over another may result in values lying within the area of a third. Thus, the nomogram, while convenient, is not a substitute for the equations in Table 5-1.

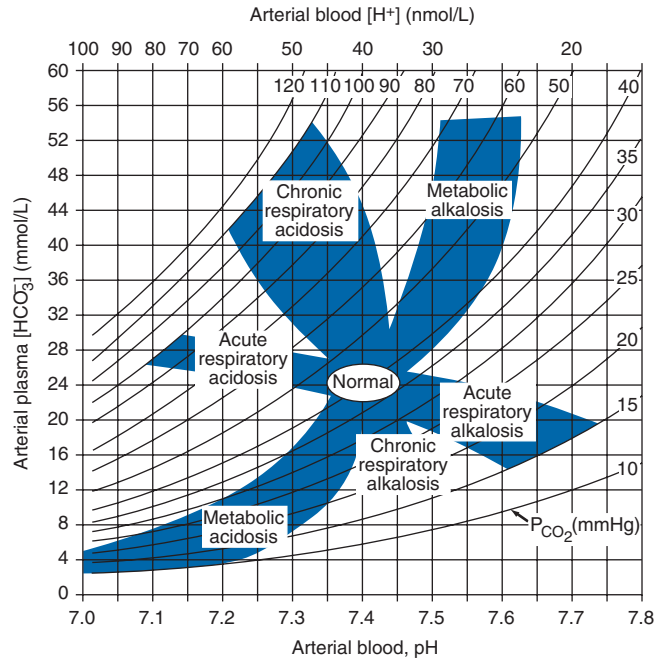


FIGURE 5-1

Acid-base nomogram. Shown are the 90% confidence limits (range of values) of the normal respiratory and metabolic compensations for primary acid-base disturbances. (*From TD DuBose Jr: Acid-base disorders, in Brenner and Rector's The Kidney, 8th ed, BM Brenner [ed]. Philadelphia Saunders, 2008, pp 505-546; used with permission.*)

MIXED ACID-BASE DISORDERS

Mixed acid-base disorders—defined as independently coexisting disorders, not merely compensatory responses—are often seen in patients in critical care units and can lead to dangerous extremes of pH **(Table 5-2)**. A patient with diabetic ketoacidosis (metabolic acidosis) may develop an independent respiratory problem (e.g., pneumonia) leading to respiratory acidosis or alkalosis. Patients with underlying pulmonary disease [e.g., chronic obstructive pulmonary disease (COPD)] may not respond to metabolic acidosis with an appropriate ventilatory response because of insufficient respiratory reserve. Such imposition of respiratory acidosis on metabolic acidosis can lead to severe acidemia. When metabolic acidosis and metabolic alkalosis coexist in the same patient, the pH may be normal or near normal. When the pH is normal, an elevated anion gap (AG; see below) reliably denotes the presence of an AG metabolic acidosis. A discrepancy in the ΔAG (prevailing

TABLE 5-2

EXAMPLES OF MIXED ACID-BASE DISORDERS

Mixed Metabolic and Respiratory
Metabolic acidosis—respiratory alkalosis
Key: High- or normal-AG metabolic acidosis; prevailing Pa_{co_2} *below* predicted value (Table 5-1)
Example: Na^+, 140; K^+, 4.0; Cl^-, 106; HCO_3^-, 14; AG, 20; Pa_{co_2}, 24; pH, 7.39 (lactic acidosis, sepsis in ICU)
Metabolic acidosis—respiratory acidosis
Key: High- or normal-AG metabolic acidosis; prevailing Pa_{co_2} *above* predicted value (Table 5-1)
Example: Na^+, 140; K^+, 4.0; Cl^-, 102; HCO_3^-, 18; AG, 20; Pa_{co_2}, 38; pH, 7.30 (severe pneumonia, pulmonary edema)
Metabolic alkalosis—respiratory alkalosis
Key: Pa_{co_2} does not increase as predicted; pH higher than expected
Example: Na^+, 140; K^+, 4.0; Cl^-, 91; HCO_3^-, 33; AG, 16; Pa_{co_2}, 38; pH, 7.55 (liver disease and diuretics)
Metabolic alkalosis—respiratory acidosis
Key: Pa_{co_2} higher than predicted; pH normal
Example: Na^+, 140; K^+, 3.5; Cl^-, 88; HCO_3^-, 42; AG, 10; Pa_{co_2}, 67; pH, 7.42 (COPD and diuretics)
Mixed Metabolic Disorders
Metabolic acidosis—metabolic alkalosis
Key: Only detectable with high-AG acidosis; $\Delta AG >> \Delta HCO_3^-$
Example: Na^+, 140; K^+, 3.0; Cl^-, 95; HCO_3^-, 25; AG, 20; Pa_{co_2}, 40; pH, 7.42 (uremia with vomiting)
Metabolic acidosis—metabolic acidosis
Key: Mixed high-AG—normal-AG acidosis; ΔHCO_3^- accounted for by combined change in ΔAG and ΔCl^-
Example: Na^+, 135; K^+, 3.0; Cl^-, 110; HCO_3^-, 10; AG, 15; Pa_{co_2}, 25; pH, 7.20 (diarrhea and lactic acidosis, toluene toxicity, treatment of diabetic ketoacidosis)

Abbreviations: AG, anion gap; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

minus normal AG) and the ΔHCO_3^- (normal minus prevailing HCO_3^-) indicates the presence of a mixed high-gap acidosis—metabolic alkalosis (see example below). A diabetic patient with ketoacidosis may have renal dysfunction resulting in simultaneous metabolic acidosis. Patients who have ingested an overdose of drug combinations such as sedatives and salicylates may have mixed disturbances as a result of the acid-base response to the individual drugs (metabolic acidosis mixed with respiratory acidosis or respiratory alkalosis, respectively). Triple acid-base disturbances are more complex. For example, patients with metabolic acidosis due to alcoholic ketoacidosis may develop metabolic alkalosis due to vomiting and superimposed respiratory alkalosis due to the hyperventilation of hepatic dysfunction or alcohol withdrawal.

APPROACH TO THE PATIENT: Acid-Base Disorders

A stepwise approach to the diagnosis of acid-base disorders follows (Table 5-3). Care should be taken when measuring blood gases to obtain the arterial blood sample without using excessive heparin. Blood for electrolytes and arterial blood gases should be drawn simultaneously prior to therapy, because an increase in $[HCO_3^-]$ occurs with metabolic alkalosis and respiratory acidosis. Conversely, a decrease in $[HCO_3^-]$ occurs in metabolic acidosis and respiratory alkalosis. In the determination of arterial blood gases by the clinical laboratory, both pH and Pa_{co_2} are measured, and the $[HCO_3^-]$ is calculated from the Henderson-Hasselbalch equation. This calculated value should be compared with the measured $[HCO_3^-]$ (total CO_2) on the electrolyte panel. These two values should agree within 2 mmol/L. If they do not, the values may not have been drawn simultaneously, a laboratory error may be present, or an error could have been made in calculating the $[HCO_3^-]$. After verifying the blood acid-base values, the precise acid-base disorder can then be identified.

CALCULATE THE ANION GAP All evaluations of acid-base disorders should include a simple calculation of the AG; it represents those unmeasured anions in plasma (normally 10 to 12 mmol/L) and is calculated as follows: $AG = Na^+ - (Cl^- + HCO_3^-)$. The unmeasured anions include anionic proteins, (e.g., albumin), phosphate, sulfate, and organic anions. When acid anions, such as acetoacetate and lactate, accumulate in extracellular fluid, the AG increases, causing a high-AG acidosis. An increase in the AG is most often due to an increase in unmeasured anions and, less commonly, is due to a decrease in unmeasured cations (calcium, magnesium, potassium). In addition, the AG may increase with an increase in anionic albumin, because of either increased albumin concentration or alkalosis, which alters albumin charge. A decrease in the AG

TABLE 5-3

STEPS IN ACID-BASE DIAGNOSIS

1. Obtain arterial blood gas (ABG) and electrolytes simultaneously.
2. Compare $[HCO_3^-]$ on ABG and electrolytes to verify accuracy.
3. Calculate anion gap (AG).
4. Know four causes of high-AG acidosis (ketoacidosis, lactic acid acidosis, renal failure, and toxins).
5. Know two causes of hyperchloremic or nongap acidosis (bicarbonate loss from GI tract, renal tubular acidosis).
6. Estimate compensatory response (Table 5-1).
7. Compare ΔAG and ΔHCO_3^-.
8. Compare change in $[Cl^-]$ with change in $[Na^+]$.

can be due to (1) an increase in unmeasured cations; (2) the addition to the blood of abnormal cations, such as lithium (lithium intoxication) or cationic immunoglobulins (plasma cell dyscrasias); (3) a reduction in the major plasma anion albumin concentration (nephrotic syndrome); (4) a decrease in the effective anionic charge on albumin by acidosis; or (5) hyperviscosity and severe hyperlipidemia, which can lead to an underestimation of sodium and chloride concentrations. A fall in serum albumin by 1 g/dL from the normal value (4.5 g/dL) decreases the AG by 2.5 meq/L. Know the common causes of a high-AG acidosis (Table 5-3).

In the face of a normal serum albumin, a high AG is usually due to non–chloride containing acids that contain inorganic (phosphate, sulfate), organic (ketoacids, lactate, uremic organic anions), exogenous (salicylate or ingested toxins with organic acid production), or unidentified anions. The high AG is significant even if an additional acid-base disorder is superimposed to modify the [HCO_3^-] independently. Simultaneous metabolic acidosis of the high-AG variety plus either chronic respiratory acidosis or metabolic alkalosis represents such a situation in which [HCO_3^-] may be normal or even high (Table 5-3). Compare the change in [HCO_3^-] (ΔHCO_3^-) and the change in the AG (ΔAG).

Similarly, normal values for [HCO_3^-], Pa_{co_2}, and pH do not ensure the absence of an acid-base disturbance. For instance, an alcoholic who has been vomiting may develop a metabolic alkalosis with a pH of 7.55, Pa_{co_2} of 47 mmHg, [HCO_3^-] of 40 mmol/L, [Na^+] of 135, [Cl^-] of 80, and [K^+] of 2.8. If such a patient were then to develop a superimposed alcoholic ketoacidosis with a β-hydroxybutyrate concentration of 15 m*M*, arterial pH would fall to 7.40, [HCO_3^-] to 25 mmol/L, and the Pa_{co_2} to 40 mmHg. Although these blood gases are normal, the AG is elevated at 30 mmol/L, indicating a mixed metabolic alkalosis and metabolic acidosis. A mixture of high-gap acidosis and metabolic alkalosis is recognized easily by comparing the differences (Δ values) in the normal to prevailing patient values. In this example, the ΔHCO_3^- is 0 (25 – 25 mmol/L) but the ΔAG is 20 (30 – 10 mmol/L). Therefore, 20 mmol/L is unaccounted for in the Δ/Δ value (ΔAG to ΔHCO_3^-).

METABOLIC ACIDOSIS

Metabolic acidosis can occur because of an increase in endogenous acid production (such as lactate and ketoacids), loss of bicarbonate (as in diarrhea), or accumulation of endogenous acids (as in renal failure). Metabolic acidosis has profound effects on the respiratory, cardiac, and nervous systems. The fall in blood pH is accompanied by a characteristic increase in ventilation, especially the tidal volume (Kussmaul respiration). Intrinsic cardiac contractility may be depressed, but inotropic function can be normal because of catecholamine release. Both peripheral arterial vasodilation and central venoconstriction can be present; the decrease in central and pulmonary vascular compliance predisposes to pulmonary edema with even minimal volume overload. CNS function is depressed, with headache, lethargy, stupor, and, in some cases, even coma. Glucose intolerance may also occur.

There are two major categories of clinical metabolic acidosis: high-AG and normal-AG, or hyperchloremic, acidosis (Table 5-3 and **Table 5-4**).

TABLE 5-4

CAUSES OF HIGH ANION–GAP METABOLIC ACIDOSIS

Lactic acidosis	Toxins
Ketoacidosis	Ethylene glycol
Diabetic	Methanol
Alcoholic	Salicylates
Starvation	Propylene glycol
	Pyroglutamic acid
	Renal failure (acute and chronic)

TREATMENT **Metabolic Acidosis**

Treatment of metabolic acidosis with alkali should be reserved for severe acidemia except when the patient has no "potential HCO_3^-" in plasma. Potential [HCO_3^-] can be estimated from the increment (Δ) in the AG (ΔAG = patient's AG – 10). It must be determined if the acid anion in plasma is metabolizable (i.e., β-hydroxybutyrate, acetoacetate, and lactate) or nonmetabolizable (anions that accumulate in chronic renal failure and after toxin ingestion). The latter requires return of renal function to replenish the [HCO_3^-] deficit, a slow and often unpredictable process. Consequently, patients with a normal AG acidosis (hyperchloremic acidosis), a slightly elevated AG (mixed hyperchloremic and AG acidosis), or an AG attributable to a nonmetabolizable anion in the face of renal failure should receive alkali therapy, either PO ($NaHCO_3$ or Shohl's solution) or IV ($NaHCO_3$), in an amount necessary to slowly increase the plasma [HCO_3^-] into the 20–22 mmol/L range.

Controversy exists, however, in regard to the use of alkali in patients with a pure AG acidosis owing to accumulation of a metabolizable organic acid anion (ketoacidosis or lactic acidosis). In general, severe acidosis (pH <7.10) warrants the IV administration of 50–100 meq of $NaHCO_3$ over 30–45 min during the initial 1–2 h of therapy. Provision of such modest quantities of alkali in this situation seems to provide an added measure of safety, but it is essential to monitor plasma electrolytes during the course of therapy, because the [K^+] may decline as pH rises. The goal is to increase the [HCO_3^-] to 10 meq/L and the pH to 7.20, not to increase these values to normal.

HIGH–ANION GAP ACIDOSES

APPROACH TO THE PATIENT

High–Anion Gap Acidoses

There are four principal causes of a high-AG acidosis: (1) lactic acidosis, (2) ketoacidosis, (3) ingested toxins, and (4) acute and chronic renal failure (Table 5-4). Initial screening to differentiate the high-AG acidoses should include (1) a probe of the history for evidence of drug and toxin ingestion and measurement of arterial blood gas to detect coexistent respiratory alkalosis (salicylates); (2) determination of whether diabetes mellitus is present (diabetic ketoacidosis); (3) a search for evidence of alcoholism or increased levels of β-hydroxybutyrate (alcoholic ketoacidosis); (4) observation for clinical signs of uremia and determination of the blood urea nitrogen (BUN) and creatinine (uremic acidosis); (5) inspection of the urine for oxalate crystals (ethylene glycol); and (6) recognition of the numerous clinical settings in which lactate levels may be increased (hypotension, shock, cardiac failure, leukemia, cancer, and drug or toxin ingestion).

Lactic acidosis

An increase in plasma l-lactate may be secondary to poor tissue perfusion [type A—circulatory insufficiency (shock, cardiac failure), severe anemia, mitochondrial enzyme defects, and inhibitors (carbon monoxide, cyanide] or to aerobic disorders [type B—malignancies, nucleoside analogue reverse transcriptase inhibitors in HIV, diabetes mellitus, renal or hepatic failure, thiamine deficiency, severe infections (cholera, malaria), seizures, or drugs/toxins (biguanides, ethanol, methanol, propylene glycol, isoniazid, and fructose)]. Propylene glycol may be used as a vehicle for IV medications including lorazepam, and toxicity has been reported in several settings. Unrecognized bowel ischemia or infarction in a patient with severe atherosclerosis or cardiac decompensation receiving vasopressors is a common cause of lactic acidosis. Pyroglutamic acidemia has been reported in critically ill patients receiving acetaminophen, which is associated with depletion of glutathione. D-Lactic acid acidosis, which may be associated with jejunoileal bypass, short bowel syndrome, or intestinal obstruction, is due to formation of D-lactate by gut bacteria.

APPROACH TO THE PATIENT

Lactic Acid Acidosis

The underlying condition that disrupts lactate metabolism must first be corrected; tissue perfusion must be restored when inadequate. Vasoconstrictors should be avoided, if possible, because they may worsen tissue perfusion. Alkali therapy is generally advocated for acute, severe acidemia (pH <7.15) to improve cardiac function and lactate use. However, $NaHCO_3$ therapy may paradoxically depress cardiac performance and exacerbate acidosis by enhancing lactate production (HCO_3^- stimulates phosphofructokinase). While the use of alkali in moderate lactic acidosis is controversial, it is generally agreed that attempts to return the pH or [HCO_3^-] to normal by administration of exogenous $NaHCO_3$ are deleterious. A reasonable approach is to infuse sufficient $NaHCO_3$ to raise the arterial pH to no more than 7.2 over 30–40 min.

$NaHCO_3$ therapy can cause fluid overload and hypertension because the amount required can be massive when accumulation of lactic acid is relentless. Fluid administration is poorly tolerated because of central venoconstriction, especially in the oliguric patient. When the underlying cause of the lactic acidosis can be remedied, blood lactate will be converted to HCO_3^- and may result in an overshoot alkalosis.

Ketoacidosis

Diabetic ketoacidosis (DKA)

This condition is caused by increased fatty acid metabolism and the accumulation of ketoacids (acetoacetate and β-hydroxybutyrate). DKA usually occurs in insulin-dependent diabetes mellitus in association with cessation of insulin or an intercurrent illness such as an infection, gastroenteritis, pancreatitis, or myocardial infarction, which increases insulin requirements temporarily and acutely. The accumulation of ketoacids accounts for the increment in the AG and is accompanied most often by hyperglycemia [glucose >17 mmol/L (300 mg/dL)]. The relationship between the ΔAG and ΔHCO_3^- is typically ~1:1 in DKA. It should be noted that, because insulin prevents production of ketones, bicarbonate therapy is rarely needed except with extreme acidemia (pH <7.1), and then in only limited amounts. Patients with DKA are typically volume depleted and require fluid resuscitation with isotonic saline. Volume overexpansion with IV-fluid administration is not uncommon, however, and contributes to the development of a hyperchloremic acidosis during treatment of DKA. The mainstay for treatment of this condition is IV regular insulin.

Alcoholic ketoacidosis (AKA)

Chronic alcoholics can develop ketoacidosis when alcohol consumption is abruptly curtailed and nutrition is poor. AKA is usually associated with binge drinking, vomiting, abdominal pain, starvation, and volume depletion. The glucose concentration is variable, and acidosis may be severe because of elevated ketones, predominantly β-hydroxybutyrate. Hypoperfusion may enhance lactic acid production; chronic respiratory

alkalosis may accompany liver disease; and metabolic alkalosis can result from vomiting (refer to the relationship between ΔAG and ΔHCO_3^-). Thus, mixed acid-base disorders are common in AKA. As the circulation is restored by administration of isotonic saline, the preferential accumulation of β-hydroxybutyrate is then shifted to acetoacetate. This explains the common clinical observation of an increasingly positive nitroprusside reaction as the patient improves. The nitroprusside ketone reaction (Acetest) can detect acetoacetic acid but not β-hydroxybutyrate, so that the degree of ketosis and ketonuria can not only change with therapy, but can be underestimated initially. Patients with AKA usually present with relatively normal renal function, as opposed to DKA, where renal function is often compromised because of volume depletion (osmotic diuresis) or diabetic nephropathy. The AKA patient with normal renal function may excrete relatively large quantities of ketoacids in the urine, therefore, and may have a relatively normal AG and a discrepancy in the $\Delta AG/\Delta HCO_3^-$ relationship.

TREATMENT **Alcoholic Ketoacidosis**

Extracellular fluid deficits almost always accompany AKA and should be repleted by IV administration of saline and glucose (5% dextrose in 0.9% NaCl). Hypophosphatemia, hypokalemia, and hypomagnesemia may coexist and should be corrected. Hypophosphatemia usually emerges 12–24 h after admission, may be exacerbated by glucose infusion, and, if severe, may induce rhabdomyolysis. Upper gastrointestinal hemorrhage, pancreatitis, and pneumonia may accompany this disorder.

Drug- and toxin-induced acidosis

Salicylates

Salicylate intoxication in adults usually causes respiratory alkalosis or a mixture of high-AG metabolic acidosis and respiratory alkalosis. Only a portion of the AG is due to salicylates. Lactic acid production is also often increased.

TREATMENT **Salicylate-Induced Acidosis**

Vigorous gastric lavage with isotonic saline (not $NaHCO_3$) should be initiated immediately, followed by administration of activated charcoal per nasogastric (NG) tube. In the acidotic patient, to facilitate removal of salicylate, intravenous $NaHCO_3$ is administered in amounts adequate to alkalinize the urine and to maintain urine output (urine pH >7.5). While this form of therapy is straightforward in acidotic patients, a coexisting respiratory alkalosis may make this approach hazardous. Alkalemic patients should not receive $NaHCO_3$. Acetazolamide may be administered in the face of alkalemia, when an alkaline diuresis cannot be achieved, or to ameliorate volume overload associated with $NaHCO_3$ administration, but this drug can cause systemic metabolic acidosis if HCO_3^- is not replaced. Hypokalemia should be anticipated with an alkaline diuresis and should be treated promptly and aggressively. Glucose-containing fluids should be administered because of the danger of hypoglycemia. Excessive insensible fluid losses may cause severe volume depletion and hypernatremia. If renal failure prevents rapid clearance of salicylate, hemodialysis can be performed against a bicarbonate dialysate.

Alcohols

Under most physiologic conditions, sodium, urea, and glucose generate the osmotic pressure of blood. Plasma osmolality is calculated according to the following expression: $P_{osm} = 2Na^+ + Glu + BUN$ (all in mmol/L), or, using conventional laboratory values in which glucose and BUN are expressed in milligrams per deciliter: $P_{osm} = 2Na^+ + Glu/18 + BUN/2.8$. The calculated and determined osmolality should agree within 10–15 mmol/kg H_2O. When the measured osmolality exceeds the calculated osmolality by >15–20 mmol/kg H_2O, one of two circumstances prevails. Either the serum sodium is spuriously low, as with hyperlipidemia or hyperproteinemia (pseudohyponatremia), or osmolytes other than sodium salts, glucose, or urea have accumulated in plasma. Examples of such osmolytes include mannitol, radiocontrast media, ethanol, isopropyl alcohol, ethylene glycol, propylene glycol, methanol, and acetone. In this situation, the difference between the calculated osmolality and the measured osmolality (*osmolar gap*) is proportional to the concentration of the unmeasured solute. With an appropriate clinical history and index of suspicion, identification of an osmolar gap is helpful in identifying the presence of poison-associated AG acidosis. Three alcohols may cause fatal intoxications: ethylene glycol, methanol, and isopropyl alcohol. All cause an elevated osmolal gap, but only the first two cause a high-AG acidosis.

Ethylene glycol

Ingestion of ethylene glycol (commonly used in antifreeze) leads to a metabolic acidosis and severe damage to the CNS, heart, lungs, and kidneys. The increased AG and osmolar gap are attributable to ethylene glycol and its metabolites, oxalic acid, glycolic acid, and other organic acids. Lactic acid production increases secondary to inhibition of the tricarboxylic acid cycle and

altered intracellular redox state. Diagnosis is facilitated by recognizing oxalate crystals in the urine, the presence of an osmolar gap in serum, and a high-AG acidosis. Treatment should not be delayed while awaiting measurement of ethylene glycol levels in this setting.

TREATMENT Ethylene Glycol–Induced Acidosis

This includes the prompt institution of a saline or osmotic diuresis, thiamine and pyridoxine supplements, fomepizole or ethanol, and hemodialysis. The IV administration of the alcohol dehydrogenase inhibitor fomepizole (4-methylpyrazole; 15 mg/kg as a loading dose) or ethanol IV to achieve a level of 22 mmol/L (100 mg/dL) serves to lessen toxicity because they compete with ethylene glycol for metabolism by alcohol dehydrogenase. Fomepizole, although expensive, is the agent of choice and offers the advantages of a predictable decline in ethylene glycol levels without excessive obtundation during ethyl alcohol infusion. Hemodialysis is indicated when the arterial pH is <7.3, or the osmolar gap exceeds 20 mOsm/kg.

Methanol

The ingestion of methanol (wood alcohol) causes metabolic acidosis, and its metabolites formaldehyde and formic acid cause severe optic nerve and CNS damage. Lactic acid, ketoacids, and other unidentified organic acids may contribute to the acidosis. Due to its low molecular mass (32 Da), an osmolar gap is usually present.

TREATMENT Methanol-Induced Acidosis

This is similar to that for ethylene glycol intoxication, including general supportive measures, fomepizole, and hemodialysis (as above).

Isopropyl alcohol

Ingested isopropanol is absorbed rapidly and may be fatal when as little as 150 mL of rubbing alcohol, solvent, or de-icer is consumed. A plasma level >400 mg/dL is life threatening. Isopropyl alcohol differs from ethylene glycol and methanol in that the parent compound, not the metabolites, causes toxicity, and an AG acidosis is not present because acetone is rapidly excreted.

TREATMENT Isopropyl Alcohol Toxicity

Isopropanol alcohol toxicity is treated by watchful waiting and supportive therapy; IV fluids, pressors, ventilatory support if needed, and occasionally hemodialysis for prolonged coma or levels >400 mg/dL.

Renal failure

(See also Chap. 11) The hyperchloremic acidosis of moderate renal insufficiency is eventually converted to the high-AG acidosis of advanced renal failure. Poor filtration and reabsorption of organic anions contribute to the pathogenesis. As renal disease progresses, the number of functioning nephrons eventually becomes insufficient to keep pace with net acid production. Uremic acidosis is characterized, therefore, by a reduced rate of NH_4^+ production and excretion. The acid retained in chronic renal disease is buffered by alkaline salts from bone. Despite significant retention of acid (up to 20 mmol/d), the serum [HCO_3^-] does not decrease further, indicating participation of buffers outside the extracellular compartment. Chronic metabolic acidosis results in significant loss of bone mass due to reduction in bone calcium carbonate. Chronic acidosis also increases urinary calcium excretion, proportional to cumulative acid retention.

TREATMENT Renal Failure

Because of the association of renal failure acidosis with muscle catabolism and bone disease, both uremic acidosis and the hyperchloremic acidosis of renal failure require oral alkali replacement to maintain the [HCO_3^-] between 20 and 24 mmol/L. This can be accomplished with relatively modest amounts of alkali (1.0–1.5 mmol/kg body weight per day). Sodium citrate (Shohl's solution) or $NaHCO_3$ tablets (650-mg tablets contain 7.8 meq) are equally effective alkalinizing salts. Citrate enhances the absorption of aluminum from the gastrointestinal tract and should never be given together with aluminum-containing antacids because of the risk of aluminum intoxication. When hyperkalemia is present, furosemide (60–80 mg/d) should be added.

NON–ANION GAP METABOLIC ACIDOSES

Alkali can be lost from the gastrointestinal tract in diarrhea or from the kidneys (renal tubular acidosis, RTA). In these disorders **(Table 5-5)**, reciprocal changes in [Cl^-] and [HCO_3^-] result in a normal AG. In pure non-AG acidosis, therefore, the increase in [Cl^-] above the normal value approximates the decrease in [HCO_3^-]. The absence of such a relationship suggests a mixed disturbance.

TABLE 5-5

CAUSES OF NON–ANION GAP ACIDOSIS

I. Gastrointestinal bicarbonate loss
- A. Diarrhea
- B. External pancreatic or small-bowel drainage
- C. Ureterosigmoidostomy, jejunal loop, ileal loop
- D. Drugs
  - 1. Calcium chloride (acidifying agent)
  - 2. Magnesium sulfate (diarrhea)
  - 3. Cholestyramine (bile acid diarrhea)

II. Renal acidosis
- A. Hypokalemia
  - 1. Proximal RTA (type 2)
    Drug induced: acetazolamide, topiramate
  - 2. Distal (classic) RTA (type 1)
    Drug induced: amphotericin B, ifosfamide
- B. Hyperkalemia
  - 1. Generalized distal nephron dysfunction (type 4 RTA)
    - a. Mineralocorticoid deficiency
    - b. Mineralocorticoid resistance (autosomal dominant PHA I)
    - c. Voltage defect (autosomal dominant PHA I and PHA II)
    - d. Tubulointerstitial disease

III. Drug-induced hyperkalemia (with renal insufficiency)
- A. Potassium-sparing diuretics (amiloride, triamterene, spironolactone)
- B. Trimethoprim
- C. Pentamidine
- D. ACE-Is and ARBs
- E. Nonsteroidal anti-inflammatory drugs
- F. Cyclosporine and tacrolimus

IV. Other
- A. Acid loads (ammonium chloride, hyperalimentation)
- B. Loss of potential bicarbonate: ketosis with ketone excretion
- C. Expansion acidosis (rapid saline administration)
- D. Hippurate
- E. Cation exchange resins

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PHA, pseudohypoaldosteronism; RTA, renal tubular acidosis.

TREATMENT Non–Anion Gap Metabolic Acidoses

In diarrhea, stools contain a higher $[HCO_3^-]$ and decomposed HCO_3^- than plasma so that metabolic acidosis develops along with volume depletion. Instead of an acid urine pH (as anticipated with systemic acidosis), urine pH is usually around 6 because metabolic acidosis and hypokalemia increase renal synthesis and excretion of NH_4^+, thus providing a urinary buffer that increases urine pH. Metabolic acidosis due to gastrointestinal losses with a high urine pH can be differentiated from RTA because urinary NH_4^+ excretion is typically low in RTA and high with diarrhea. Urinary NH_4^+ levels can be estimated by calculating the urine anion gap (UAG): $UAG = [Na^+ + K^+]_u - [Cl^-]_u$. When $[Cl^-]_u > [Na^+ + K^+]_u$, the UAG is negative by definition. This indicates that the urine ammonium level is appropriately increased, suggesting an extrarenal cause of the acidosis. Conversely, when the UAG is positive, the urine ammonium level is low, suggesting a renal cause of the acidosis.

Loss of functioning renal parenchyma by progressive renal disease leads to hyperchloremic acidosis when the glomerular filtration rate (GFR) is between 20 and 50 mL/min and to uremic acidosis with a high AG when the GFR falls to <20 mL/min. In advanced renal failure, ammoniagenesis is reduced in proportion to the loss of functional renal mass, and ammonium accumulation and trapping in the outer medullary collecting tubule may also be impaired. Because of adaptive increases in K^+ secretion by the collecting duct and colon, the acidosis of chronic renal insufficiency is typically normokalemic.

Proximal RTA (type 2 RTA) (Chap. 16) is most often due to generalized proximal tubular dysfunction manifested by glycosuria, generalized aminoaciduria, and phosphaturia (Fanconi syndrome). With a low plasma $[HCO_3^-]$, the urine pH is acid (pH <5.5). The fractional excretion of $[HCO_3^-]$ may exceed 10–15% when the serum HCO_3^- >20 mmol/L. Because HCO_3^- is not reabsorbed normally in the proximal tubule, therapy with $NaHCO_3$ will enhance renal potassium wasting and hypokalemia.

The typical findings in acquired or inherited forms of classic distal RTA (type 1 RTA) include hypokalemia, non-AG metabolic acidosis, low urinary NH_4^+ excretion (positive UAG, low urine $[NH_4^+]$), and inappropriately high urine pH (pH >5.5). Most patients have hypocitraturia and hypercalciuria, so nephrolithiasis, nephrocalcinosis, and bone disease are common. In generalized distal nephron dysfunction (type 4 RTA), hyperkalemia is disproportionate to the reduction in GFR because of coexisting dysfunction of potassium and acid secretion. Urinary ammonium excretion is invariably depressed, and renal function may be compromised, for example, due to diabetic nephropathy, obstructive uropathy, or chronic tubulointerstitial disease.

Hyporeninemic hypoaldosteronism typically causes non-AG metabolic acidosis, most commonly in older adults with diabetes mellitus or tubulointerstitial disease and renal insufficiency. Patients usually have mild to moderate CKD (GFR, 20–50 mL/min) and acidosis, with elevation in serum [K+] (5.2–6.0 mmol/L), concurrent hypertension, and congestive heart failure. Both the metabolic acidosis and the hyperkalemia are out of proportion to impairment in GFR. Nonsteroidal anti-inflammatory drugs, trimethoprim, pentamidine, and angiotensin-converting enzyme (ACE) inhibitors can

also cause non-AG metabolic acidosis in patients with renal insufficiency (Table 5-5).

METABOLIC ALKALOSIS

Metabolic alkalosis is manifested by an elevated arterial pH, an increase in the serum [HCO_3^-], and an increase in Pa_{co_2} as a result of compensatory alveolar hypoventilation (Table 5-1). It is often accompanied by hypochloremia and hypokalemia. The arterial pH establishes the diagnosis, because it is increased in metabolic alkalosis and decreased or normal in respiratory acidosis. Metabolic alkalosis frequently occurs in association with other disorders such as respiratory acidosis or alkalosis, or metabolic acidosis.

PATHOGENESIS

Metabolic alkalosis occurs as a result of net gain of [HCO_3^-] or loss of nonvolatile acid (usually HCl by vomiting) from the extracellular fluid. For HCO_3^- to be added to the extracellular fluid, it must be administered exogenously or synthesized endogenously, in part or entirely by the kidneys. Because it is unusual for alkali to be added to the body, the disorder involves a generative stage, in which the loss of acid usually causes alkalosis, and a maintenance stage, in which the kidneys fail to compensate by excreting HCO_3^-.

Under normal circumstances, the kidneys have an impressive capacity to excrete HCO_3^-. Continuation of metabolic alkalosis represents a failure of the kidneys to eliminate HCO_3^- in the usual manner. The kidneys will retain, rather than excrete, the excess alkali and maintain the alkalosis if (1) volume deficiency, chloride deficiency, and K^+ deficiency exist in combination with a reduced GFR, which augments distal tubule H^+ secretion; or (2) hypokalemia exists because of autonomous hyperaldosteronism. In the first example, alkalosis is corrected by administration of NaCl and KCl, whereas, in the latter, it is necessary to repair the alkalosis by pharmacologic or surgical intervention, not with saline administration.

DIFFERENTIAL DIAGNOSIS

To establish the cause of metabolic alkalosis **(Table 5-6)**, it is necessary to assess the status of the extracellular fluid volume (ECFV), the recumbent and upright blood pressure, the serum [K^+], and the renin-aldosterone system. For example, the presence of chronic hypertension and chronic hypokalemia in an alkalotic patient suggests either mineralocorticoid excess or that the hypertensive patient is receiving diuretics. Low plasma renin activity and normal urine [Na^+] and [Cl^-] in a patient who is not taking diuretics indicate a primary mineralocorticoid excess syndrome. The combination of hypokalemia and alkalosis in a normotensive, nonedematous patient can be due to

TABLE 5-6

CAUSES OF METABOLIC ALKALOSIS

- I. Exogenous HCO_3^- loads
  - A. Acute alkali administration
  - B. Milk-alkali syndrome
- II. Effective ECFV contraction, normotension, K^+ deficiency, and secondary hyperreninemic hyperaldosteronism
  - A. Gastrointestinal origin
    - 1. Vomiting
    - 2. Gastric aspiration
    - 3. Congenital chloridorrhea
    - 4. Villous adenoma
  - B. Renal origin
    - 1. Diuretics
    - 2. Posthypercapnic state
    - 3. Hypercalcemia/hypoparathyroidism
    - 4. Recovery from lactic acidosis or ketoacidosis
    - 5. Nonreabsorbable anions including penicillin, carbenicillin
    - 6. Mg^{2+} deficiency
    - 7. K^+ depletion
    - 8. Bartter's syndrome (loss of function mutations in TALH)
    - 9. Gitelman's syndrome (loss of function mutation in Na^+-Cl^- cotransporter in DCT)
- III. ECFV expansion, hypertension, K^+ deficiency, and mineralocorticoid excess
  - A. High renin
    - 1. Renal artery stenosis
    - 2. Accelerated hypertension
    - 3. Renin-secreting tumor
    - 4. Estrogen therapy
  - B. Low renin
    - 1. Primary aldosteronism
      - a. Adenoma
      - b. Hyperplasia
      - c. Carcinoma
    - 2. Adrenal enzyme defects
      - a. 11 β-Hydroxylase deficiency
      - b. 17 α-Hydroxylase deficiency
    - 3. Cushing's syndrome or disease
    - 4. Other
      - a. Licorice
      - b. Carbenoxolone
      - c. Chewer's tobacco
- IV. Gain-of-function mutation of renal sodium channel with ECFV expansion, hypertension, K^+ deficiency, and hyporeninemic-hypoaldosteronism
  - A. Liddle's syndrome

Abbreviations: DCT, distal convoluted tubule; ECFV, extracellular fluid volume; TALH, thick ascending limb of Henle's loop.

Bartter's or Gitelman's syndrome, magnesium deficiency, vomiting, exogenous alkali, or diuretic ingestion. Determination of urine electrolytes (especially the urine [Cl^-]) and screening of the urine for diuretics may be helpful. If the urine is alkaline, with an elevated [Na^+] and [K^+] but low [Cl^-], the diagnosis is usually either vomiting (overt or surreptitious) or alkali ingestion. If the urine is relatively acid and has low concentrations of Na^+, K^+, and Cl^-, the most likely possibilities are prior vomiting, the posthypercapnic state, or prior diuretic ingestion. If, on the other hand, neither the urine sodium, potassium, nor chloride concentrations are depressed, magnesium deficiency, Bartter's or Gitelman's syndrome, or current diuretic ingestion should be considered. Bartter's syndrome is distinguished from Gitelman's syndrome because of hypocalciuria and hypomagnesemia in the latter disorder.

Alkali administration

Chronic administration of alkali to individuals with normal renal function rarely causes alkalosis. However, in patients with coexistent hemodynamic disturbances, alkalosis can develop because the normal capacity to excrete HCO_3^- may be exceeded or there may be enhanced reabsorption of HCO_3^-. Such patients include those who receive HCO_3^- (PO or IV), acetate loads (parenteral hyperalimentation solutions), citrate loads (transfusions), or antacids plus cation-exchange resins (aluminum hydroxide and sodium polystyrene sulfonate). Nursing-home patients receiving tube feedings have a higher incidence of metabolic alkalosis than nursing-home patients receiving oral feedings.

METABOLIC ALKALOSIS ASSOCIATED WITH ECFV CONTRACTION, K^+ DEPLETION, AND SECONDARY HYPERRENINEMIC HYPERALDOSTERONISM

Gastrointestinal origin

Gastrointestinal loss of H^+ from vomiting or gastric aspiration results in retention of HCO_3^-. The loss of fluid and NaCl in vomitus or nasogastric suction results in contraction of the ECFV and an increase in the secretion of renin and aldosterone. Volume contraction through a reduction in GFR results in an enhanced capacity of the renal tubule to reabsorb HCO_3^-. During active vomiting, however, the filtered load of bicarbonate is acutely increased to the point that the reabsorptive capacity of the proximal tubule for HCO_3^- is exceeded. The excess $NaHCO_3$ issuing out of the proximal tubule reaches the distal tubule, where H^+ secretion is enhanced by an aldosterone and the delivery of the poorly reabsorbed anion, HCO_3^-. Correction of the contracted ECFV with NaCl and repair of K^+ deficits corrects the acid-base disorder, and chloride deficiency.

Renal origin

Diuretics

Drugs that induce chloruresis, such as thiazides and loop diuretics (furosemide, bumetanide, torsemide, and ethacrynic acid), acutely diminish the ECFV without altering the total body bicarbonate content. The serum [HCO_3^-] increases because the reduced ECFV "contracts" the [HCO_3^-] in the plasma (contraction alkalosis). The chronic administration of diuretics tends to generate an alkalosis by increasing distal salt delivery, so that K^+ and H^+ secretion are stimulated. The alkalosis is maintained by persistence of the contraction of the ECFV, secondary hyperaldosteronism, K^+ deficiency, and the direct effect of the diuretic (as long as diuretic administration continues). Repair of the alkalosis is achieved by providing isotonic saline to correct the ECFV deficit.

Solute losing disorders: Bartter's syndrome and Gitelman's syndrome

See Chap. 16.

Nonreabsorbable anions and magnesium deficiency

Administration of large quantities of nonreabsorbable anions, such as penicillin or carbenicillin, can enhance distal acidification and K^+ secretion by increasing the transepithelial potential difference. Mg^{2+} deficiency results in hypokalemic alkalosis by enhancing distal acidification through stimulation of renin and hence aldosterone secretion.

Potassium depletion

Chronic K^+ depletion may cause metabolic alkalosis by increasing urinary acid excretion. Both NH_4^+ production and absorption are enhanced and HCO_3^- reabsorption is stimulated. Chronic K^+ deficiency upregulates the renal H^+, K^+-ATPase to increase K^+ absorption at the expense of enhanced H^+ secretion. Alkalosis associated with severe K^+ depletion is resistant to salt administration, but repair of the K^+ deficiency corrects the alkalosis.

After treatment of lactic acidosis or ketoacidosis

When an underlying stimulus for the generation of lactic acid or ketoacid is removed rapidly, as with repair of circulatory insufficiency or with insulin therapy, the lactate or ketones are metabolized to yield an equivalent amount of HCO_3^-. Other sources of new HCO_3^- are additive with the original amount generated by organic anion metabolism to create a surfeit of HCO_3^-. Such sources include (1) new HCO_3^- added to the blood by the kidneys as a result of enhanced acid excretion during the preexisting period of acidosis, and (2) alkali therapy during the treatment phase of the acidosis. Acidosis-induced contraction of the ECFV and K^+ deficiency act to sustain the alkalosis.

Posthypercapnia

Prolonged CO_2 retention with chronic respiratory acidosis enhances renal HCO_3^- absorption and the generation of new HCO_3^- (increased net acid excretion). If the Pa_{co_2} is returned to normal, metabolic alkalosis results from the persistently elevated [HCO_3^-]. Alkalosis develops if the elevated Pa_{co_2} is abruptly returned toward normal by a change in mechanically controlled ventilation. Associated ECFV contraction does not allow complete repair of the alkalosis by correction of the Pa_{co_2} alone, and alkalosis persists until Cl^- supplementation is provided.

METABOLIC ALKALOSIS ASSOCIATED WITH ECFV EXPANSION, HYPERTENSION, AND HYPERALDOSTERONISM

Increased aldosterone levels may be the result of autonomous primary adrenal overproduction or of secondary aldosterone release due to renal overproduction of renin. Mineralocorticoid excess increases net acid excretion and may result in metabolic alkalosis, which may be worsened by associated K^+ deficiency. ECFV expansion from salt retention causes hypertension. The kaliuresis persists because of mineralocorticoid excess and distal Na^+ absorption causing enhanced K^+ excretion, continued K^+ depletion with polydipsia, inability to concentrate the urine, and polyuria.

Liddle's syndrome (Chap. 16) results from increased activity of the collecting duct Na^+ channel (ENaC) and is a rare monogenic form of hypertension due to volume expansion manifested as hypokalemic alkalosis and normal aldosterone levels.

Symptoms

With metabolic alkalosis, changes in CNS and peripheral nervous system function are similar to those of hypocalcemia. Symptoms include mental confusion; obtundation; and a predisposition to seizures, paresthesia, muscular cramping, tetany, aggravation of arrhythmias, and hypoxemia in chronic obstructive pulmonary disease. Related electrolyte abnormalities include hypokalemia and hypophosphatemia.

TREATMENT **Metabolic Alkalosis**

This is primarily directed at correcting the underlying stimulus for HCO_3^- generation. If primary aldosteronism, renal artery stenosis, or Cushing's syndrome is present, correction of the underlying cause will reverse the alkalosis. [H^+] loss by the stomach or kidneys can be mitigated by the use of proton pump inhibitors or the discontinuation of diuretics. The second aspect of treatment is to remove the factors that sustain the inappropriate increase in HCO_3^- reabsorption, such as ECFV contraction or K^+ deficiency. K^+ deficits should always be repaired. Isotonic saline is usually sufficient to reverse the alkalosis if ECFV contraction is present.

If associated conditions preclude infusion of saline, renal HCO_3^- loss can be accelerated by administration of acetazolamide, a carbonic anhydrase inhibitor, which is usually effective in patients with adequate renal function but can worsen K^+ losses. Dilute hydrochloric acid (0.1 *N* HCl) is also effective, but can cause hemolysis, and must be delivered centrally and slowly. Hemodialysis against a dialysate low in [HCO_3^-] and high in [Cl^-] can be effective when renal function is impaired.

RESPIRATORY ACIDOSIS

Respiratory acidosis can be due to severe pulmonary disease, respiratory muscle fatigue, or abnormalities in ventilatory control and is recognized by an increase in Pa_{co_2} and decrease in pH **(Table 5-7)**. In acute respiratory acidosis, there is an immediate compensatory elevation (due to cellular buffering mechanisms) in HCO_3^-, which increases 1 mmol/L for every 10-mmHg increase in Pa_{co_2}. In chronic respiratory acidosis (>24 h), renal adaptation increases the [HCO_3^-] by 4 mmol/L for every 10-mmHg increase in Pa_{co_2}. The serum HCO_3^- usually does not increase above 38 mmol/L.

The clinical features vary according to the severity and duration of the respiratory acidosis, the underlying disease, and whether there is accompanying hypoxemia. A rapid increase in Pa_{co_2} may cause anxiety, dyspnea, confusion, psychosis, and hallucinations and may progress to coma. Lesser degrees of dysfunction in chronic hypercapnia include sleep disturbances; loss of memory; daytime somnolence; personality changes; impairment of coordination; and motor disturbances such as tremor, myoclonic jerks, and asterixis. Headaches and other signs that mimic raised intracranial pressure, such as papilledema, abnormal reflexes, and focal muscle weakness, are due to vasoconstriction secondary to loss of the vasodilator effects of CO_2.

Depression of the respiratory center by a variety of drugs, injury, or disease can produce respiratory acidosis. This may occur acutely with general anesthetics, sedatives, and head trauma or chronically with sedatives, alcohol, intracranial tumors, and the syndromes of sleep-disordered breathing including the primary alveolar and obesity-hypoventilation syndromes. Abnormalities or disease in the motor neurons, neuromuscular junction, and skeletal muscle can cause hypoventilation via respiratory muscle fatigue. Mechanical ventilation, when not properly adjusted and supervised, may result in respiratory acidosis, particularly if CO_2 production suddenly rises (because of fever, agitation, sepsis, or overfeeding) or alveolar ventilation falls because of worsening

TABLE 5-7

RESPIRATORY ACID-BASE DISORDERS

I. Alkalosis
- A. Central nervous system stimulation
  - 1. Pain
  - 2. Anxiety, psychosis
  - 3. Fever
  - 4. Cerebrovascular accident
  - 5. Meningitis, encephalitis
  - 6. Tumor
  - 7. Trauma
- B. Hypoxemia or tissue hypoxia
  - 1. High altitude
  - 2. Pneumonia, pulmonary edema
  - 3. Aspiration
  - 4. Severe anemia
- C. Drugs or hormones
  - 1. Pregnancy, progesterone
  - 2. Salicylates
  - 3. Cardiac failure
- D. Stimulation of chest receptors
  - 1. Hemothorax
  - 2. Flail chest
  - 3. Cardiac failure
  - 4. Pulmonary embolism
- E. Miscellaneous
  - 1. Septicemia
  - 2. Hepatic failure
  - 3. Mechanical hyperventilation
  - 4. Heat exposure
  - 5. Recovery from metabolic acidosis

II. Acidosis
- A. Central
  - 1. Drugs (anesthetics, morphine, sedatives)
  - 2. Stroke
  - 3. Infection
- B. Airway
  - 1. Obstruction
  - 2. Asthma
- C. Parenchyma
  - 1. Emphysema
  - 2. Pneumoconiosis
  - 3. Bronchitis
  - 4. Adult respiratory distress syndrome
  - 5. Barotrauma
- D. Neuromuscular
  - 1. Poliomyelitis
  - 2. Kyphoscoliosis
  - 3. Myasthenia
  - 4. Muscular dystrophies
- E. Miscellaneous
  - 1. Obesity
  - 2. Hypoventilation
  - 3. Permissive hypercapnia

pulmonary function. High levels of positive end-expiratory pressure in the presence of reduced cardiac output may cause hypercapnia as a result of large increases in alveolar dead space. Permissive hypercapnia is being used with increasing frequency because of studies suggesting lower mortality rates than with conventional mechanical ventilation, especially with severe CNS or heart disease. The respiratory acidosis associated with permissive hypercapnia may require administration of $NaHCO_3$ to increase the arterial pH to 7.25, but overcorrection of the acidemia may be deleterious.

Acute hypercapnia follows sudden occlusion of the upper airway or generalized bronchospasm as in severe asthma, anaphylaxis, inhalational burn, or toxin injury. Chronic hypercapnia and respiratory acidosis occur in end-stage obstructive lung disease. Restrictive disorders involving both the chest wall and the lungs can cause respiratory acidosis because the high metabolic cost of respiration causes ventilatory muscle fatigue. Advanced stages of intrapulmonary and extrapulmonary restrictive defects present as chronic respiratory acidosis.

The diagnosis of respiratory acidosis requires the measurement of Pa_{co_2} and arterial pH. A detailed history and physical examination often indicate the cause. Pulmonary function studies, including spirometry, diffusion capacity for carbon monoxide, lung volumes, and arterial Pa_{co_2} and O_2 saturation, usually make it possible to determine if respiratory acidosis is secondary to lung disease. The workup for nonpulmonary causes should include a detailed drug history, measurement of hematocrit, and assessment of upper airway, chest wall, pleura, and neuromuscular function.

TREATMENT **Respiratory Acidosis**

The management of respiratory acidosis depends on its severity and rate of onset. Acute respiratory acidosis can be life threatening, and measures to reverse the underlying cause should be undertaken simultaneously with restoration of adequate alveolar ventilation. This may necessitate tracheal intubation and assisted mechanical ventilation. Oxygen administration should be titrated carefully in patients with severe obstructive pulmonary disease and chronic CO_2 retention who are breathing spontaneously. When oxygen is used injudiciously, these patients may experience progression of the respiratory acidosis. Aggressive and rapid correction of hypercapnia should be avoided, because the falling Pa_{co_2} may provoke the same complications noted with acute respiratory alkalosis (i.e., cardiac arrhythmias, reduced cerebral perfusion, and seizures). The Pa_{co_2} should be lowered gradually in chronic respiratory acidosis, aiming to restore the Pa_{co_2} to baseline levels and to provide sufficient Cl^- and K^+ to enhance the renal excretion of HCO_3^-.

Chronic respiratory acidosis is frequently difficult to correct, but measures aimed at improving lung function can help some patients and forestall further deterioration in most.

RESPIRATORY ALKALOSIS

Alveolar hyperventilation decreases Pa_{co_2} and increases the HCO_3^-/Pa_{co_2} ratio, thus increasing pH (Table 5-7). Nonbicarbonate cellular buffers respond by consuming HCO_3^-. Hypocapnia develops when a sufficiently strong ventilatory stimulus causes CO_2 output in the lungs to exceed its metabolic production by tissues. Plasma pH and $[HCO_3^-]$ appear to vary proportionately with Pa_{co_2} over a range from 40 to 15 mmHg. The relationship between arterial $[H^+]$ concentration and Pa_{co_2} is ~0.7 mmol/L per mmHg (or 0.01 pH unit/mmHg), and that for plasma $[HCO_3^-]$ is 0.2 mmol/L per mmHg. Hypocapnia sustained for >2–6 h is further compensated by a decrease in renal ammonium and titratable acid excretion and a reduction in filtered HCO_3^- reabsorption. Full renal adaptation to respiratory alkalosis may take several days and requires normal volume status and renal function. The kidneys appear to respond directly to the lowered Pa_{co_2} rather than to alkalosis per se. In chronic respiratory alkalosis a 1-mmHg fall in Pa_{co_2} causes a 0.4- to 0.5-mmol/L drop in $[HCO_3^-]$ and a 0.3-mmol/L fall (or 0.003 rise in pH) in $[H^+]$.

The effects of respiratory alkalosis vary according to duration and severity but are primarily those of the underlying disease. Reduced cerebral blood flow as a consequence of a rapid decline in Pa_{co_2} may cause dizziness, mental confusion, and seizures, even in the absence of hypoxemia. The cardiovascular effects of acute hypocapnia in the conscious human are generally minimal, but in the anesthetized or mechanically ventilated patient, cardiac output and blood pressure may fall because of the depressant effects of anesthesia and positive-pressure ventilation on heart rate, systemic resistance, and venous return. Cardiac arrhythmias may occur in patients with heart disease as a result of changes in oxygen unloading by blood from a left shift in the hemoglobin-oxygen dissociation curve (Bohr effect). Acute respiratory alkalosis causes intracellular shifts of Na^+, K^+, and PO_4^{2-} and reduces free $[Ca^{2+}]$ by increasing the protein-bound fraction. Hypocapnia-induced hypokalemia is usually minor.

Chronic respiratory alkalosis is the most common acid-base disturbance in critically ill patients and, when severe, portends a poor prognosis. Many cardiopulmonary disorders manifest respiratory alkalosis in their early to intermediate stages, and the finding of normocapnia and hypoxemia in a patient with hyperventilation may herald the onset of rapid respiratory failure and should prompt an assessment to determine if the patient is becoming fatigued. Respiratory alkalosis is common during mechanical ventilation.

The hyperventilation syndrome may be disabling. Paresthesia; circumoral numbness; chest wall tightness or pain; dizziness; inability to take an adequate breath; and, rarely, tetany may be sufficiently stressful to perpetuate the disorder. Arterial blood-gas analysis demonstrates an acute or chronic respiratory alkalosis, often with hypocapnia in the range of 15–30 mmHg and no hypoxemia. CNS diseases or injury can produce several patterns of hyperventilation and sustained Pa_{co_2} levels of 20–30 mmHg. Hyperthyroidism, high caloric loads, and exercise raise the basal metabolic rate, but ventilation usually rises in proportion so that arterial blood gases are unchanged and respiratory alkalosis does not develop. Salicylates are the most common cause of drug-induced respiratory alkalosis as a result of direct stimulation of the medullary chemoreceptor. The methylxanthines, theophylline, and aminophylline stimulate ventilation and increase the ventilatory response to CO_2. Progesterone increases ventilation and lowers arterial Pa_{co_2} by as much as 5–10 mmHg. Therefore, chronic respiratory alkalosis is a common feature of pregnancy. Respiratory alkalosis is also prominent in liver failure, and the severity correlates with the degree of hepatic insufficiency. Respiratory alkalosis is often an early finding in gram-negative septicemia, before fever, hypoxemia, or hypotension develops.

The diagnosis of respiratory alkalosis depends on measurement of arterial pH and Pa_{co_2}. The plasma $[K^+]$ is often reduced and the $[Cl^-]$ increased. In the acute phase, respiratory alkalosis is not associated with increased renal HCO_3^- excretion, but within hours net acid excretion is reduced. In general, the HCO_3^- concentration falls by 2.0 mmol/L for each 10-mmHg decrease in Pa_{co_2}. Chronic hypocapnia reduces the serum $[HCO_3^-]$ by 4.0 mmol/L for each 10-mmHg decrease in Pa_{co_2}. It is unusual to observe a plasma HCO_3^- <12 mmol/L as a result of a pure respiratory alkalosis.

When a diagnosis of respiratory alkalosis is made, its cause should be investigated. The diagnosis of hyperventilation syndrome is made by exclusion. In difficult cases, it may be important to rule out other conditions such as pulmonary embolism, coronary artery disease, and hyperthyroidism.

TREATMENT Respiratory Alkalosis

The management of respiratory alkalosis is directed toward alleviation of the underlying disorder. If respiratory alkalosis complicates ventilator management, changes in dead space, tidal volume, and frequency can minimize the hypocapnia. Patients with the hyperventilation syndrome may benefit from reassurance, rebreathing from a paper bag during symptomatic attacks, and attention to underlying psychological stress. Antidepressants and sedatives are not recommended. β-Adrenergic blockers may ameliorate peripheral manifestations of the hyperadrenergic state.

CHAPTER 6

FLUID AND ELECTROLYTE DISTURBANCES

David B. Mount

SODIUM AND WATER

COMPOSITION OF BODY FLUIDS

Water is the most abundant constituent in the body, accounting for ~50% of body weight in women and 60% in men. Total body water is distributed in two major compartments: 55–75% is intracellular [intracellular fluid (ICF)], and 25–45% is extracellular [extracellular fluid (ECF)]. ECF is subdivided into intravascular (plasma water) and extravascular (interstitial) spaces in a ratio of 1:3. Fluid movement between the intravascular and interstitial spaces occurs across the capillary wall and is determined by Starling forces, i.e., capillary hydraulic pressure and colloid osmotic pressure. The transcapillary hydraulic pressure gradient exceeds the corresponding oncotic pressure gradient, thus favoring the movement of plasma ultrafiltrate into the extravascular space. The return of fluid into the intravascular compartment occurs via lymphatic flow.

The solute or particle concentration of a fluid is known as its osmolality and is expressed as milliosmoles per kilogram of water (mosmol/kg). Water easily diffuses across most cell membranes to achieve osmotic equilibrium (ECF osmolality = ICF osmolality). Notably, the extracellular and intracellular solute compositions differ considerably, owing to the activity of various transporters, channels, and ATP-driven membrane pumps. The major ECF particles are Na^+ and its accompanying anions Cl^- and HCO_3^-, whereas K^+ and organic phosphate esters (ATP, creatine phosphate, and phospholipids) are the predominant ICF osmoles. Solutes that are restricted to the ECF or the ICF determine the tonicity or effective osmolality of that compartment. Certain solutes, particularly urea, do not contribute to water shifts across most membranes and are thus known as *ineffective osmoles*.

Water balance

Vasopressin secretion, water ingestion, and renal water transport collaborate to maintain human body fluid osmolality between 280 and 295 mosmol/kg. Vasopressin (AVP) is synthesized in magnocellular neurons within the hypothalamus; the distal axons of those neurons project to the posterior pituitary or neurohypophysis, from which AVP is released into the circulation. A network of central osmoreceptor neurons that includes the AVP-expressing magnocellular neurons themselves sense circulating osmolality via nonselective, stretch-activated cation channels. These osmoreceptor neurons are activated or inhibited by modest increases and decreases in circulating osmolality, respectively; activation leads to AVP release and thirst.

AVP secretion is stimulated as systemic osmolality increases above a threshold level of ~285 mosmol/kg, above which there is a linear relationship between osmolality and circulating AVP (Fig. 6-1). Thirst and

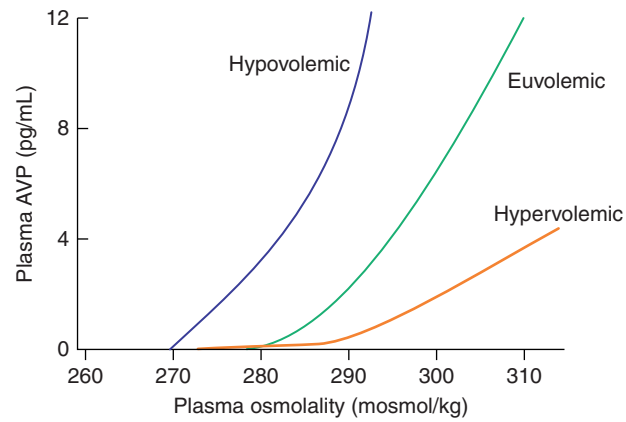


FIGURE 6-1

Circulating levels of vasopressin (AVP) in response to changes in osmolality. Plasma vasopressin becomes detectable in euvolemic, healthy individuals at a threshold of ~285 mosmol/kg, above which there is a linear relationship between osmolality and circulating AVP. The vasopressin response to osmolality is modulated strongly by volume status. The osmotic threshold is thus slightly lower in hypovolemia, with a steeper response curve; hypervolemia reduces the sensitivity of circulating AVP levels to osmolality.

thus water ingestion also are activated at ~285 mosmol/kg, beyond which there is an equivalent linear increase in the perceived intensity of thirst as a function of circulating osmolality. Changes in blood volume and blood pressure are also direct stimuli for AVP release and thirst, albeit with a less sensitive response profile. Of perhaps greater clinical relevance to the pathophysiology of water homeostasis, ECF volume strongly modulates the relationship between circulating osmolality and AVP release so that *hypovolemia* reduces the osmotic threshold and increases the slope of the response curve to osmolality; *hypervolemia* has the opposite effect, increasing the osmotic threshold and reducing the slope of the response curve (Fig. 6-1). Notably, AVP has a half-life in the circulation of only 10–20 min; thus, changes in extracellular fluid volume and/or circulating osmolality can affect water homeostasis rapidly. In addition to volume status, a number of nonosmotic stimuli have potent activating effects on osmosensitive neurons and AVP release, including nausea, intracerebral angiotensin II, serotonin, and multiple drugs.

The excretion or retention of electrolyte-free water by the kidney is modulated by circulating AVP. AVP acts on renal V_2-type receptors in the thick ascending limb of Henle and principal cells of the collecting duct (CD), increasing cyclic adenosine monophosphate (AMP) and activating protein kinase A (PKA)-dependent phosphorylation of multiple transport proteins. The AVP- and PKA-dependent activation of Na^+-Cl^- and K^+ transport by the thick ascending limb of the loop of Henle (TALH) is a key participant in the countercurrent mechanism **(Fig. 6-2)**. The countercurrent mechanism ultimately increases the interstitial osmolality in the inner medulla of the kidney, driving water absorption across the renal collecting duct. However, water, salt, and solute transport by both proximal and distal nephron segments participates in the renal concentrating mechanism (Fig. 6-2). Water transport across apical and basolateral aquaporin-1 water channels in the descending thin limb of the loop of Henle is thus involved, as is passive absorption of Na^+-Cl^- by the thin ascending limb, via apical and basolateral CLC-K1 chloride channels and paracellular Na^+ transport. Renal urea transport in turn plays important roles in the generation of the medullary osmotic gradient and the ability to excrete solute-free water under conditions of both high and low protein intake (Fig. 6-2).

AVP-induced, PKA-dependent phosphorylation of the aquaporin-2 water channel in principal cells stimulates the insertion of active water channels into the lumen of the collecting duct, resulting in transepithelial water absorption down the medullary osmotic gradient **(Fig. 6-3)**. Under antidiuretic conditions, with increased circulating AVP, the kidney reabsorbs water filtered by the glomerulus, equilibrating the osmolality across the collecting duct epithelium to excrete a

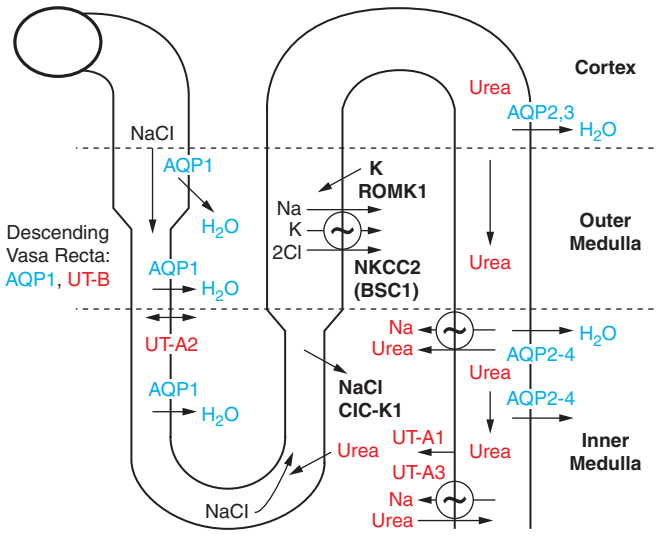


FIGURE 6-2

The renal concentrating mechanism. Water, salt, and solute transport by both proximal and distal nephron segments participates in the renal concentrating mechanism (see text for details). Diagram showing the location of the major transport proteins involved; a loop of Henle is depicted on the left, a collecting duct on the right. AQP, aquaporin; CLC-K1, chloride channel; NKCC2, Na-K-2Cl cotransporter; ROMK, renal outer medullary K^+ channel; UT, urea transporter. (*From JM Sands: J Am Soc Nephrol 13:2795, 2002; with permission.*)

hypertonic, concentrated urine (osmolality of up to 1200 mosmol/kg). In the absence of circulating AVP, insertion of aquaporin-2 channels and water absorption across the collecting duct are essentially abolished, resulting in secretion of a hypotonic, dilute urine (osmolality as low as 30–50 mosmol/kg). Abnormalities in this final common pathway are involved in most disorders of water homeostasis, e.g., a reduced or absent insertion of active aquaporin-2 water channels into the membrane of principal cells in diabetes insipidus.

Maintenance of arterial circulatory integrity

Sodium is actively pumped out of cells by the Na^+, K^+-ATPase membrane pump. In consequence, 85–90% of body Na^+ is extracellular, and the extracellular fluid volume (ECFV) is a function of total-body Na^+ content. Arterial perfusion and circulatory integrity are, in turn, determined by renal Na^+ retention or excretion, in addition to the modulation of systemic arterial resistance. Within the kidney, Na^+ is filtered by the glomeruli and then sequentially reabsorbed by the renal tubules. The Na^+ cation typically is reabsorbed with the chloride anion (Cl^-); thus, chloride homeostasis also affects the ECFV. On a quantitative level, at a glomerular filtration rate (GFR) of 180 L/d and serum Na^+ of ~140 m*M*, the kidney filters some 25,200 mmol/d of Na^+. This is equivalent to ~1.5 kg of salt, which would

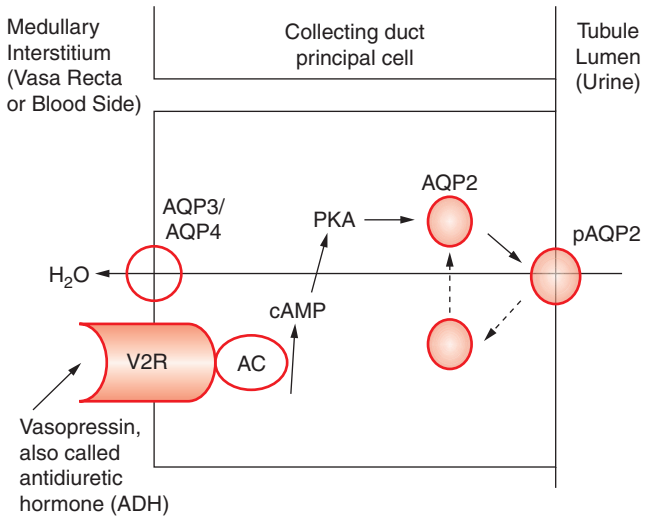


FIGURE 6-3

Vasopressin and the regulation of water permeability in the renal collecting duct. Vasopressin binds to the type 2 vasopressin receptor (V2R) on the basolateral membrane of principal cells, activates adenylyl cyclase (AC), increases intracellular cyclic adenosine monophosphatase (cAMP), and stimulates protein kinase A (PKA) activity. Cytoplasmic vesicles carrying aquaporin-2 (AQP) water channel proteins are inserted into the luminal membrane in response to vasopressin, increasing the water permeability of this membrane. When vasopressin stimulation ends, water channels are retrieved by an endocytic process and water permeability returns to its low basal rate. The AQP3 and AQP4 water channels are expressed on the basolateral membrane and complete the transcellular pathway for water reabsorption. pAQP2, phosphorylated aquaporin-2. (*From JM Sands, DG Bichet: Ann Intern Med 144:186, 2006; with permission.*)

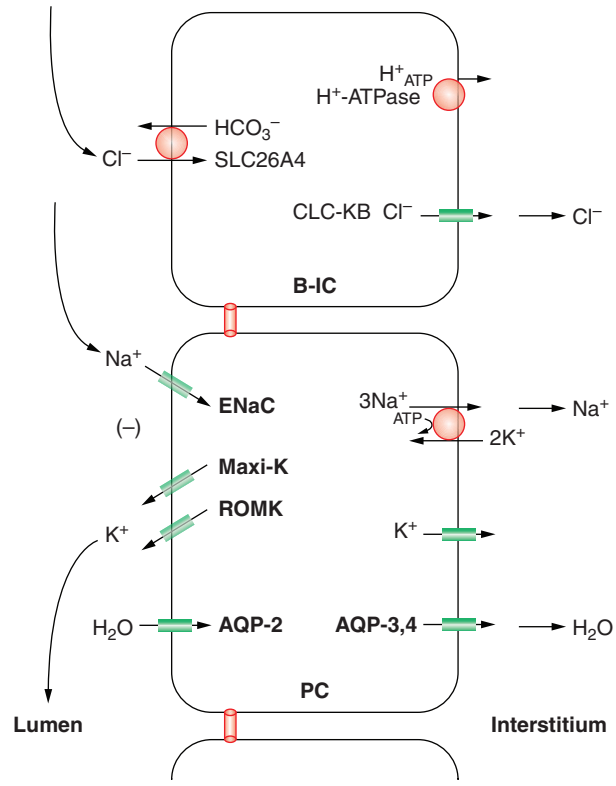


FIGURE 6-4

Sodium, water, and potassium transport in principal cells (PC) and adjacent a-intercalated cells (B-IC). The absorption of Na^+ via the amiloride-sensitive epithelial sodium channel (ENaC) generates a lumen-negative potential difference that drives K^+ excretion through the apical secretory K^+ channel ROMK (renal outer medullary K^+ channel) and/or the flow-dependent maxi-K channel. Transepithelial Cl^- transport occurs in adjacent β-intercalated cells via apical Cl^--HCO_3^- and Cl^--OH^- exchange (SLC26A4 anion exchanger, also known as pendrin) basolateral CLC chloride channels. Water is absorbed down the osmotic gradient by principal cells, through the apical aquaporin-2 (AQP-2) and basolateral aquaporin-3 and aquaporin-4 (Fig. 6-3).

occupy roughly 10 times the extracellular space; 99.6% of filtered Na^+-Cl^- must be reabsorbed to excrete 100 m*M* per day. Minute changes in renal Na^+-Cl^- excretion will thus have significant effects on the ECFV, leading to edema syndromes or hypovolemia.

Approximately two-thirds of filtered Na^+-Cl^- is reabsorbed by the renal proximal tubule via both paracellular and transcellular mechanisms. The TALH subsequently reabsorbs another 25–30% of filtered Na^+-Cl^- via the apical, furosemide-sensitive Na^+-K^+-$2Cl^-$ cotransporter. The adjacent aldosterone-sensitive distal nephron, which encompasses the distal convoluted tubule (DCT), connecting tubule (CNT), and collecting duct, accomplishes the "fine-tuning" of renal Na^+-Cl^- excretion. The thiazide-sensitive apical Na^+-Cl^- cotransporter (NCC) reabsorbs 5–10% of filtered Na^+-Cl^- in the DCT. Principal cells in the CNT and CD reabsorb Na^+ via electrogenic, amiloride-sensitive epithelial Na^+ channels (ENaC); Cl^- ions are reabsorbed primarily by adjacent intercalated cells via apical Cl^- exchange (Cl^--OH^- and Cl^--HCO_3^- exchange, mediated by the SLC26A4 anion exchanger) **(Fig. 6-4)**.

Renal tubular reabsorption of filtered Na^+-Cl^- is regulated by multiple circulating and paracrine hormones in addition to the activity of renal nerves. Angiotensin II activates proximal Na^+-Cl^- reabsorption, as do adrenergic receptors under the influence of renal sympathetic innervation; locally generated dopamine, in contrast, has a *natriuretic* effect. Aldosterone primarily activates Na^+-Cl^- reabsorption within the aldosterone-sensitive distal nephron. In particular, aldosterone activates the ENaC channel in principal cells, inducing Na^+ absorption and promoting K^+ excretion (see Fig. 6-4).

Circulatory integrity is critical for the perfusion and function of vital organs. Underfilling of the arterial circulation is sensed by ventricular and vascular pressure receptors, resulting in a neurohumoral activation (increased sympathetic tone, activation of the renin-angiotensin-aldosterone axis, and increased circulating AVP)

that synergistically increases renal Na^+-Cl^- reabsorption, vascular resistance, and renal water reabsorption. This occurs in the context of decreased cardiac output, as occurs in hypovolemic states, low-output cardiac failure, decreased oncotic pressure, and/or increased capillary permeability. Alternatively, excessive arterial vasodilation results in *relative* arterial underfilling, leading to neurohumoral activation in the defense of tissue perfusion. These physiologic responses play important roles in many of the disorders discussed in this chapter. In particular, it is important to appreciate that AVP functions in the defense of circulatory integrity, inducing vasoconstriction, increasing sympathetic nervous system tone, increasing renal retention of both water and Na^+-Cl^-, and modulating the arterial baroreceptor reflex. Most of these responses involve activation of systemic V_{1A} AVP receptors, but concomitant activation of V_2 receptors in the kidney can result in renal water retention and hyponatremia.

HYPOVOLEMIA

Etiology

True volume depletion, or hypovolemia, generally refers to a state of combined salt and water loss that leads to contraction of the ECFV. The loss of salt and water may be renal or nonrenal in origin.

Renal causes

Excessive urinary Na^+-Cl^- and water loss is a feature of several conditions. A high filtered load of endogenous solutes, such as glucose and urea, can impair tubular reabsorption of Na^+-Cl^- and water, leading to an osmotic diuresis. Exogenous mannitol, which often is used to decrease intracerebral pressure, is filtered by glomeruli but not reabsorbed by the proximal tubule, thus causing an osmotic diuresis. Pharmacologic diuretics selectively impair Na^+-Cl^- reabsorption at specific sites along the nephron, leading to increased urinary Na^+-Cl^- excretion. Other drugs can induce natriuresis as a side effect. For example, acetazolamide can inhibit proximal tubular Na^+-Cl^- absorption through its inhibition of carbonic anhydrase; other drugs, such as the antibiotics trimethoprim and pentamidine, inhibit distal tubular Na^+ reabsorption through the amiloride-sensitive ENaC channel, leading to urinary Na^+-Cl^- loss. Hereditary defects in renal transport proteins also are associated with reduced reabsorption of filtered Na^+-Cl^- and/or water. Alternatively, mineralocorticoid deficiency, mineralocorticoid resistance, or inhibition of the mineralocorticoid receptor (MLR) can reduce Na^+-Cl^- reabsorption by the aldosterone-sensitive distal nephron. Finally, tubulointerstitial injury, as occurs in interstitial nephritis, acute tubular injury, or obstructive uropathy, can reduce distal tubular Na^+-Cl^- and/or water absorption.

Excessive excretion of free water, i.e., water without electrolytes, also can lead to hypovolemia. However, the effect on ECFV is usually less marked in light of the fact that two-thirds of the water volume is lost from the ICF. Excessive renal water excretion occurs in the setting of decreased circulating AVP or renal resistance to AVP (central and nephrogenic diabetes insipidus, respectively).

Extrarenal causes

Nonrenal causes of hypovolemia include fluid loss from the gastrointestinal tract, skin, and respiratory system. Accumulations of fluid within specific tissue compartments—typically the interstitium, peritoneum, or gastrointestinal tract—also can cause hypovolemia.

Approximately 9 L of fluid enters the gastrointestinal tract daily, 2 L by ingestion and 7 L by secretion; almost 98% of this volume is absorbed so that daily fecal fluid loss is only 100–200 mL. Impaired gastrointestinal reabsorption or enhanced secretion of fluid can cause hypovolemia. Since gastric secretions have a low pH (high H^+ concentration), whereas biliary, pancreatic, and intestinal secretions are alkaline (high HCO_3^- concentration), vomiting and diarrhea often are accompanied by metabolic alkalosis and acidosis, respectively.

Evaporation of water from the skin and respiratory tract (so-called insensible losses) is the major route for loss of solute-free water, which is typically 500–650 mL/d in healthy adults. This evaporative loss can increase during febrile illness or prolonged heat exposure. Hyperventilation also can increase insensible losses via the respiratory tract, particularly in ventilated patients; the humidity of inspired air is another determining factor. In addition, increased exertion and/or ambient temperature will increase insensible losses via sweat, which is hypotonic to plasma. Profuse sweating without adequate repletion of water and Na^+-Cl^- thus can lead to both hypovolemia and hypertonicity. Alternatively, replacement of these insensible losses with a surfeit of free water without adequate replacement of electrolytes may lead to hypovolemic hyponatremia.

Excessive fluid accumulation in interstitial and/or peritoneal spaces also can cause intravascular hypovolemia. Increases in vascular permeability and/or a reduction in oncotic pressure (hypoalbuminemia) alter Starling forces, resulting in excessive "third spacing" of the ECFV. This occurs in sepsis syndrome, burns, pancreatitis, nutritional hypoalbuminemia, and peritonitis. Alternatively, distributive hypovolemia can result from accumulation of fluid within specific compartments, for example, within the bowel lumen in gastrointestinal obstruction or ileus. Hypovolemia also can occur after extracorporeal hemorrhage or after significant hemorrhage into an expandable space, for example, the retroperitoneum.

Diagnostic evaluation

A careful history usually determines the etiologic cause of hypovolemia. Symptoms of hypovolemia are nonspecific and include fatigue, weakness, thirst, and postural dizziness; more severe symptoms and signs include oliguria, cyanosis, abdominal and chest pain, and confusion or obtundation. Associated electrolyte disorders may cause additional symptoms, for example, muscle weakness in patients with hypokalemia. On examination, diminished skin turgor and dry oral mucous membranes are less than ideal markers of a decreased ECFV in adult patients; reliable signs of hypovolemia include a decreased jugular venous pressure (JVP), orthostatic tachycardia (an increase of >15–20 beats per minute upon standing), and orthostatic hypotension (a >10- to 20-mmHg drop in blood pressure on standing). More severe fluid loss leads to hypovolemic shock, with hypotension, tachycardia, peripheral vasoconstriction, and peripheral hypoperfusion; these patients may exhibit peripheral cyanosis, cold extremities, oliguria, and altered mental status.

Routine chemistries may reveal an increase in blood urea nitrogen (BUN) and creatinine, reflecting a decrease in GFR. Creatinine is the more dependable measure of GFR, since BUN levels may be influenced by an increase in tubular reabsorption (prerenal azotemia), an increase in urea generation in catabolic states, hyperalimentation, or gastrointestinal bleeding and/or a decreased urea generation in decreased protein intake. In hypovolemic shock, liver function tests and cardiac biomarkers may show evidence of hepatic and cardiac ischemia, respectively. Routine chemistries and/or blood gases may reveal evidence of acid-base disorders. For example, bicarbonate loss due to diarrheal illness is a very common cause of metabolic acidosis; alternatively, patients with severe hypovolemic shock may develop lactic acidosis with an elevated anion gap.

The neurohumoral response to hypovolemia stimulates an increase in renal tubular Na^+ and water reabsorption. Therefore, the urine Na^+ concentration is typically <20 m*M* in nonrenal causes of hypovolemia, with a urine osmolality of >450 mosmol/kg. The reduction in both GFR and distal tubular Na^+ delivery may cause a defect in renal potassium excretion, with an increase in plasma K^+ concentration. Of note, patients with hypovolemia and a hypochloremic alkalosis due to vomiting, diarrhea, or diuretics typically have a urine Na^+ concentration >20 m*M* and urine pH >7.0 due to the increase in filtered HCO_3^-; the urine Cl^- concentration in this setting is a more accurate indicator of volume status, with a level <25 m*M* suggestive of hypovolemia. The urine Na^+ concentration is often >20 m*M* in patients with *renal* causes of hypovolemia, such as acute tubular necrosis; similarly, patients with diabetes insipidus will have an inappropriately dilute urine.

TREATMENT **Hypovolemia**

The therapeutic goals in hypovolemia are to restore normovolemia and replace ongoing fluid losses. Mild hypovolemia usually can be treated with oral hydration and resumption of a normal maintenance diet. More severe hypovolemia requires intravenous hydration, with the choice of solution tailored to the underlying pathophysiology. Isotonic, "normal" saline (0.9% NaCl, 154 m*M* Na^+) is the most appropriate resuscitation fluid for normonatremic or hyponatremic patients with severe hypovolemia; colloid solutions such as intravenous albumin are not demonstrably superior for this purpose. Hypernatremic patients should receive a hypotonic solution: 5% dextrose if there has been only water loss (as in diabetes insipidus) or hypotonic saline (1/2 or 1/4 normal saline) if there has been water and Na^+-Cl^- loss. Patients with bicarbonate loss and metabolic acidosis, as occurs frequently in diarrhea, should receive intravenous bicarbonate, either an isotonic solution (150 meq of Na^+-HCO_3^- in 5% dextrose) or a more hypotonic bicarbonate solution in dextrose or dilute saline. Patients with severe hemorrhage or anemia should receive red cell transfusions without increasing the hematocrit beyond 35%.

SODIUM DISORDERS

Disorders of serum Na^+ concentration are caused by abnormalities in water homeostasis that lead to changes in the relative ratio of Na^+ to body water. Water intake and circulating AVP constitute the two key effectors in the defense of serum osmolality; defects in one or both of these defense mechanisms cause most cases of hyponatremia and hypernatremia. In contrast, abnormalities in sodium homeostasis per se lead to a deficit or surplus of whole-body Na^+-Cl^- content, a key determinant of the ECFV and circulatory integrity. Notably, volume status also modulates the release of AVP by the posterior pituitary so that hypovolemia is associated with higher circulating levels of the hormone at each level of serum osmolality. Similarly, in hypervolemic causes of arterial underfilling, e.g., heart failure and cirrhosis, the associated neurohumoral activation is associated with an increase in circulating AVP, leading to water retention and hyponatremia. Therefore, a key concept in sodium disorders is that the absolute plasma Na^+ concentration tells one nothing about the volume status of a specific patient; this must be taken into account in the diagnostic and therapeutic approach.

HYPONATREMIA

Hyponatremia, which is defined as a plasma Na^+ concentration <135 m*M*, is a very common disorder,

occurring in up to 22% of hospitalized patients. This disorder is almost always the result of an increase in circulating AVP and/or increased renal sensitivity to AVP, combined with any intake of free water; a notable exception is hyponatremia due to low solute intake (see below). The underlying pathophysiology for the exaggerated or inappropriate AVP response differs in patients with hyponatremia as a function of their ECFV. Hyponatremia thus is subdivided diagnostically into three groups, depending on clinical history and volume status: hypovolemic, euvolemic, and hypervolemic **(Fig. 6-5)**.

Hypovolemic hyponatremia

Hypovolemia causes a marked neurohumoral activation, increasing circulating levels of AVP. The increase in circulating AVP helps preserve blood pressure via vascular and baroreceptor V_{1A} receptors and increases water reabsorption via renal V_2 receptors; activation of V_2 receptors can lead to hyponatremia in the setting of increased free-water intake. Nonrenal causes of hypovolemic hyponatremia include gastrointestinal (GI) loss (vomiting, diarrhea, tube drainage, etc.) and insensible loss (sweating, burns) of Na^+-Cl^- and water in the absence of adequate oral replacement; urine Na^+ concentration is typically <20 m*M*. Notably, these patients may be clinically classified as euvolemic, with only the reduced urinary Na^+ concentration to indicate the cause of their hyponatremia. Indeed, a urine Na^+ concentration <20 m*M* in the absence of a cause of hypervolemic hyponatremia predicts a rapid increase in plasma Na^+ concentration in response to intravenous normal saline; saline induces a water diuresis in this setting, as circulating AVP levels plummet.

The *renal* causes of hypovolemic hyponatremia share an inappropriate loss of Na^+-Cl^- in the urine, leading to volume depletion and an increase in circulating AVP; urine Na^+ concentration is typically >20 m*M* (Fig. 6-5). A deficiency in circulating aldosterone and/or its renal effects can lead to hyponatremia in primary adrenal insufficiency and other causes of hypoaldosteronism; hyperkalemia and hyponatremia in a hypotensive and/or hypovolemic patient with high urine Na^+ concentration (much >20 m*M*) should strongly suggest this diagnosis. Salt-losing nephropathies may lead to hyponatremia when sodium intake is reduced due to impaired renal tubular function; typical causes include reflux nephropathy, interstitial nephropathies, post-obstructive uropathy, medullary cystic disease, and the recovery phase of acute tubular necrosis. Thiazide diuretics cause hyponatremia via a number of mechanisms, including polydipsia and diuretic-induced volume depletion. Notably, thiazides do not inhibit the renal concentrating mechanism so that circulating AVP has a maximal effect on renal water retention. In contrast, loop diuretics, which are associated less frequently with hyponatremia, inhibit Na^+-Cl^- and K^+ absorption by the TALH, blunting the countercurrent mechanism and reducing the ability to concentrate the urine. Increased excretion of an osmotically active nonreabsorbable or poorly reabsorbable solute also can lead to volume depletion and hyponatremia; important causes include glycosuria, ketonuria (e.g., in starvation or in diabetic or alcoholic ketoacidosis), and bicarbonaturia (e.g., in renal tubular

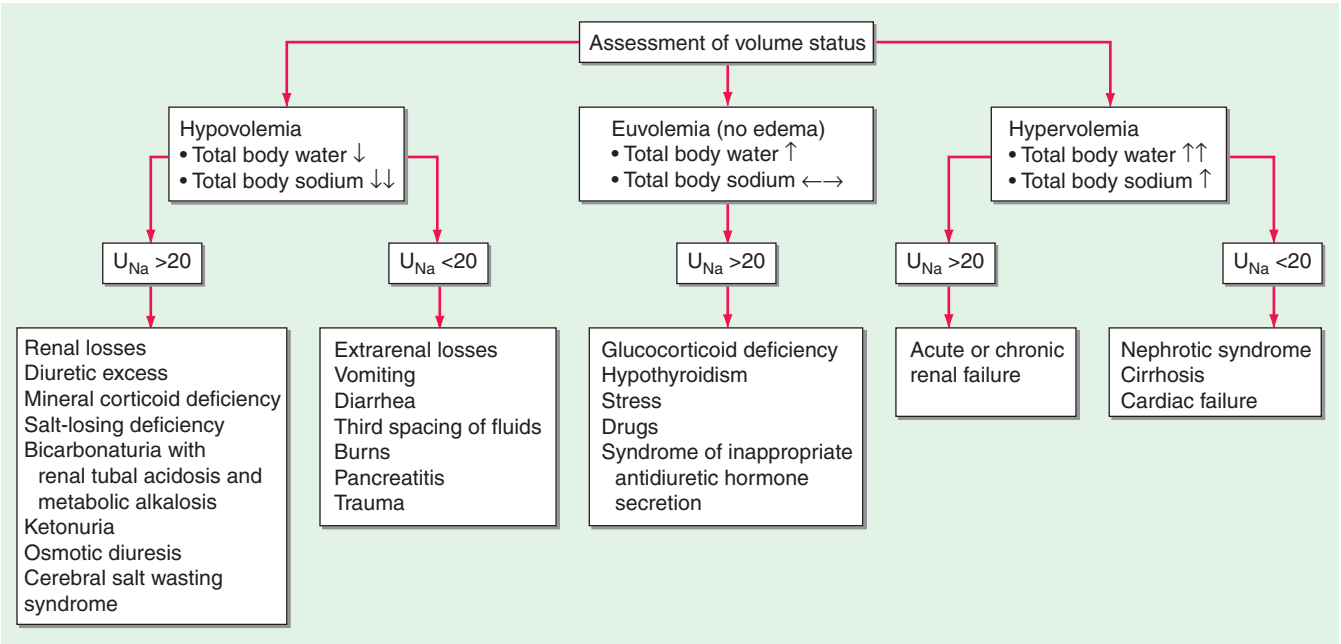


FIGURE 6-5

The diagnostic approach to hyponatremia. (*From S Kumar, T Berl: Diseases of water metabolism, in Atlas of Diseases of the Kidney, RW Schrier* [*ed*]. *Philadelphia, Current Medicine, Inc, 1999; with permission.*)

acidosis or metabolic alkalosis, in which the associated bicarbonaturia leads to loss of Na^+).

Finally, the syndrome of "cerebral salt wasting" is a rare cause of hypovolemic hyponatremia, encompassing hyponatremia with clinical hypovolemia and inappropriate natriuresis in association with intracranial disease; associated disorders include subarachnoid hemorrhage, traumatic brain injury, craniotomy, encephalitis, and meningitis. Distinction from the more common syndrome of inappropriate antidiuresis (SIAD) is critical, since cerebral salt wasting typically responds to aggressive Na^+-Cl^- repletion.

Hypervolemic hyponatremia

Patients with hypervolemic hyponatremia develop an increase in total body Na^+-Cl^- that is accompanied by a proportionately *greater* increase in total body water, leading to a reduced plasma Na^+ concentration. As in hypovolemic hyponatremia, the causative disorders can be separated by the effect on urine Na^+ concentration, with acute or chronic renal failure uniquely associated with an increase in urine Na^+ concentration (Fig. 6-5). The pathophysiology of hyponatremia in the sodium-avid edematous disorders [congestive heart failure (CHF), cirrhosis, and nephrotic syndrome] is similar to that in hypovolemic hyponatremia except that arterial filling and circulatory integrity are decreased due to the specific etiologic factors, e.g., cardiac dysfunction in CHF and peripheral vasodilation in cirrhosis. Urine Na^+ concentration is typically very low, i.e., <10 m*M*, even after hydration with normal saline; this Na^+-avid state may be obscured by diuretic therapy. The degree of hyponatremia provides an indirect index of the associated neurohumoral activation and is an important prognostic indicator in hypervolemic hyponatremia.

Euvolemic hyponatremia

Euvolemic hyponatremia can occur in moderate to severe hypothyroidism, with correction after the achievement of a euthyroid state. Severe hyponatremia also can be a consequence of secondary adrenal insufficiency due to pituitary disease; whereas the deficit in circulating aldosterone in primary adrenal insufficiency causes *hypovolemic* hyponatremia, the predominant glucocorticoid deficiency in secondary adrenal failure is associated with *euvolemic* hyponatremia. Glucocorticoids exert a negative feedback on AVP release by the posterior pituitary so that hydrocortisone replacement in these patients will rapidly normalize the AVP response to osmolality, reducing circulating AVP.

The syndrome of inappropriate antidiuresis is the most common cause of euvolemic hyponatremia **(Table 6-1)**. The generation of hyponatremia in SIAD requires an intake of free water, with persistent intake at serum osmolalities that are lower than the usual threshold for thirst; as one would expect, the osmotic threshold and osmotic response curves for the sensation of thirst are shifted downward in patients with SIAD. Four distinct patterns of AVP secretion have been recognized in patients with SIAD, independent for the most part of the underlying cause. Unregulated, erratic AVP secretion is seen in about a third of patients, with no obvious correlation between serum osmolality and circulating AVP levels. Other patients fail to suppress AVP secretion at lower serum osmolalities, with a normal response curve to hyperosmolar conditions; others have a reset osmostat, with a lower threshold osmolality and a left-shifted osmotic response curve. The fourth subset consists of patients who have essentially no detectable circulating AVP, suggesting either a gain in function in renal water reabsorption or a circulating antidiuretic substance that is distinct from AVP. Gain-in-function mutations of a single specific residue in the V^2 vasopressin receptor have been described in some of these patients, leading to constitutive activation of the receptor in the absence of AVP and a nephrogenic subset of SIAD.

Strictly speaking, patients with SIAD are not euvolemic but are subclinically volume expanded due to AVP-induced water and Na^+-Cl^- retention; vasopressin escape mechanisms invoked by sustained increases in AVP serve to limit distal renal tubular transport, preserving a modestly hypervolemic steady state. Serum uric acid is often low (<4 mg/dL) in patients with SIAD, consistent with suppressed proximal tubular transport in the setting of increased distal tubular Na^+-Cl^- and water transport; in contrast, patients with hypovolemic hyponatremia are often hyperuricemic due to a shared activation of proximal tubular Na^+-Cl^- and urate transport.

Common causes of SIAD include pulmonary disease (pneumonia, tuberculosis, pleural effusion, etc.) and central nervous system (CNS) diseases (tumor, subarachnoid hemorrhage, meningitis, etc.). SIAD also occurs with malignancies, most commonly with small cell lung carcinoma (75% of cases of malignancy-associated SIAD); ~10% of patients with this tumor will have a plasma Na^+ concentration <130 m*M* at presentation. SIAD is also a common complication of certain drugs, most commonly the selective serotonin reuptake inhibitors (SSRIs). Other drugs can potentiate the renal effect of AVP without exerting direct effects on circulating AVP levels (Table 6-1).

Low solute intake and hyponatremia

Hyponatremia occasionally can occur in patients with a very low intake of dietary solutes. Classically, this occurs in alcoholics whose sole nutrient is beer, hence the diagnostic label "beer potomania"; beer is very low in protein and salt content, containing only 1–2 millimoles of Na^+ per liter. The syndrome also has been described

TABLE 6-1

CAUSES OF THE SYNDROME OF INAPPROPRIATE ANTIDIURESIS

MALIGNANT DISEASES	PULMONARY DISORDERS	DISORDERS OF THE CENTRAL NERVOUS SYSTEM	DRUGS	OTHER CAUSES
Carcinoma	Infections	Infection	Drugs that stimulate release of AVP or enhance its action	Hereditary (gain-of-function mutations in the vasopressin V_2 receptor)
Lung	Bacterial pneumonia	Encephalitis	Chlorpropamide	Idiopathic
Small cell	Viral pneumonia	Meningitis	SSRIs	Transient
Mesothelioma	Pulmonary abscess	Brain abscess	Tricyclic antidepressants	Endurance exercise
Oropharynx	Tuberculosis	Rocky Mountain spotted fever	Clofibrate	General anesthesia
Gastrointestinal tract	Aspergillosis	AIDS	Carbamazepine	Nausea
Stomach	Asthma	Bleeding and masses	Vincristine	Pain
Duodenum	Cystic fibrosis	Subdural hematoma	Nicotine	Stress
Pancreas	Respiratory failure associated with positive-pressure breathing	Subarachnoid hemorrhage	Narcotics	
Genitourinary tract		Cerebrovascular accident	Antipsychotic drugs	
Ureter		Brain tumors	Ifosfamide	
Bladder		Head trauma	Cyclophosphamide	
Prostate		Hydrocephalus	Nonsteroidal anti-inflammatory drugs	
Endometrium		Cavernous sinus thrombosis	MDMA (ecstasy)	
Endocrine thymoma		Other	AVP analogues	
Lymphomas		Multiple sclerosis	Desmopressin	
Sarcomas		Guillain-Barré syndrome	Oxytocin	
Ewing's sarcoma		Shy-Drager syndrome	Vasopressin	
		Delerium tremens		
		Acute intermittent polyphyria		

Abbreviations: AIDS, acquired immunodeficiency syndrome; AVP, vasopressin; MDMA, 3,4-methylenedioxymethamphetamine (ecstasy); SSRI, selective serotonin reuptake inhibitor.

Source: From DH Ellison and T Berl: N Engl J Med 356:2064, 2007.

in nonalcoholic patients with highly restricted solute intake due to nutrient-restricted diets, e.g., extreme vegetarian diets. Patients with hyponatremia due to low solute intake typically present with a very low urine osmolality, <100–200 mosmol/kg, with a urine Na^+ concentration that is <10–20 m*M*. The fundamental abnormality is the inadequate dietary intake of solutes; the reduced urinary solute excretion limits water excretion so that hyponatremia ensues after relatively modest polydipsia. The ability to excrete a free-water load is thus a function of urinary solute excretion; at a urine osmolality of 80 mosmol/kg, free-water clearance is 2.7 L daily for a solute excretion of 300 mosmol/d, 5.4 L daily at 600 mosmol/d, and 8.1 L at 900 mosmol/d. AVP levels have not been reported in patients with beer potomania but are expected to be suppressed or rapidly suppressible with saline hydration; this fits with the overly rapid correction in plasma Na^+ concentration that can be seen with saline hydration. Resumption of a normal diet and/or saline hydration also will correct the causative deficit in urinary solute excretion so that patients with beer potomania typically correct their plasma Na^+ concentration promptly after admission to the hospital.

Clinical features of hyponatremia

Hyponatremia induces generalized cellular swelling, a consequence of water movement down the osmotic gradient from the hypotonic ECF to the ICF. The symptoms of hyponatremia are primarily neurologic, reflecting the development of cerebral edema within a rigid skull. The initial CNS response to acute hyponatremia is an increase in interstitial pressure, leading to shunting of ECF and solutes from the interstitial space into the cerebrospinal fluid and then into the systemic circulation. This is accompanied by an efflux of the major intracellular ions—Na^+, K^+, and Cl^-—from brain cells. Acute hyponatremic encephalopathy ensues when these volume regulatory mechanisms are overwhelmed by a rapid decrease in tonicity, resulting in acute cerebral edema. Early symptoms can include nausea, headache, and vomiting. However, severe complications can evolve rapidly, including seizure activity, brainstem

herniation, coma, and death. A key complication of acute hyponatremia is normocapnic or hypercapnic respiratory failure; the associated hypoxemia may amplify the neurologic injury. Normocapnic respiratory failure in this setting typically is due to noncardiogenic, neurogenic pulmonary edema, with a normal pulmonary capillary wedge pressure.

Acute symptomatic hyponatremia is a medical emergency that occurs in a number of specific settings (Table 6-2). Women, particularly before menopause, are much more likely to develop encephalopathy and severe neurologic sequelae. Acute hyponatremia often has an iatrogenic component, e.g., when hypotonic intravenous fluids are given to postoperative patients with an increase in circulating AVP. Exercise-associated hyponatremia, an important clinical issue at marathons and other endurance events, similarly has been linked to both a nonosmotic increase in circulating AVP and excessive free-water intake. The recreational drug ecstasy (MDMA, 3,4-methylenedioxymethamphetamine) causes a rapid and potent induction of both thirst and AVP, leading to severe acute hyponatremia.

Persistent, chronic hyponatremia results in an efflux of organic osmolytes (creatine, betaine, glutamate, myoinositol, and taurine) from brain cells; this response reduces intracellular osmolality and the osmotic gradient, favoring water entry. This reduction in intracellular osmolytes is largely complete within 48 h, the time period that clinically defines chronic hyponatremia; this temporal definition has considerable relevance for the treatment of hyponatremia (see below). The cellular response to chronic hyponatremia does not fully protect patients from symptoms, which can include vomiting, nausea, confusion, and seizures, usually at a plasma Na^+ concentration <125 m*M*. Even patients who are judged asymptomatic can manifest subtle gait and cognitive defects that reverse with correction of hyponatremia; notably, chronic asymptomatic hyponatremia increases the risk of falls. Chronic hyponatremia also increases the risk of bony fractures owing to the associated neurologic dysfunction and to a hyponatremia-associated reduction in bone density. Therefore, every attempt should be made to correct plasma Na^+ concentration safely in patients with chronic hyponatremia, even in the absence of overt symptoms (see the section on treatment of hyponatremia, later).

TABLE 6-2

CAUSES OF ACUTE HYPONATREMIA
Iatrogenic
Postoperative: premenopausal women
Hypotonic fluids with cause of ↑ vasopressin
Glycine irrigation: TURP, uterine surgery
Colonoscopy preparation
Recent institution of thiazides
Polydipsia
MDMA ingestion
Exercise induced
Multifactorial, e.g., thiazide and polydipsia

Abbreviations: MDMA, 3,4-methylenedioxymethamphetamine (ecstasy); TURP, transurethral resection of the prostate.

The management of chronic hyponatremia is complicated significantly by the asymmetry of the cellular response to correction of plasma Na^+ concentration. Specifically, the *reaccumulation* of organic osmolytes by brain cells is attenuated and delayed as osmolality increases after correction of hyponatremia, sometimes resulting in degenerative loss of oligodendrocytes and an osmotic demyelination syndrome (ODS). Overly rapid correction of hyponatremia (>8–10 m*M* in 24 h or 18 m*M* in 48 h) also is associated with a disruption in integrity of the blood-brain barrier, allowing the entry of immune mediators that may contribute to demyelination. The lesions of ODS classically affect the pons, a structure in which the delay in the reaccumulation of osmotic osmolytes is particularly pronounced; clinically, patients with central pontine myelinolysis can present one or more days after overcorrection of hyponatremia with para- or quadraparesis, dysphagia, dysarthria, diplopia, a "locked-in syndrome," and/or loss of consciousness. Other regions of the brain also can be involved in ODS, most commonly in association with lesions of the pons but occasionally in isolation; in order of frequency, the lesions of extrapontine myelinolysis can occur in the cerebellum, lateral geniculate body, thalamus, putamen, and cerebral cortex or subcortex. The clinical presentation of ODS therefore can vary as a function of the extent and localization of extrapontine myelinolysis, with the reported development of ataxia, mutism, parkinsonism, dystonia, and catatonia. Relowering of plasma Na^+ concentration after overly rapid correction can prevent or attenuate ODS (see the section on treatment of hyponatremia, later). However, even appropriately slow correction can be associated with ODS, particularly in patients with additional risk factors; these factors include alcoholism, malnutrition, hypokalemia, and liver transplantation.

Diagnostic evaluation of hyponatremia

Clinical assessment of hyponatremic patients should focus on the underlying cause; a detailed drug history is particularly crucial (Table 6-1). A careful clinical assessment of volume status is obligatory for the classical diagnostic approach to hyponatremia (Fig. 6-5). Hyponatremia is frequently multifactorial, particularly when severe; clinical evaluation should consider *all* the possible

causes for excessive circulating AVP, including volume status, drugs, and the presence of nausea and/or pain. Radiologic imaging also may be appropriate to assess whether patients have a pulmonary or CNS cause for hyponatremia. A screening chest x-ray may fail to detect a small cell carcinoma of the lung; CT scanning of the thorax should be considered in patients at high risk for this tumor, e.g., patients with a history of smoking.

Laboratory investigation should include a measurement of serum osmolality to exclude pseudohyponatremia, which is defined as the coexistence of hyponatremia with a normal or increased plasma tonicity. Most clinical laboratories measure plasma Na^+ concentration by testing diluted samples with automated ion-sensitive electrodes, correcting for this dilution by assuming that plasma is 93% water; this correction factor can be inaccurate in patients with pseudohyponatremia due to extreme hyperlipidemia and/or hyperproteinemia, in whom serum lipid or protein makes up a greater percentage of plasma volume. The measured osmolality also should be converted to the effective osmolality (tonicity) by subtracting the measured concentration of urea (divided by 2.8 if in mg/dL); patients with hyponatremia have an effective osmolality <275 mosmol/kg.

Elevated BUN and creatinine in routine chemistries also can indicate renal dysfunction as a potential cause of hyponatremia, whereas hyperkalemia may suggest adrenal insufficiency or hypoaldosteronism. Serum glucose also should be measured; plasma Na^+ concentration falls by ~1.6 to 2.4 m*M* for every 100-mg/dL increase in glucose due to glucose-induced water efflux from cells; this "true" hyponatremia resolves after correction of hyperglycemia. Measurement of serum uric acid also should be performed; whereas patients with SIAD-type physiology typically will be hypouricemic (serum uric acid <4 mg/dL), volume-depleted patients often will be hyperuricemic. In the appropriate clinical setting, thyroid, adrenal, and pituitary function should also be tested; hypothyroidism and secondary adrenal failure due to pituitary insufficiency are important causes of euvolemic hyponatremia, whereas primary adrenal failure causes hypovolemic hyponatremia. A cosyntropin stimulation test is necessary to assess for primary adrenal insufficiency.

Urine electrolytes and osmolality are crucial tests in the initial evaluation of hyponatremia. A urine Na^+ concentration <20–30 m*M* is consistent with hypovolemic hyponatremia in the clinical absence of a hypervolemic, Na^+-avid syndrome such as CHF (Fig. 6-5). In contrast, patients with SIAD typically excrete urine with a Na^+ concentration that is >30 m*M*. However, there can be substantial overlap in urine Na^+ concentration values in patients with SIAD and hypovolemic hyponatremia, particularly in the elderly; the ultimate "gold standard" for the diagnosis of hypovolemic hyponatremia is the demonstration that plasma Na^+ concentration corrects after hydration with normal saline. Patients with thiazide-associated hyponatremia also may present with a higher than expected urine Na^+ concentration and other findings suggestive of SIAD; one should defer making a diagnosis of SIAD in these patients until 1–2 weeks after discontinuation of the thiazide. A urine osmolality <100 mosmol/kg is suggestive of polydipsia; urine osmolality >400 mosmol/kg indicates that AVP excess is playing a more dominant role, whereas intermediate values are more consistent with multifactorial pathophysiology (e.g., AVP excess with a significant component of polydipsia). Patients with hyponatremia due to decreased solute intake (beer potomania) typically have urine Na^+ concentration <20 m*M* and urine osmolality in the range of <100 to the low 200s. Finally, the measurement of urine K^+ concentration is required to calculate the urine:plasma electrolyte ratio, which is useful to predict the response to fluid restriction (see the section on treatment of hyponatremia, below).

TREATMENT Hyponatremia

Three major considerations guide therapy for hyponatremia. First, the presence and/or severity of symptoms determine the urgency and goals of therapy. Patients with acute hyponatremia (Table 6-2) present with symptoms that can range from headache, nausea, and/or vomiting to seizures, obtundation, and central herniation; patients with chronic hyponatremia that is present for >48 h are less likely to have severe symptoms. Second, patients with chronic hyponatremia are at risk for ODS if plasma Na^+ concentration is corrected by >8–10 m*M* within the first 24 h and/or by >18 m*M* within the first 48 h. Third, the response to interventions such as hypertonic saline, isotonic saline, vasopressin antagonists can be highly unpredictable, so frequent monitoring of plasma Na^+ concentration during corrective therapy is imperative.

Once the urgency in correcting the plasma Na^+ concentration has been established and appropriate therapy instituted, the focus should be on treatment or withdrawal of the underlying cause. Patients with euvolemic hyponatremia due to SIAD, hypothyroidism, or secondary adrenal failure will respond to successful treatment of the underlying cause, with an increase in plasma Na^+ concentration. However, not all causes of SIAD are immediately reversible, necessitating pharmacologic therapy to increase the plasma Na^+ concentration (see below). Hypovolemic hyponatremia will respond to intravenous hydration with isotonic normal saline, with a rapid reduction in circulating AVP and a brisk water diuresis; it may be necessary to reduce the rate of correction if the history suggests that hyponatremia has been chronic, i.e., present for more than 48 h

(see below). Hypervolemic hyponatremia due to congestive heart failure often responds to improved therapy of the underlying cardiomyopathy, e.g., after the institution or intensification of angiotensin-converting enzyme (ACE) inhibition. Finally, patients with hyponatremia due to beer potomania and low solute intake respond very rapidly to intravenous saline and the resumption of a normal diet. Notably, patients with beer potomania have a very high risk of developing ODS due to the associated hypokalemia, alcoholism, and malnutrition and the high risk of overcorrecting the plasma Na^+ concentration.

Water deprivation has long been a cornerstone of therapy for chronic hyponatremia. However, patients who are excreting minimal electrolyte-free water will require aggressive fluid restriction; this can be very difficult for patients with SIAD to tolerate because their thirst is also inappropriately stimulated. The urine:plasma electrolyte ratio (urinary $[Na^+] + [K^+]$/plasma $[Na^+]$) can be exploited as a quick indicator of electrolyte-free water excretion (Table 6-3); patients with a ratio >1 should be restricted more aggressively (<500 mL/d), those with a ratio ~1 should be restricted to 500–700 mL/d, and those with a ratio <1 should be restricted to <1 L/d. In hypokalemic patients, potassium replacement will serve to increase plasma Na^+ concentration in light of the fact that the plasma Na^+ concentration is a function of both exchangeable Na^+ and exchangeable K^+ divided by total body water; a corollary is that aggressive repletion of K^+ has the potential to overcorrect the plasma Na^+ concentration even in the absence of hypertonic saline. Plasma Na^+ concentration also tends to respond to an increase in dietary solute intake, which increases the ability to excrete free water; however, the use of oral urea and/or salt tablets for this purpose is generally not practical or well tolerated.

Patients in whom therapy with fluid restriction, potassium replacement, and/or increased solute intake fails may require pharmacologic therapy to increase their plasma Na^+ concentration. Many patients with SIAD respond to combined therapy with oral furosemide, 20 mg twice a day (higher doses may be necessary in renal insufficiency), and oral salt tablets; furosemide serves to inhibit the renal countercurrent mechanism and blunt urinary concentrating ability, whereas the salt tablets counteract diuretic-associated natriuresis. Demeclocycline is a potent inhibitor of principal cells and can be utilized in patients whose Na^+ levels do not increase in response to furosemide and salt tablets. However, this agent can be associated with a reduction in GFR due to excessive natriuresis and/or direct renal toxicity; it should be avoided in cirrhotic patients in particular, who are at higher risk of nephrotoxicity due to drug accumulation.

Vasopressin antagonists (vaptans) are highly effective in treating SIAD and hypervolemic hyponatremia due to heart failure or cirrhosis, reliably increasing plasma Na^+ concentration as a result of their aquaretic effects (augmentation of free-water clearance). Most of these agents specifically antagonize the V_2 vasopressin receptor; tolvaptan is currently the only oral V_2 antagonist approved by the U.S. Food and Drug Administration. Conivaptan, the only available intravenous vaptan, is a mixed V_{1A}/V_2 antagonist with a modest risk of hypotension due to V_{1A} receptor inhibition. Therapy with vaptans must be initiated in a hospital setting, with a liberalization of fluid restriction (>2 L/d) and close monitoring of plasma Na^+ concentration. Although these agents are approved for the management of all but hypovolemic hyponatremia and acute hyponatremia, the clinical indications for them are not completely clear. Oral tolvaptan is perhaps most appropriate for the management of significant and persistent SIAD (e.g., in small cell lung carcinoma) that has not responded to water restriction and/or oral furosemide and salt tablets.

Treatment of acute symptomatic hyponatremia should include hypertonic 3% saline (513 m*M*) to acutely increase plasma Na^+ concentration by 1–2 m*M*/h to a total of 4–6 m*M*; this modest increase is typically sufficient to alleviate severe acute symptoms, after which corrective guidelines for "chronic" hyponatremia are appropriate (see below). A number of equations have been developed to estimate the required rate of hypertonic saline. The traditional approach is to calculate a

TABLE 6-3

MANAGEMENT OF HYPERNATREMIA

Water Deficit
1. Estimate total-body water (TBW): 50% of body weight in women and 60% in men 2. Calculate free-water deficit: {([Na^+]-140)/140} × TBW 3. Administer deficit over 48–72 h, without decreasing the plasma Na^+ concentration by >10 m*M*/24 h
Ongoing Water Losses
4. Calculate electrolyte-free water clearance, C_eH_2O: $C_eH_2O = \frac{V(1-[U_{Na}+U_K]/P_{Na})}{P_{Na}}$ where V is urinary volume, U_{Na} is urinary $[Na^+]$, U_K is urinary $[K^+]$, and P_{Na} is plasma $[Na^+]$
Insensible Losses
5. ~10 mL/kg per day: less if ventilated, more if febrile
TOTAL
6. Add components to determine water deficit and ongoing water loss; correct the water deficit over 48–72 h and replace daily water loss. Avoid correction of plasma $[Na^+]$ by >10 m*M*/*d*

Na^+ deficit, in which the Na^+ deficit = 0.6 × body weight × (target plasma Na^+ concentration − starting plasma Na^+ concentration), followed by a calculation of the required rate. Regardless of the method used to determine the rate of administration, the increase in plasma Na^+ concentration can be highly unpredictable during treatment with hypertonic saline due to rapid changes in the underlying physiology; plasma Na^+ concentration should be monitored every 2–4 h during treatment, with appropriate changes in therapy based on the observed rate of change. The administration of supplemental oxygen and ventilatory support is also critical in the management of patients with acute hyponatremia who develop acute pulmonary edema or hypercapnic respiratory failure. Intravenous loop diuretics will help treat acute pulmonary edema and also increase free-water excretion by interfering with the renal countercurrent multiplication system. Vasopressin antagonists do *not* have an approved role in the management of acute hyponatremia.

The rate of correction should be comparatively slow in *chronic* hyponatremia (<8–10 m*M* in the first 24 h and <18 m*M* in the first 48 h) to avoid ODS. Overcorrection of the plasma Na^+ concentration can occur when AVP levels rapidly normalize, for example, after treatment of patients with chronic hypovolemic hyponatremia with intravenous saline or after glucocorticoid replacement in patients with hypopituitarism and secondary adrenal failure. Approximately 10% of patients treated with vaptans will overcorrect; the risk is increased if water intake is not liberalized. If the plasma Na^+ concentration overcorrects after therapy—whether with hypertonic saline, isotonic saline, or a vaptan—hyponatremia can be reinduced safely or stabilized by the administration of the vasopressin *agonist* desmopressin acetate (DDAVP) and/or the administration of free water, typically intravenous D5W; the goal is to prevent or reverse the development of ODS.

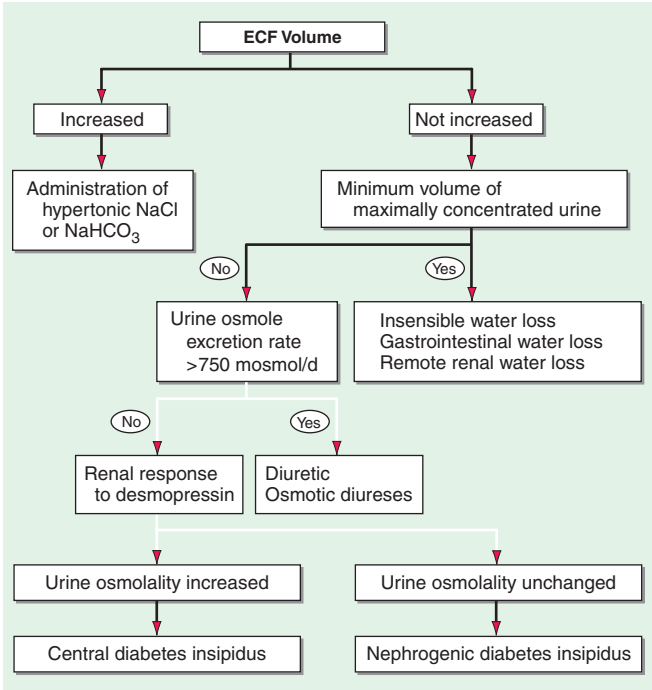


FIGURE 6-6
The diagnostic approach to hypernatremia. ECF, extracellular fluid.

HYPERNATREMIA

Etiology

Hypernatremia is defined as an increase in the plasma Na^+ concentration to >145 m*M*. Considerably less common than hyponatremia, hypernatremia nonetheless is associated with mortality rates as high as 40–60%, mostly due to the severity of the associated underlying disease processes. Hypernatremia is usually the result of a combined water and electrolyte deficit, with losses of H_2O in excess of those of Na^+. Less frequently, the ingestion or iatrogenic administration of excess Na^+ can be causative, for example, after IV administration of excessive hypertonic Na^+-Cl^- or Na^+-HCO_3^- **(Fig. 6-6)**.

Elderly individuals with reduced thirst and/or diminished access to fluids are at the highest risk of developing hypernatremia. Patients with hypernatremia may rarely have a central defect in hypothalamic osmoreceptor function, with a mixture of both decreased thirst and reduced AVP secretion. Causes of this adipsic diabetes insipidus include primary or metastatic tumor, occlusion or ligation of the anterior communicating artery, trauma, hydrocephalus, and inflammation.

Hypernatremia can develop after the loss of water via both renal and nonrenal routes. Insensible losses of water may increase in the setting of fever, exercise, heat exposure, severe burns, or mechanical ventilation. Diarrhea is the most common gastrointestinal cause of hypernatremia. Notably, osmotic diarrhea and viral gastroenteritis typically generate stools with Na^+ and K^+ <100 m*M*, thus leading to water loss and hypernatremia; in contrast, secretory diarrhea typically results in isotonic stool and thus hypovolemia with or without hypovolemic hyponatremia.

Common causes of renal water loss include osmotic diuresis secondary to hyperglycemia, excess urea, postobstructive diuresis, and mannitol; these disorders share an increase in urinary solute excretion and urinary osmolality (see "Diagnostic Approach," below). Hypernatremia due to a water diuresis occurs in central or nephrogenic diabetes insipidus (DI).

Nephrogenic DI (NDI) is characterized by renal resistance to AVP, which can be partial or complete (see "Diagnostic Approach," below). Genetic causes include loss-of-function mutations in the X-linked V_2 receptor; mutations in the AVP-responsive aquaporin-2

water channel can cause autosomal recessive and autosomal dominant nephrogenic DI, whereas recessive deficiency of the aquaporin-1 water channel causes a more modest concentrating defect (Fig. 6-2). Hypercalcemia also can cause polyuria and NDI; calcium signals directly through the calcium-sensing receptor to downregulate Na^+, K^+, and Cl^- transport by the TALH and water transport in principal cells, thus reducing renal concentrating ability in hypercalcemia. Another common acquired cause of NDI is hypokalemia, which inhibits the renal response to AVP and downregulates aquaporin-2 expression. Several drugs can cause acquired NDI, in particular lithium, ifosfamide, and several antiviral agents. Lithium causes NDI by multiple mechanisms, including direct inhibition of renal glycogen synthase kinase-3 (GSK3), a kinase thought to be the pharmacologic target of lithium in bipolar disease; GSK3 is required for the response of principal cells to AVP. The entry of lithium through the amiloride-sensitive Na^+ channel ENaC (Fig. 6-4) is required for the effect of the drug on principal cells; thus, combined therapy with lithium and amiloride can mitigate lithium-associated NDI. However, lithium causes chronic tubulointerstitial scarring and chronic kidney disease after prolonged therapy so that patients may have a persistent NDI long after stopping the drug, with a reduced therapeutic benefit from amiloride.

Finally, gestational diabetes insipidus is a rare complication of late-term pregnancy in which increased activity of a circulating placental protease with vasopressinase activity leads to reduced circulating AVP and polyuria, often accompanied by hypernatremia. DDAVP is an effective therapy for this syndrome because of its resistance to the vasopressinase enzyme.

Clinical features

Hypernatremia increases osmolality of the ECF, generating an osmotic gradient between the ECF and the ICF, an efflux of intracellular water, and cellular shrinkage. As in hyponatremia, the symptoms of hypernatremia are predominantly neurologic. Altered mental status is the most common manifestation, ranging from mild confusion and lethargy to deep coma. The sudden shrinkage of brain cells in acute hypernatremia may lead to parenchymal or subarachnoid hemorrhages and/or subdural hematomas; however, these vascular complications are encountered primarily in pediatric and neonatal patients. Osmotic damage to muscle membranes also can lead to hypernatremic rhabdomyolysis. Brain cells accommodate to a chronic increase in ECF osmolality (>48 h) by activating membrane transporters that mediate influx and intracellular accumulation of organic osmolytes (creatine, betaine, glutamate, *myo*-inositol, and taurine); this results in an increase in ICF water and normalization of brain parenchymal volume. In consequence, patients with *chronic* hypernatremia are less likely to develop severe neurologic compromise. However, the cellular response to chronic hypernatremia predisposes these patients to the development of cerebral edema and seizures during overly rapid hydration (overcorrection of plasma Na^+ concentration by >10 m*M*/d).

Diagnostic approach

The history should focus on the presence or absence of thirst, polyuria, and/or an extrarenal source for water loss, such as diarrhea. The physical examination should include a detailed neurologic exam and an assessment of the ECFV; patients with a particularly large water deficit and/or a combined deficit in electrolytes and water may be hypovolemic, with reduced JVP and orthostasis. Accurate documentation of daily fluid intake and daily urine output is also critical for the diagnosis and management of hypernatremia.

Laboratory investigation should include a measurement of serum and urine osmolality in addition to urine electrolytes. The appropriate response to hypernatremia and a serum osmolality >295 mosmol/kg is an increase in circulating AVP and the excretion of low volumes (<500 mL/d) of maximally concentrated urine, i.e., urine with osmolality >800 mosmol/kg; if this is the case, an extrarenal source of water loss is primarily responsible for the generation of hypernatremia. Many patients with hypernatremia are polyuric; if an osmotic diuresis is responsible, with excessive excretion of Na^+-Cl^-, glucose, and/or urea, solute excretion will be >750–1000 mosmol/d (>15 mosmol/kg body water per day) (Fig. 6-6). More commonly, patients with hypernatremia and polyuria will have a predominant water diuresis, with excessive excretion of hypotonic, dilute urine.

Adequate differentiation between nephrogenic and central causes of DI requires the measurement of the response in urinary osmolality to DDAVP, combined with measurement of circulating AVP in the setting of hypertonicity. By definition, patients with baseline hypernatremia are hypertonic, with an adequate stimulus for AVP by the posterior pituitary. Therefore, in contrast to polyuric patients with a normal or reduced baseline plasma Na^+ concentration and osmolality, a water deprivation test (Chap. 3) is unnecessary in hypernatremia; indeed, water deprivation is absolutely contraindicated in this setting because of the risk for worsening the hypernatremia. Patients with NDI will fail to respond to DDAVP, with a urine osmolality that increases by <50% or <150 mosmol/kg from baseline, in combination with a normal or high circulating AVP level; patients with central DI will respond to DDAVP, with a reduced circulating AVP. Patients may exhibit a partial response to DDAVP, with a >50% rise in urine osmolality that nonetheless fails to reach 800 mosmol/kg; the level of

circulating AVP will help differentiate the underlying cause, i.e., nephrogenic versus central DI. In pregnant patients, AVP assays should be drawn in tubes containing the protease inhibitor 1,10-phenanthroline to prevent in vitro degradation of AVP by placental vasopressinase.

For patients with hypernatremia due to renal loss of water it is critical to quantify *ongoing* daily losses using the calculated electrolyte-free water clearance in addition to calculation of the baseline water deficit (the relevant formulas are discussed in Table 6-3). This requires daily measurement of urine electrolytes, combined with accurate measurement of daily urine volume.

TREATMENT **Hypernatremia**

The underlying cause of hypernatremia should be withdrawn or corrected, whether it is drugs, hyperglycemia, hypercalcemia, hypokalemia, or diarrhea. The approach to the correction of hypernatremia is outlined in Table 6-3. It is imperative to correct hypernatremia slowly to avoid cerebral edema, typically replacing the calculated free-water deficit over 48 h. Notably, the plasma Na^+ concentration should be corrected by no more than 10 m*M*/d, which may take longer than 48 h in patients with severe hypernatremia (>160 m*M*). A rare exception is patients with acute hypernatremia (<48 h) due to sodium loading, who can safely be corrected rapidly at a rate of 1 m*M*/h.

Water ideally should be administered by mouth or by nasogastric tube as the most direct way to provide free water, i.e., water without electrolytes. Alternatively, patients can receive free water in dextrose-containing IV solutions such as 5% dextrose (D5W); blood glucose should be monitored to avoid hyperglycemia. Depending on the history, blood pressure, or clinical volume status, it may be appropriate to treat initially with hypotonic saline solutions (1/4 or 1/2 normal saline); normal saline is usually inappropriate in the absence of very severe hypernatremia, in which normal saline is proportionally more hypotonic relative to plasma, or frank hypotension. Calculation of urinary electrolyte-free water clearance (see Table 6-3) is required to estimate daily, ongoing loss of free water in patients with nephrogenic or central DI, which should be replenished daily.

Additional therapy may be feasible in specific cases. Patients with central DI should respond to the administration of intravenous, intranasal, or oral DDAVP. Patients with NDI due to lithium may reduce their polyuria with amiloride (2.5–10 mg/d), which decreases entry of lithium into principal cells by inhibiting ENaC (see above); in practice, however, most patients with lithium-associated DI are able to compensate for their polyuria simply by increasing their daily water intake. Thiazides may reduce polyuria due to NDI, ostensibly by inducing hypovolemia and increasing proximal tubular water reabsorption. Occasionally, nonsteroidal anti-inflammatory drugs (NSAIDs) have been used to treat polyuria associated with NDI, reducing the negative effect of intrarenal prostaglandins on urinary concentrating mechanisms; however, this creates the risk of NSAID-associated gastric and/or renal toxicity. Furthermore, it must be emphasized that thiazides, amiloride, and NSAIDs are appropriate only for *chronic* management of polyuria from NDI and have *no* role in the acute management of associated hypernatremia, in which the focus is on replacing free-water deficits and ongoing free-water loss.

POTASSIUM DISORDERS

Homeostatic mechanisms maintain plasma K^+ concentration between 3.5 and 5.0 m*M* despite marked variation in dietary K^+ intake. In a healthy individual at steady state, the entire daily intake of potassium is excreted, approximately 90% in the urine and 10% in the stool; the kidney thus plays a dominant role in potassium homeostasis. However, more than 98% of total-body potassium is intracellular, chiefly in muscle; buffering of extracellular K^+ by this large intracellular pool plays a crucial role in the regulation of plasma K^+ concentration. Changes in the exchange and distribution of intra- and extracellular K^+ thus can lead to marked hypo- or hyperkalemia. A corollary is that massive necrosis and the attendant release of tissue K^+ can cause severe hyperkalemia, particularly in the setting of acute kidney injury and reduced excretion of K^+.

Changes in whole-body K^+ content are mediated primarily by the kidney, which *reabsorbs* filtered K^+ in hypokalemic, K^+-deficient states and *secretes* K^+ in hyperkalemic, K^+-replete states. Although K^+ is transported along the entire nephron, it is the principal cells of the connecting tubule (CNT) and cortical collecting duct (CD) that play a dominant role in renal K^+ secretion, whereas alpha-intercalated cells of the outer medullary CD function in renal tubular reabsorption of filtered K^+ in K^+-deficient states. In principal cells, apical Na^+ entry via the amiloride-sensitive ENaC generates a lumen-negative potential difference that drives passive K^+ exit through apical K^+ channels (Fig. 6-4). Two major K^+ channels mediate distal tubular K^+ secretion: the secretory K^+ channel ROMK (the renal outer medullary K^+ channel, also known as Kir1.1 or KcnJ1) and the flow-sensitive maxi-K K^+ channel (also known as the BK K^+ channel). ROMK is thought to mediate the bulk of constitutive K^+ secretion, whereas increases in distal flow rate and/or genetic absence of ROMK activate K^+ secretion via the maxi-K channel.

An appreciation of the relationship between ENaC-dependent Na^+ entry and distal K^+ secretion (Fig. 6-4)

is required for the bedside interpretation of potassium disorders. For example, decreased distal delivery of Na^+, as occurs in hypovolemic, prerenal states, tends to blunt the ability to excrete K^+, leading to hyperkalemia; in contrast, an *increase* in distal delivery of Na^+ and distal flow rate, as occurs after treatment with thiazide and loop diuretics, can enhance K^+ secretion and lead to hypokalemia. Hyperkalemia is also a predictable consequence of drugs that directly inhibit ENaC due to the role of this Na^+ channel in generating a lumen-negative potential difference. Aldosterone in turn has a major influence on potassium excretion, increasing the activity of ENaC channels and thus amplifying the driving force for K^+ secretion across the luminal membrane of principal cells. Abnormalities in the renin-angiotensin-aldosterone system thus can cause both hypokalemia and hyperkalemia. Notably, however, potassium excess and potassium restriction have opposing, aldosterone-independent effects on the density and activity of apical K^+ channels in the distal nephron; i.e., other factors modulate the renal capacity to secrete K^+. In addition, potassium restriction and hypokalemia activate aldosterone-independent distal *reabsorption* of filtered K^+, activating apical H^+/K^+-ATPase activity in intercalated cells within the outer medullary CD. Reflective perhaps of this physiology, changes in plasma K^+ concentration are not universal in disorders associated with changes in aldosterone activity.

HYPOKALEMIA

Hypokalemia, defined as a plasma K^+ concentration <3.6 m*M*, occurs in up to 20% of hospitalized patients. Hypokalemia is associated with a tenfold increase in in-hospital mortality rates due to adverse effects on cardiac rhythm, blood pressure, and cardiovascular morbidity rate. Mechanistically, hypokalemia can be caused by redistribution of K^+ between tissues and the ECF or by renal and nonrenal loss of K^+ **(Table 6-4)**. Systemic hypomagnesemia also can cause treatment-resistant hypokalemia due to a combination of reduced cellular uptake of K^+ and exaggerated renal secretion. Spurious hypokalemia or pseudohypokalemia occasionally can result from in vitro cellular uptake of K^+ after venipuncture, for example, due to profound leukocytosis in acute leukemia.

Redistribution and hypokalemia

Insulin, β_2-adrenergic activity, and thyroid hormone promote Na^+,K^+-ATPase–mediated cellular uptake of K^+, leading to hypokalemia. Inhibition of passive *efflux* of K^+ also can cause hypokalemia, albeit rarely; this typically occurs in the setting of systemic inhibition of K^+ channels by toxic barium ions. Exogenous insulin can cause iatrogenic hypokalemia, particularly during

TABLE 6-4

CAUSES OF HYPOKALEMIA

- I. Decreased intake
  - A. Starvation
  - B. Clay ingestion
- II. Redistribution into cells
  - A. Acid-base
    - 1. Metabolic alkalosis
  - B. Hormonal
    - 1. Insulin
    - 2. Increased β_2-adrenergic sympathetic activity: post-myocardial infarction, head injury
    - 3. β_2-Adrenergic agonists: bronchodilators, tocolytics
    - 4. α-Adrenergic antagonists
    - 5. Thyrotoxic periodic paralysis
    - 6. Downstream stimulation of Na^+/K^+-ATPase: theophylline, caffeine
  - C. Anabolic state
    - 1. Vitamin B_{12} or folic acid administration (red blood cell production)
    - 2. Granulocyte-macrophage colony-stimulating factor (white blood cell production)
    - 3. Total parenteral nutrition
  - D. Other
    - 1. Pseudohypokalemia
    - 2. Hypothermia
    - 3. Familial hypokalemic periodic paralysis
    - 4. Barium toxicity: systemic inhibition of "leak" K^+ channels
- III. Increased loss
  - A. Nonrenal
    - 1. Gastrointestinal loss (diarrhea)
    - 2. Integumentary loss (sweat)
  - B. Renal
    - 1. Increased distal flow and distal Na^+ delivery: diuretics, osmotic diuresis, salt-wasting nephropathies
    - 2. Increased secretion of potassium
      - a. Mineralocorticoid excess: primary hyperaldosteronism [aldosterone-producing adenomas (APAs), primary or unilateral adrenal hyperplasia (PAH), idiopathic hyperaldosteronism (IHA) due to bilateral adrenal hyperplasia, and adrenal carcinoma], familial hyperaldosteronism (FH-I, FH-II, congenital adrenal hyperplasias), secondary hyperaldosteronism (malignant hypertension, renin-secreting tumors, renal artery stenosis, hypovolemia), Cushing's syndrome, Bartter's syndrome, Gitelman's syndrome
      - b. Apparent mineralocorticoid excess: genetic deficiency of 11β-dehydrogenase-2 (syndrome of apparent mineralocorticoid excess), inhibition of 11β-dehydrogenase-2 (glycyrrhetinic/glycyrrhizinic acid and/or carbenoxolone; licorice, food products, drugs), Liddle's syndrome [genetic activation of epithelial Na^+ channels (ENaC)]
      - c. Distal delivery of nonreabsorbed anions: vomiting, nasogastric suction, proximal renal tubular acidosis, diabetic ketoacidosis, glue sniffing (toluene abuse), penicillin derivatives (penicillin, nafcillin, dicloxacillin, ticarcillin, oxacillin, and carbenicillin)
    - 3. Magnesium deficiency

the management of K^+-deficient states such as diabetic ketoacidosis. Alternatively, the stimulation of *endogenous* insulin can provoke hypokalemia, hypomagnesemia, and/or hypophosphatemia in malnourished patients who are given a carbohydrate load. Alterations in the activity of the endogenous sympathetic nervous system can cause hypokalemia in several settings, including alcohol withdrawal, hyperthyroidism, acute myocardial infarction, and severe head injury. β_2 agonists, including both bronchodilators and tocolytics (ritodrine), are powerful activators of cellular K^+ uptake; "hidden" sympathomimetics such as pseudoephedrine and ephedrine in cough syrup or dieting agents also may cause unexpected hypokalemia. Finally, xanthine-dependent activation of cyclic AMP–dependent signaling downstream of the β_2 receptor can lead to hypokalemia, usually in the setting of overdose (theophylline) or marked overingestion (dietary caffeine).

Redistributive hypokalemia also can occur in the setting of hyperthyroidism, with periodic attacks of hypokalemic paralysis [thyrotoxic periodic paralysis (TPP)]. Similar episodes of hypokalemic weakness in the absence of thyroid abnormalities occur in *familial* hypokalemic periodic paralysis, usually caused by missense mutations of voltage sensor domains within the α_1 subunit of L-type calcium channels or the skeletal Na^+ channel; these mutations generate an abnormal gating pore current activated by hyperpolarization. TPP develops more frequently in patients of Asian or Hispanic origin; this shared predisposition has been linked to genetic variation in Kir2.6, a muscle-specific, thyroid hormone–responsive K^+ channel. Patients typically present with weakness of the extremities and limb girdles, with paralytic episodes that occur most frequently between 1 and 6 A.M. Signs and symptoms of hyperthyroidism are not invariably present. Hypokalemia is usually profound and almost invariably is accompanied by hypophosphatemia and hypomagnesemia. The hypokalemia in TPP is attributed to both direct and indirect activation of Na^+,K^+-ATPase, resulting in increased uptake of K^+ by muscle and other tissues. Increases in β-adrenergic activity play an important role in that high-dose propranolol (3 mg/kg) rapidly reverses the associated hypokalemia, hypophosphatemia, and paralysis.

Nonrenal loss of potassium

The loss of K^+ in sweat is typically low except under extremes of physical exertion. Direct gastric losses of K^+ due to vomiting or nasogastric suctioning are also minimal; however, the ensuing hypochloremic alkalosis results in persistent kaliuresis due to secondary hyperaldosteronism and bicarbonaturia, i.e., a *renal* loss of K^+. Intestinal loss of K^+ due to diarrhea is a globally important cause of hypokalemia in light of the worldwide prevalence of diarrheal disease. Noninfectious gastrointestinal processes such as celiac disease, ileostomy, villous adenomas, VIPomas, and chronic laxative abuse also can cause significant hypokalemia. Colonic pseudo-obstruction (Ogilvie's syndrome) can lead to hypokalemia from secretory diarrhea with an abnormally high potassium content caused by a marked activation of colonic K^+ secretion.

Renal loss of potassium

Drugs can increase renal K^+ excretion by a variety of different mechanisms. Diuretics are a particularly common cause due to associated increases in distal tubular Na^+ delivery and distal tubular flow rate in addition to secondary hyperaldosteronism. Thiazides have an effect on plasma K^+ concentration greater than that of loop diuretics despite their lesser natriuretic effect. The higher propensity of thiazides to cause hypokalemia may be secondary to thiazide-associated hypocalciuria versus the *hypercalciuria* seen with loop diuretics; increases in downstream luminal calcium in response to loop diuretics will inhibit ENaC in principal cells, thus reducing the lumen-negative potential difference and attenuating distal K^+ excretion. High doses of penicillin-related antibiotics (nafcillin, dicloxacillin, ticarcillin, oxacillin, and carbenicillin) can increase obligatory K^+ excretion by acting as nonreabsorbable anions in the distal nephron. Finally, several renal tubular toxins cause renal K^+ and magnesium wasting, leading to hypokalemia and hypomagnesemia; these drugs include aminoglycosides, amphotericin, foscarnet, cisplatin, and ifosfamide (see also "Magnesium Deficiency and Hypokalemia," later).

Aldosterone activates the ENaC channel in principal cells via multiple synergistic mechanisms, thus increasing the driving force for K^+ excretion. In consequence, increases in aldosterone bioactivity and/or gains in function of aldosterone-dependent signaling pathways are associated with hypokalemia. Increases in circulating aldosterone (hyperaldosteronism) may be primary or secondary. Increased levels of circulating renin in secondary forms of hyperaldosteronism lead to increased angiotensin II (AT-II) and thus aldosterone; renal artery stenosis is perhaps the most common cause (Table 6-4). Primary hyperaldosteronism may be genetic or acquired. Hypertension and hypokalemia due to increases in circulating 11-deoxycorticosterone occur in patients with congenital adrenal hyperplasia caused by defects in either steroid 11β-hydroxylase or steroid 17α-hydroxylase; deficient 11β-hydroxylase results in associated virilization and other signs of androgen excess, whereas reduced sex steroids in 17α-hydroxylase deficiency lead to hypogonadism. The two major forms of *isolated* primary hyperaldosteronism are familial hyperaldosteronism type I [FH-I, also known as glucocorticoid-remediable hyperaldosteronism (GRA)] and familial hyperaldosteronism type II (FH-II), in which aldosterone production is not

repressible by exogenous glucocorticoids. FH-I is caused by a chimeric gene duplication between the homologous 11β-hydroxylase (*CYP11B1*) and aldosterone synthase (*CYP11B2*) genes, fusing the adrenocorticotropic hormone (ACTH)-responsive 11β-hydroxylase promoter to the coding region of aldosterone synthase; this chimeric gene is under the control of ACTH and thus is repressible by glucocorticoids.

Acquired causes of primary hyperaldosteronism include aldosterone-producing adenomas (APAs), primary or unilateral adrenal hyperplasia (PAH), idiopathic hyperaldosteronism (IHA) due to bilateral adrenal hyperplasia, and adrenal carcinoma; APA and IHA account for close to 60% and 40%, respectively, of diagnosed cases of hyperaldosteronism. Random testing of plasma renin activity (PRA) and aldosterone is a helpful screening tool in hypokalemic and/or hypertensive patients, with an aldosterone:PRA ratio >50 suggestive of primary hyperaldosteronism.

The glucocorticoid cortisol has affinity for the mineralocorticoid receptor (MLR) equal to that of aldosterone, with resultant mineralocorticoid-like activity. However, cells in the aldosterone-sensitive distal nephron are protected from this illicit activation by the enzyme 11β-hydroxysteroid dehydrogenase-2 (11βHSD-2), which converts cortisol to cortisone; cortisone has minimal affinity for the MLR. Recessive loss-of-function mutations in the *11βHSD-2* gene thus are associated with cortisol-dependent activation of the MLR and the syndrome of apparent mineralocorticoid excess (SAME), encompassing hypertension, hypokalemia, hypercalciuria, and metabolic alkalosis, with suppressed PRA and suppressed aldosterone. A similar syndrome is caused by biochemical inhibition of 11βHSD-2 by glycyrrhetinic/glycyrrhizinic acid and/or carbenoxolone. Glycyrrhizinic acid is a natural sweetener found in licorice root, typically encountered in licorice and its many guises or as a flavoring agent in tobacco and food products.

Finally, hypokalemia may occur with systemic increases in glucocorticoids. In Cushing's syndrome caused by increases in pituitary ACTH the incidence of hypokalemia is only 10%, whereas it is 60–100% in patients with ectopic secretion of ACTH despite a similar incidence of hypertension. Indirect evidence suggests that the activity of renal 11βHSD-2 is reduced in patients with ectopic ACTH compared with Cushing's syndrome, resulting in a syndrome of apparent mineralocorticoid excess.

Finally, defects in multiple renal tubular transport pathways are associated with hypokalemia. For example, loss-of-function mutations in subunits of the acidifying H^+-ATPAse in alpha-intercalated cells cause hypokalemic distal renal tubular acidosis, as do many acquired disorders of the distal nephron. Liddle's syndrome is caused by autosomal dominant gain-in-function mutations of ENaC subunits. Disease-associated mutations either activate the channel directly or abrogate aldosterone-inhibited retrieval of ENaC subunits from the plasma membrane; the end result is increased expression of activated ENaC channels at the plasma membrane of principal cells. Patients classically manifest severe hypertension with hypokalemia that is unresponsive to spironolactone yet sensitive to amiloride. Hypertension and hypokalemia are, however, variable aspects of the Liddle's phenotype; more consistent features include a blunted aldosterone response to ACTH and reduced urinary aldosterone excretion.

Loss of the transport functions of the TALH and DCT nephron segments causes two distinct subtypes of hereditary hypokalemic alkalosis, with TALH dysfunction causing Bartter's syndrome (BS) and DCT dysfunction causing Gitelman's syndrome (GS). Patients with "classic" BS typically have polyuria and polydipsia due to the reduction in renal concentrating ability. They may have an increase in urinary calcium excretion, and 20% are hypomagnesemic. Other features include marked activation of the renin-angiotensin-aldosterone axis. Patients with "antenatal" BS have a severe systemic disorder characterized by marked electrolyte wasting, polyhydramnios, and hypercalciuria with nephrocalcinosis; renal prostaglandin synthesis and excretion are increased significantly, accounting for many of the systemic symptoms. There are five disease genes for BS, all of which function in some aspect of regulated Na^+, K^+, and Cl^- transport by the TALH. Gitelman's syndrome is, in contrast, genetically homogeneous, caused almost exclusively by loss-of-function mutations in the thiazide-sensitive Na^+-Cl^- cotransporter of the DCT. Patients with GS are uniformly hypomagnesemic and exhibit marked hypocalciuria rather than the hypercalciuria typically seen in BS; urinary calcium excretion is thus a critical diagnostic test in GS. GS has a milder phenotype than BS; however, patients with GS may suffer from chondrocalcinosis, an abnormal deposition of calcium pyrophosphate dihydrate (CPPD) in joint cartilage (Chap. 16).

Magnesium deficiency and hypokalemia

Magnesium depletion has inhibitory effects on muscle Na^+,K^+-ATPase activity, reducing influx into muscle cells and causing a secondary kaliuresis. In addition, magnesium depletion causes exaggerated K^+ secretion by the distal nephron; this is attributed to a reduction in the magnesium-dependent, intracellular block of K^+ efflux through the secretory K^+ channel of principal cells (ROMK; Fig. 6-4). Regardless of the dominant mechanism(s), hypomagnesemic patients are clinically refractory to K^+ replacement in the absence of Mg^{2+} repletion. Notably, magnesium deficiency is also a common concomitant of hypokalemia, since many disorders of the distal nephron may cause both potassium and magnesium wasting (Chap. 16).

Clinical features

Hypokalemia has prominent effects on cardiac, skeletal, and intestinal muscle cells. In particular, it is a major risk factor for both ventricular and atrial arrhythmias. Hypokalemia predisposes to digoxin toxicity by a number of mechanisms, including reduced competition between K^+ and digoxin for shared binding sites on cardiac Na^+,K^+-ATPase subunits. Electrocardiographic changes in hypokalemia include broad, flat T waves, ST depression, and QT prolongation; these are most marked when serum K^+ is <2.7 mmol/L. Hypokalemia also results in hyperpolarization of skeletal muscle, thus impairing the capacity to depolarize and contract; weakness and even paralysis may ensue. It also causes a skeletal myopathy and predisposes to rhabdomyolysis. Finally, the paralytic effects of hypokalemia on intestinal smooth muscle may cause intestinal ileus.

The functional effects of hypokalemia on the kidney include Na^+-Cl^- and HCO_3^- retention, polyuria, phosphaturia, hypocitraturia, and an activation of renal ammoniagenesis. Bicarbonate retention and other acid-base effects of hypokalemia can contribute to the generation of metabolic alkalosis. Hypokalemic polyuria is due to a combination of polydipsia and an AVP-resistant renal concentrating defect. Structural changes in the kidney due to hypokalemia include a relatively specific vacuolizing injury to proximal tubular cells, interstitial nephritis, and renal cysts. Hypokalemia also predisposes to acute kidney injury and can lead to end-stage renal disease in patients with long-standing hypokalemia due to eating disorders and/or laxative abuse.

Hypokalemia and/or reduced dietary K^+ are implicated in the pathophysiology and progression of hypertension, heart failure, and stroke. For example, short-term K^+ restriction in healthy humans and patients with essential hypertension induces Na^+-Cl^- retention and hypertension. Correction of hypokalemia is particularly important in hypertensive patients treated with diuretics, in whom blood pressure improves with the establishment of normokalemia.

Diagnostic approach

The cause of hypokalemia is usually evident from history, physical examination, and/or basic laboratory tests. The history should focus on medications (e.g., laxatives, diuretics, antibiotics), diet and dietary habits (e.g., licorice), and/or symptoms that suggest a particular cause (e.g., periodic weakness, diarrhea). The physical examination should pay particular attention to blood pressure, volume status, and signs suggestive of specific hypokalemic disorders, e.g., hyperthyroidism and Cushing's syndrome. Initial laboratory evaluation should include electrolytes, BUN, creatinine, serum osmolality, Mg^{2+}, Ca^{2+}, a complete blood count, and urinary pH **(Fig. 6-7)**.

The presence of a non-anion-gap acidosis suggests a distal, hypokalemic renal tubular acidosis or diarrhea; calculation of the urinary anion gap can help differentiate these two diagnoses. Renal K^+ excretion can be assessed with a 24-h urine collection; a 24-h K^+ excretion of <15 m*M* is indicative of an extrarenal cause of hypokalemia (Fig. 6-7). Alternatively, serum and urine osmolality can be used to calculate the transtubular K^+ gradient (TTKG), which should be <3-4 in the presence of hypokalemia (see the section on hyperkalemia in this chapter). Urine Cl^- is usually decreased in patients with hypokalemia from a nonreabsorbable anion, such as antibiotics or HCO_3^-. Other causes of chronic, hypokalemic alkalosis are surreptitious vomiting, diuretic abuse, and GS. Hypokalemic patients with bulimia thus have a urinary Cl^- <10 mmol/L; urine Na^+, K^+, and Cl^- are persistently elevated in GS due to loss of function in the thiazide-sensitive Na^+-Cl^- cotransporter but less elevated in diuretic abuse and with greater variability. Urine diuretic screens for loop diuretics and thiazides may be necessary to further exclude diuretic abuse.

Other tests, such as urinary Ca^{2+}, thyroid function tests, and/or PRA and aldosterone levels, may be appropriate in specific cases. A plasma aldosterone:PRA ratio >50 is suggestive of hyperaldosteronism. Patients with hyperaldosteronism or apparent mineralocorticoid excess may require further testing, for example, adrenal vein sampling or the clinically available tests for specific genetic causes (FH-I, SAME, Liddle's syndrome, etc.). Patients with primary aldosteronism thus should be tested for the chimeric FH-I/GRA gene (see above) if they are younger than 20 years of age or have a family history of primary aldosteronism or stroke at a young age (<40 years). Preliminary differentiation of Liddle's syndrome due to mutant ENaC channels from SAME due to mutant 11βHSD-2 (see above)—both of which cause hypokalemia and hypertension with aldosterone suppression—can be made on a clinical basis; patients with Liddle's syndrome should respond to amiloride (ENaC inhibition) but not spironolactone, whereas patients with SAME will respond to spironolactone.

TREATMENT **Hypokalemia**

The goals of therapy for hypokalemia are to prevent life-threatening and/or chronic consequences, replace the associated K^+ deficit, and correct the underlying cause and/or mitigate future hypokalemia. The urgency of therapy depends on the severity of hypokalemia, associated clinical factors (cardiac disease, digoxin therapy, etc.), and the rate of decline in serum K^+. Urgent but cautious K^+ replacement should be considered in patients with severe redistributive hypokalemia (plasma K^+ concentration <2.5 m*M*) and/or when serious complications ensue; however, this creates a risk of rebound

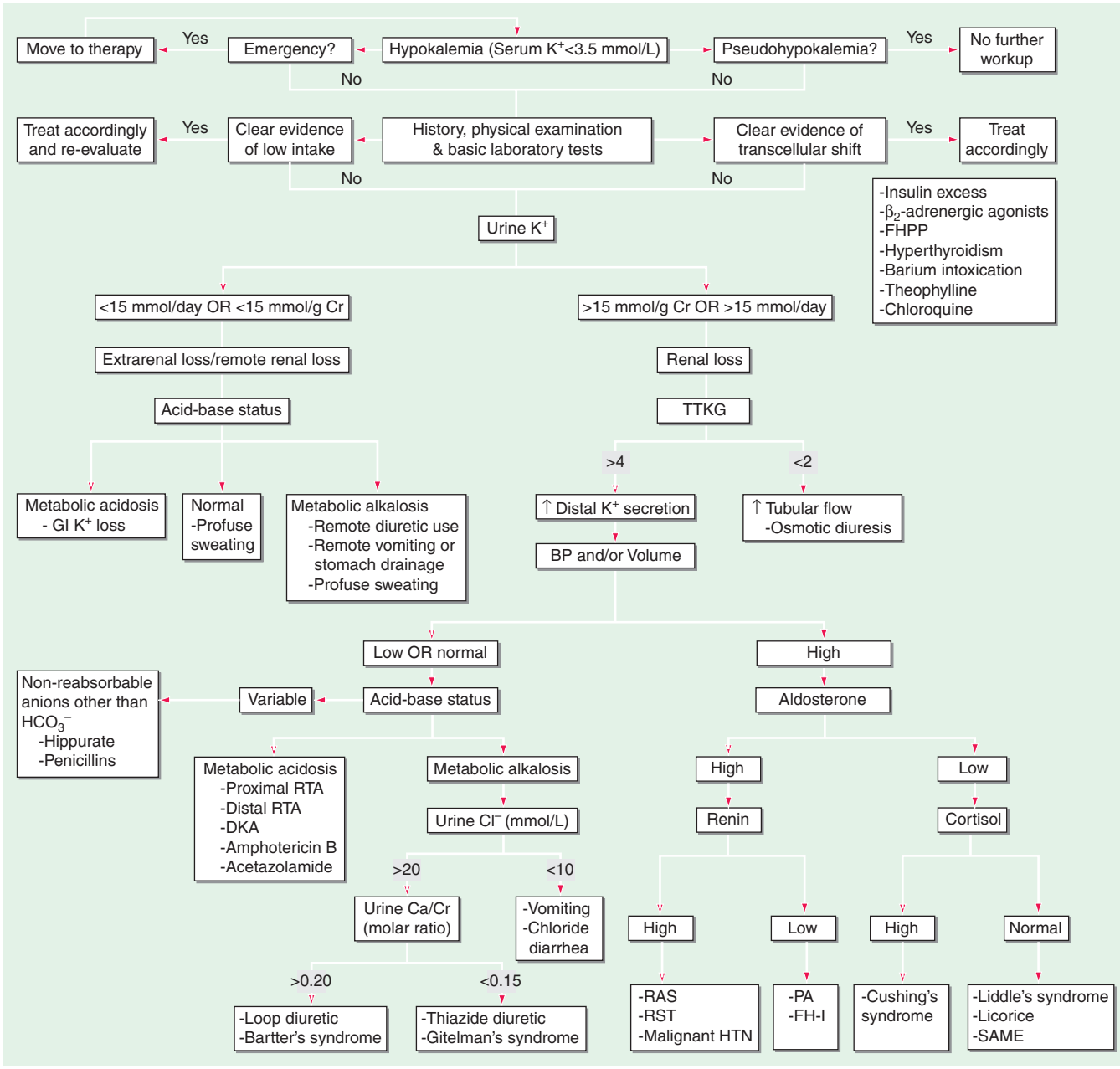


FIGURE 6-7

The diagnostic approach to hypokalemia. See text for details. BP, blood pressure; DKA, diabetic ketoacidosis; FHPP, familial hypokalemic periodic paralysis; FH-I, familial hyperaldosteronism type I; GI, gastrointestinal; HTN, hypertension; PA, primary aldosteronism; RAS, renal artery stenosis; RST, renin-secreting tumor; RTA, renal tubular acidosis; SAME, syndrome of apparent mineralocorticoid excess; TTKG, transtubular potassium gradient. (*From Mount DB, Zandi-Nejad K: Disorders of potassium balance, in Brenner and Rector's The Kidney, 8th ed, BM Brenner [ed]. Philadelphia, W.B. Saunders, 2008, pp 547-587; with permission.*)

hyperkalemia after resolution of the underlying cause. When excessive activity of the sympathetic nervous system is thought to play a dominant role in redistributive hypokalemia, as in thyrotoxic periodic paralysis, high-dose propranolol (3 mg/kg) should be considered; this nonspecific β-adrenergic blocker will correct hypokalemia without the risk of rebound hyperkalemia.

Oral replacement with K^+-Cl^- is the mainstay of therapy for hypokalemia. Potassium phosphate, oral or IV, may be appropriate in patients with combined hypokalemia and hypophosphatemia. Potassium bicarbonate or potassium citrate should be considered in patients with concomitant metabolic acidosis. Notably, hypomagnesemic patients are refractory to K^+ replacement alone, so concomitant Mg^{2+} deficiency should *always* be corrected with oral or intravenous repletion. The deficit of K^+ and the rate of correction should be estimated as accurately as possible; renal function, medications, and comorbid conditions such as diabetes should be considered to gauge the risk of overcorrection.

In the absence of abnormal K^+ redistribution, the total deficit correlates with serum K^+ so that serum K^+ drops by approximately 0.27 m*M* for every 100-mmol reduction in total-body stores; loss of 400 to 800 mmol of total-body K^+ results in a reduction in serum K^+ of approximately 2.0 m*M*. However, because of the difficulty in assessing the deficit accurately, plasma K^+ concentration must be monitored carefully during repletion.

The use of intravenous administration should be limited to patients unable to utilize the enteral route or in the setting of severe complications (paralysis, arrhythmia, etc.). Intravenous K^+-Cl^- should always be administered in saline solutions rather than dextrose since the dextrose-induced increase in insulin can acutely exacerbate hypokalemia. The peripheral intravenous dose is usually 20–40 mmol of K^+-Cl^- per liter; higher concentrations can cause localized pain from chemical phlebitis, irritation, and sclerosis. If hypokalemia is severe (<2.5 mmol/L) and/or critically symptomatic, intravenous K^+-Cl^- can be administered through a central vein with cardiac monitoring in an intensive care setting at rates of 10–20 mmol/h; higher rates should be reserved for acutely life-threatening complications. The absolute amount of administered K^+ should be restricted (e.g., 20 mmol in 100 mL of saline solution) to prevent inadvertent infusion of a large dose. Femoral veins are preferable, since infusion through internal jugular or subclavian central lines can acutely increase the local concentration of K^+ and affect cardiac conduction.

Strategies to minimize K^+ losses also should be considered. These measures may include minimizing the dose of non-K^+-sparing diuretics, restricting Na^+ intake, and using clinically appropriate combinations of non-K^+-sparing and K^+-sparing medications (e.g., loop diuretics with ACE inhibitors).

HYPERKALEMIA

Hyperkalemia is defined as a plasma potassium level of 5.5 m*M*. It occurs in up to 10% of hospitalized patients; severe hyperkalemia (>6.0 m*M*) occurs in approximately 1%, with a significantly increased risk of mortality. Although redistribution and reduced tissue uptake can acutely cause hyperkalemia, a decrease in renal K^+ excretion is the most common underlying cause **(Table 6-5)**. Excessive intake of K^+ is a rare cause because of the adaptive capacity to increase renal secretion; however, dietary intake can have a major effect in susceptible patients, e.g., diabetic patients with hyporeninemic hypoaldosteronism and chronic kidney disease. Drugs that have an impact on the renin-angiotensin-aldosterone axis are also a major cause of hyperkalemia.

TABLE 6-5

CAUSES OF HYPERKALEMIA

- I. "Pseudo" hyperkalemia
  - A. Cellular efflux: thrombocytosis, erythrocytosis, leukocytosis, in vitro hemolysis
  - B. Hereditary defects in red cell membrane transport
- II. Intra- to extracellular shift
  - A. Acidosis
  - B. Hyperosmolality; radiocontrast, hypertonic dextrose, mannitol
  - C. β-adrenergic antagonists (noncardioselective agents)
  - D. Digoxin and related glycosides (yellow oleander, foxglove, bufadienolide)
  - E. Hyperkalemic periodic paralysis
  - F. Lysine, arginine, and ε-aminocaproic acid (structurally similar, positively charged)
  - G. Succinylcholine; thermal trauma, neuromuscular injury, disuse atrophy, mucositis, or prolonged immobilization
  - H. Rapid tumor lysis
- III. Inadequate excretion
  - A. Inhibition of the renin-angiotensin-aldosterone axis; ↑ risk of hyperkalemia when used in combination
    1. Angiotensin-converting enzyme (ACE) inhibitors
    2. Renin inhibitors: aliskiren [in combination with ACE inhibitors or angiotensin receptor blockers (ARBs)]
    3. ARBs
    4. Blockade of the mineralocorticoid receptor: spironolactone, eplerenone, drospirenone
    5. Blockade of ENaC: amiloride, triamterene, trimethoprim, pentamidine, nafamostat
  - B. Decreased distal delivery
    1. Congestive heart failure
    2. Volume depletion
  - C. Hyporeninemic hypoaldosteronism
    1. Tubulointerstitial diseases: systemic lupus erythematosus (SLE), sickle cell anemia, obstructive uropathy
    2. Diabetes, diabetic nephropathy
    3. Drugs: nonsteroidal anti-inflammatory drugs, cyclooxygenase 2 (COX-2) inhibitors, beta blockers, cyclosporine, tacrolimus
    4. Chronic kidney disease, advanced age
    5. Pseudohypoaldosteronism type II: defects in WNK1 or WNK4 kinases
  - D. Renal resistance to mineralocorticoid
    1. Tubulointerstitial diseases: SLE, amyloidosis, sickle cell anemia, obstructive uropathy, post-acute tubular necrosis
    2. Hereditary: pseudohypoaldosteronism type I: defects in the mineralocorticoid receptor *or* ENaC
  - E. Advanced renal insufficiency
    1. Chronic kidney disease
    2. End-stage renal disease
    3. Acute oliguric kidney injury
  - F. Primary adrenal insufficiency
    1. Autoimmune: Addison's disease, polyglandular endocrinopathy
    2. Infectious: HIV, cytomegalovirus, tuberculosis, disseminated fungal infection
    3. Infiltrative: amyloidosis, malignancy, metastatic cancer
    4. Drug-associated: heparin, low-molecular-weight heparin
    5. Hereditary: adrenal hypoplasia congenita, congenital lipoid adrenal hyperplasia, aldosterone synthase deficiency
    6. Adrenal hemorrhage or infarction, including in antiphospholipid syndrome

Pseudohyperkalemia

Hyperkalemia should be distinguished from factitious hyperkalemia or pseudohyperkalemia, an artifactual increase in serum K^+ due to the release of K^+ during or after venipuncture. Pseudohyperkalemia can occur in the setting of excessive muscle activity during venipuncture (fist clenching, etc.), a marked increase in cellular elements (thrombocytosis, leukocytosis, and/or erythrocytosis) with in vitro efflux of K^+, and acute anxiety during venipuncture with respiratory alkalosis and redistributive hyperkalemia. Cooling of blood after venipuncture is another cause, due to reduced cellular uptake; the converse is the increased uptake of K^+ by cells at high ambient temperatures, leading to normal values for hyperkalemic patients and/or to spurious hypokalemia in normokalemic patients. Finally, there are multiple genetic subtypes of hereditary pseudohyperkalemia caused by increases in the passive K^+ permeability of erythrocytes. For example, causative mutations have been described in the red cell anion exchanger (AE1, encoded by the *SLC4A1* gene), leading to reduced red cell anion transport, hemolytic anemia, the acquisition of a novel AE1-mediated K^+ leak, and pseudohyperkalemia.

Redistribution and hyperkalemia

Several different mechanisms can induce an efflux of intracellular K^+ and hyperkalemia. Hyperkalemia due to hypertonic mannitol, hypertonic saline, and intravenous immunoglobulin generally is attributed to a "solvent drag" effect as water moves out of cells along the osmotic gradient. Diabetic patients are also prone to osmotic hyperkalemia in response to intravenous hypertonic glucose when it is given without adequate insulin. Cationic amino acids—specifically lysine, arginine, and the structurally related drug ε-aminocaproic acid—cause efflux of K^+ and hyperkalemia through an effective cation-K^+ exchange of unknown identity and mechanism. Digoxin inhibits Na^+,K^+-ATPase and impairs the uptake of K^+ by skeletal muscle so that digoxin overdose predictably results in hyperkalemia. Structurally related glycosides are found in specific plants (yellow oleander, foxglove, etc.) and in the cane toad, *Bufo marinus* (bufadienolide); ingestion of these substances and extracts from them also can cause hyperkalemia. Finally, fluoride ions also inhibit Na^+,K^+-ATPase, so fluoride poisoning is typically associated with hyperkalemia.

Succinylcholine depolarizes muscle cells, causing an efflux of K^+ through acetylcholine receptors (AChRs). The use of this agent is contraindicated in patients who have sustained thermal trauma, neuromuscular injury, disuse atrophy, mucositis, or prolonged immobilization. These disorders share a marked increase and redistribution of AChRs at the plasma membrane of muscle cells; depolarization of these upregulated AChRs by succinylcholine leads to an exaggerated efflux of K^+ through the receptor-associated cation channels, resulting in acute hyperkalemia.

Hyperkalemia due to excess intake or tissue necrosis

Increased intake of even small amounts of K^+ may provoke severe hyperkalemia in patients with predisposing factors; hence, an assessment of dietary intake is crucial. Foods rich in potassium include tomatoes, bananas, and citrus fruits; occult sources of K^+, particularly K^+-containing salt substitutes, also may contribute significantly. Iatrogenic causes include simple overreplacement with K^+-Cl^- and the administration of a potassium-containing medication (e.g., K^+-penicillin) to a susceptible patient. Red cell transfusion is a well-described cause of hyperkalemia, typically in the setting of massive transfusions. Finally, tissue necrosis, as in acute tumor lysis syndrome and rhabdomyolysis, predictably causes hyperkalemia from the release of intracellular K^+.

Hypoaldosteronism and hyperkalemia

Aldosterone release from the adrenal gland may be reduced by hyporeninemic hypoaldosteronism, medications, or primary hypoaldosteronism or by isolated deficiency of ACTH (secondary hypoaldosteronism). Primary hypoaldosteronism may be genetic or acquired but is commonly caused by autoimmunity either in Addison's disease or in the context of a polyglandular endocrinopathy. HIV has surpassed tuberculosis as the most important infectious cause of adrenal insufficiency. The adrenal involvement in HIV disease is usually subclinical; however, adrenal insufficiency may be precipitated by stress, drugs such as ketoconazole that inhibit steroidogenesis, or the acute withdrawal of steroid agents such as megestrol.

Hyporeninemic hypoaldosteronism is a very common predisposing factor in several overlapping subsets of hyperkalemic patients: diabetic patients, the elderly, and patients with renal insufficiency. Classically, these patients should have suppressed PRA and aldosterone; approximately 50% have an associated acidosis with a reduced renal excretion of NH_4^+, a positive urinary anion gap, and urine pH <5.5. Most patients are volume expanded, with secondary increases in circulating atrial natriuretic peptide (ANP) that inhibit both renal renin release and adrenal aldosterone release.

Renal disease and hyperkalemia

Chronic kidney disease and end-stage kidney disease are very common causes of hyperkalemia because of the associated deficit or absence of functioning nephrons.

Hyperkalemia is more common in oliguric acute kidney injury; distal tubular flow rate and Na^+ delivery is less of a limiting factor in nonoliguric patients. Hyperkalemia out of proportion to GFR can also be seen in the context of tubulointerstitial disease that affects the distal nephron, such as amyloidosis, sickle cell anemia, interstitial nephritis, and obstructive uropathy.

Hereditary renal causes of hyperkalemia have overlapping clinical features with hypoaldosteronism, hence the diagnostic label *pseudohypoaldosteronism* (PHA). PHA-I has both an autosomal recessive and an autosomal dominant form. The autosomal dominant form is due to loss-of-function mutations in MLR; the recessive form is caused by various combinations of mutations in the three subunits of ENaC, resulting in impaired Na^+ channel activity in principal cells and other tissues. Patients with recessive PHA-I experience lifelong salt wasting, hypotension, and hyperkalemia, whereas the phenotype of autosomal dominant PHA-I due to MLR dysfunction improves in adulthood. Pseudohypoaldosteronism type II (PHA-II, also known as hereditary hypertension with hyperkalemia) is in every respect the mirror image of GS caused by loss of function in NCC, the thiazide-sensitive Na^+-Cl^- cotransporter (see above); the clinical phenotype includes hypertension, hyperkalemia, hyperchloremic metabolic acidosis, suppressed PRA and aldosterone, hypercalciuria, and reduced bone density. PHA-II thus behaves like a gain of function in NCC, and treatment with thiazides results in resolution of the entire clinical phenotype; however, PHA-II is caused by mutations in the WNK1 and WNK4 serine-threonine kinases, which regulate NCC activity.

Medication-associated hyperkalemia

Most medications associated with hyperkalemia cause inhibition of some component of the renin-angiotensin-aldosterone axis. ACE inhibitors, angiotensin-receptor blockers, renin inhibitors, and mineralocorticoid receptors are predictable and common causes of hyperkalemia, particularly when prescribed in combination. The oral contraceptive agent Yasmin-28 contains the progestin drospirenone, which inhibits the MLR and can cause hyperkalemia in susceptible patients. Cyclosporine, tacrolimus, NSAIDs, and cyclooxygenase 2 (COX-2) inhibitors cause hyperkalemia by multiple mechanisms but share the ability to cause hyporeninemic hypoaldosteronism. Notably, most drugs that affect the renin-angiotensin-aldosterone axis also block the local adrenal response to hyperkalemia, thus attenuating the *direct* stimulation of aldosterone release by increased plasma K^+ concentration.

Inhibition of apical ENaC activity in the distal nephron by amiloride and other K^+-sparing diuretics results in hyperkalemia, often with a voltage-dependent hyperchloremic acidosis and/or hypovolemic hyponatremia. Amiloride is structurally similar to the antibiotics trimethoprim (TMP) and pentamidine, which also block ENaC; risk factors for TMP-associated hyperkalemia include the administered dose, renal insufficiency, and hyporeninemic hypoaldosteronism. Indirect inhibition of ENaC at the plasma membrane is also a cause of hyperkalemia; nafamostat, a protease inhibitor utilized in the management of pancreatitis, inhibits aldosterone-induced proteases that activate ENaC by proteolytic cleavage.

Clinical features

Hyperkalemia is a medical emergency because of its effects on the heart. Cardiac arrhythmias associated with hyperkalemia include sinus bradycardia, sinus arrest, slow idioventricular rhythms, ventricular tachycardia, ventricular fibrillation, and asystole. Mild increases in extracellular K^+ affect the repolarization phase of the cardiac action potential, resulting in changes in T-wave morphology; further increase in plasma K^+ concentration depresses intracardiac conduction, with progressive prolongation of the PR and QRS intervals. Severe hyperkalemia results in loss of the P wave and a progressive widening of the QRS complex; development of a sine-wave sinoventricular rhythm suggests impending ventricular fibrillation or asystole. Classically, the electrocardiographic manifestations in hyperkalemia progress from tall peaked T waves (5.5–6.5 m*M*), to a loss of P waves (6.5–7.5 m*M*), to a widened QRS complex (7–8 m*M*), and ultimately to a sine wave pattern (8 m*M*). However, these changes are notoriously insensitive, particularly in patients with chronic kidney disease or end-stage renal disease.

Hyperkalemia from a variety of causes can also present with ascending paralysis; this is denoted secondary hyperkalemic paralysis to differentiate it from familial hyperkalemic periodic paralysis (HYPP). The presentation may include diaphragmatic paralysis and respiratory failure. Patients with familial HYPP develop myopathic weakness during hyperkalemia induced by increased K^+ intake or rest after heavy exercise. Depolarization of skeletal muscle by hyperkalemia unmasks an inactivation defect in skeletal Na^+ channels; autosomal dominant mutations in the *SCN4A* gene encoding this channel are the predominant cause.

Within the kidney, hyperkalemia has negative effects on the ability to excrete an acid load, and so hyperkalemia per se can contribute to metabolic acidosis. This defect appears to be due in part to competition between K^+ and NH_4^+ for reabsorption by the TALH and subsequent countercurrent multiplication, ultimately reducing the medullary gradient for NH_3/NH_4 excretion by the distal nephron. Regardless of the underlying mechanism, restoration of normokalemia can in many instances correct hyperkalemic metabolic acidosis.

Diagnostic approach

The first priority in the management of hyperkalemia is to assess the need for emergency treatment, followed by a comprehensive workup to determine the cause (Fig. 6-8). History and physical examination should focus on medications, diet and dietary supplements, risk factors for kidney failure, reduction in urine output, blood pressure, and volume status. Initial laboratory tests should include electrolytes, BUN, creatinine, serum osmolality, Mg^{2+} and Ca^{2+}, a complete blood count, and urinary pH. A urine Na^+ concentration <20 m*M* indicates that distal Na^+ delivery is a limiting factor in K^+ excretion; volume repletion with 0.9% saline or treatment with furosemide may be effective in reducing plasma K^+ concentration. Serum and urine osmolality is required for calculation of the TTKG (Fig. 6-8). The expected values of the TTKG

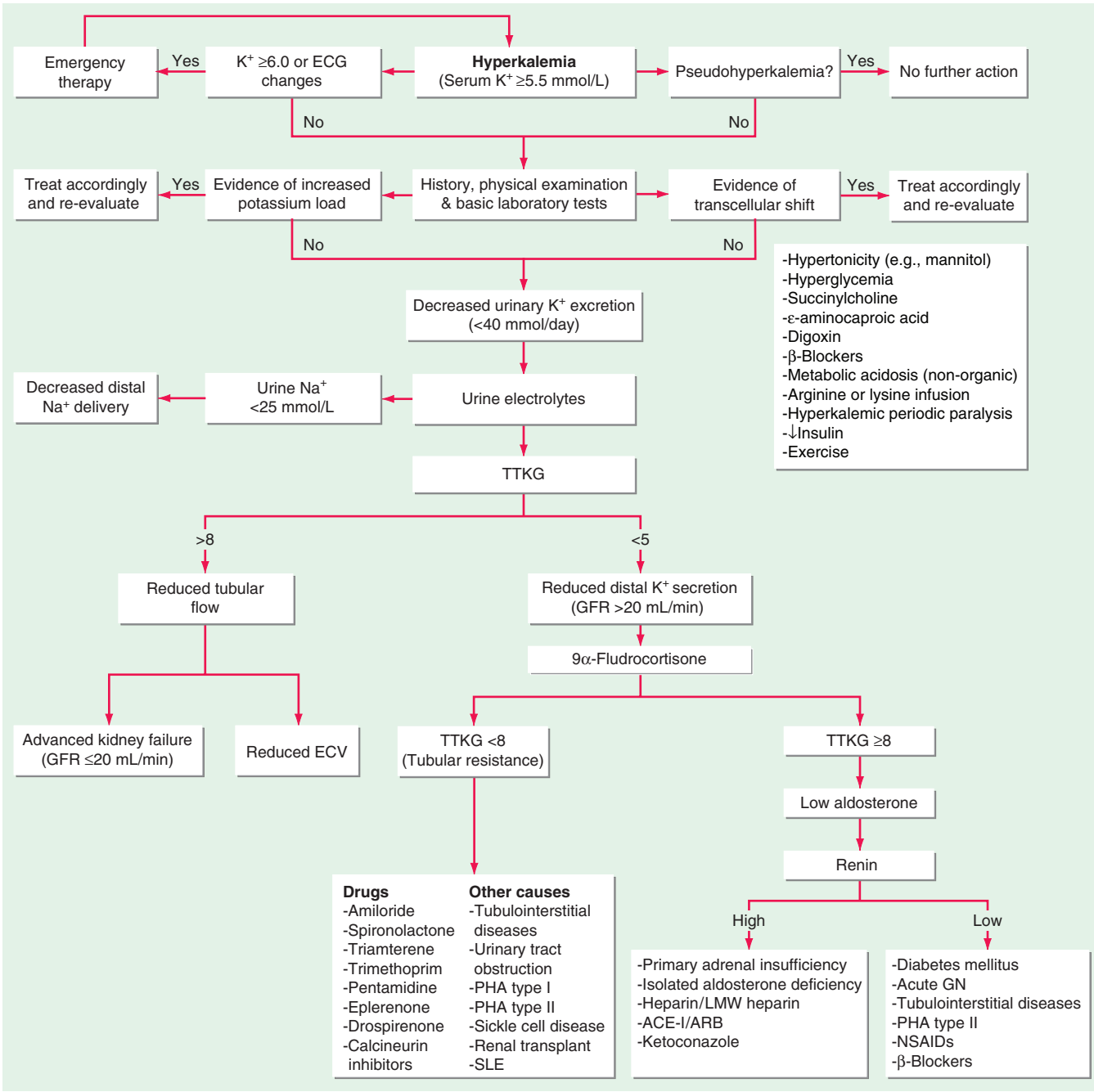


FIGURE 6-8

The diagnostic approach to hyperkalemia. See text for details. ACE-I, angiotensin-converting enzyme inhibitor; acute GN, acute glomerulonephritis; ARB, angiotensin II receptor blocker; ECG, electrocardiogram; ECV, effective circulatory volume; GFR, glomerular filtration rate; LMW heparin, low-molecular-weight heparin; NSAIDs, nonsteroidal anti-inflammatory drugs; PHA, pseudohypoaldosteronism; SLE, systemic lupus erythematosus; TTKG, transtubular potassium gradient. (*From Mount DB, Zandi-Nejad K: Disorders of potassium balance, in Brenner and Rector's The Kidney, 8th ed, BM Brenner [ed]. Philadelphia, W.B. Saunders, 2008, pp 547-587; with permission.*)

are largely based on historic data and are <3–4 in the presence of hypokalemia and >6–7 in the presence of hyperkalemia. TTKG is measured as follows:

$$\text{TTKG} = \frac{[K^+]_{\text{urine}} \quad \text{osmol}_{\text{serum}}}{[K^+]_{\text{serum}} \quad \text{osmol}_{\text{urine}}}$$

TREATMENT Hyperkalemia

Electrocardiographic manifestations of hyperkalemia should be considered a medical emergency and treated urgently. However, patients with significant hyperkalemia (plasma K^+ concentration ≥6.5–7 m*M*) in the absence of ECG changes should be aggressively managed because of the limitations of ECG changes as a predictor of cardiac toxicity. Urgent management of hyperkalemia includes admission to the hospital, continuous cardiac monitoring, and immediate treatment. The treatment of hyperkalemia is divided into three stages:

1. *Immediate antagonism of the cardiac effects of hyperkalemia*. Intravenous calcium serves to protect the heart while measures are taken to correct hyperkalemia. Calcium raises the action potential threshold and reduces excitability without changing the resting membrane potential. By restoring the difference between the resting and threshold potentials, calcium reverses the depolarization blockade caused by hyperkalemia. The recommended dose is 10 mL of 10% calcium gluconate (3–4 mL of calcium chloride), infused intravenously over 2 to 3 min with cardiac monitoring. The effect of the infusion starts in 1–3 min and lasts 30–60 min; the dose should be repeated if there is no change in ECG findings or if they recur after initial improvement. Hypercalcemia potentiates the cardiac toxicity of digoxin; hence, intravenous calcium should be used with extreme caution in patients taking this medication. If judged necessary, 10 mL of 10% calcium gluconate can be added to 100 mL of 5% dextrose in water and infused over 20–30 min to avoid acute hypercalcemia.
2. *Rapid reduction in plasma K^+ concentration by redistribution into cells*. Insulin lowers plasma K^+ concentration by shifting K^+ into cells. The recommended dose is 10 units of IV regular insulin followed immediately by 50 mL of 50% dextrose (D50W, 25 g of glucose total); the effect begins in 10–20 min, peaks at 30–60 min, and lasts 4 to 6 h. Bolus D50W without insulin is *never* appropriate because of the risk of acutely worsening hyperkalemia due to the osmotic effect of hypertonic glucose. Hypoglycemia is common with insulin plus glucose; hence, this should be followed by an infusion of 10% dextrose at 50 to 75 mL/h, with close monitoring of plasma glucose concentration. In hyperkalemic patients with glucose concentrations ≥200–250 mg/dL, insulin should be administered *without* glucose, again with close monitoring of glucose concentrations.
3. β_2-Agonists, most commonly albuterol, are effective but underutilized agents for the acute management of hyperkalemia. Albuterol and insulin with glucose have an additive effect on plasma K^+ concentration; however, ~20% of patients with end-stage renal disease are resistant to the effect of β_2-agonists; hence, these drugs should not be used without insulin. The recommended dose for inhaled albuterol is 10–20 mg of nebulized albuterol in 4 mL of normal saline, inhaled over 10 min; the effect starts at about 30 min, reaches its peak at about 90 min, and lasts 2–6 h. Hyperglycemia is a side effect, along with tachycardia; β_2-agonists should be used with caution in hyperkalemic patients with known cardiac disease.

Intravenous bicarbonate has no role in the routine treatment of hyperkalemia. It should be reserved for patients with hyperkalemia and concomitant metabolic acidosis, and only if judged appropriate for management of the acidosis. It should not be given as a hypertonic intravenous bolus in light of the risk of hypernatremia but should be infused in an isotonic or hypotonic fluid (e.g., 150 meq in 1 L of D5W).

Removal of potassium. This typically is accomplished by using cation exchange resins, diuretics, and/or dialysis. Sodium polystyrene sulfonate (SPS) exchanges Na^+ for K^+ in the gastrointestinal tract and increases the fecal excretion of K^+. The recommended dose of SPS is 15–30 g, typically given in a premade suspension with 33% sorbitol to avoid constipation. The effect of SPS on plasma K^+ concentration is slow; the full effect may take up to 24 h and usually requires repeated doses every 4–6 h. Intestinal necrosis is the most serious complication of SPS. Studies in experimental animals suggest that sorbitol is required for the intestinal injury; however, SPS crystals can often be detected in the injured human intestine, suggesting a direct role for SPS crystals in this complication. Regardless, in light of the risk of intestinal necrosis, the U.S. Food and Drug Administration has recently stated that the administration of sorbitol with SPS is no longer recommended; however, administering SPS without sorbitol might not eliminate the risk of intestinal necrosis, given the evident role for the SPS resin. Therefore, clinicians must carefully consider whether emergency treatment with SPS is necessary and appropriate for the treatment of hyperkalemia; for example, SPS is unnecessary if acute dialysis is appropriate and immediately available. If SPS is administered, the preparation should ideally not contain sorbitol. Reasonable substitutes for the laxative effect of sorbitol include lactulose and some

preparations of polyethylene glycol 3350; however, data demonstrating the efficacy and safety of these laxatives with SPS are not available. SPS should not be administered in patients at higher risk for intestinal necrosis, including postoperative patients, patients with a history of bowel obstruction, patients with slow intestinal transit, patients with ischemic bowel disease, and renal transplant patients. Loop and thiazide diuretics can be utilized to reduce plasma K^+ concentration in volume-replete or hypervolemic patients with sufficient renal function for a diuretic response. Finally, hemodialysis is the most effective and reliable method to reduce plasma K^+ concentration; peritoneal dialysis is considerably less effective. The amount of K^+ removed during hemodialysis depends on the relative distribution of K^+ between ICF and ECF (potentially affected by prior therapy for hyperkalemia), the type and surface area of the dialyzer used, dialysate and blood flow rates, dialysis duration, and the plasma to dialysate K^+ gradient.

CHAPTER 7

HYPERCALCEMIA AND HYPOCALCEMIA

Sundeep Khosla

The calcium ion plays a critical role in normal cellular function and signaling, regulating diverse physiologic processes such as neuromuscular signaling, cardiac contractility, hormone secretion, and blood coagulation. Thus, extracellular calcium concentrations are maintained within an exquisitely narrow range through a series of feedback mechanisms that involve parathyroid hormone (PTH) and the active vitamin D metabolite 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. These feedback mechanisms are orchestrated by integrating signals between the parathyroid glands, kidney, intestine, and bone **(Fig. 7-1)**.

Disorders of serum calcium concentration are relatively common and often serve as a harbinger of underlying disease. This chapter provides a brief summary of the approach to patients with altered serum calcium levels.

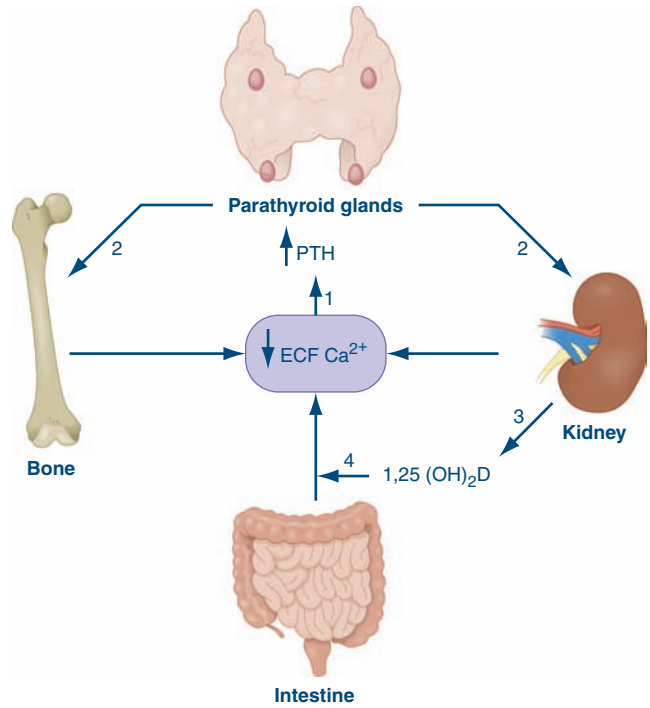


FIGURE 7-1
Feedback mechanisms maintaining extracellular calcium concentrations within a narrow, physiologic range [8.9–10.1 mg/dL (2.2–2.5 m*M*)]. A decrease in extracellular (ECF) calcium (Ca^{2+}) triggers an increase in parathyroid hormone (PTH) secretion (1) via the calcium sensor receptor on parathyroid cells. PTH, in turn, results in increased tubular reabsorption of calcium by the kidney (2) and resorption of calcium from bone (2) and also stimulates renal 1,25$(OH)_2$D production (3). 1,25$(OH)_2$D, in turn, acts principally on the intestine to increase calcium absorption (4). Collectively, these homeostatic mechanisms serve to restore serum calcium levels to normal.

HYPERCALCEMIA

ETIOLOGY

The causes of hypercalcemia can be understood and classified based on derangements in the normal feedback mechanisms that regulate serum calcium **(Table 7-1)**. Excess PTH production, which is not appropriately suppressed by increased serum calcium concentrations, occurs in primary neoplastic disorders of the parathyroid glands (parathyroid adenomas, hyperplasia, or, rarely, carcinoma) that are associated with increased parathyroid cell mass and impaired feedback inhibition by calcium. Inappropriate PTH secretion for the ambient level of serum calcium also occurs with heterozygous inactivating calcium sensor receptor (CaSR) mutations, which impair extracellular calcium sensing by the parathyroid glands and the kidneys, resulting in familial hypocalciuric hypercalcemia (FHH). Although PTH secretion by tumors is extremely rare, many solid tumors produce PTH-related peptide (PTHrP), which shares homology with PTH in the first 13 amino acids and binds the PTH receptor, thus mimicking effects of PTH on bone and the kidney. In PTHrP-mediated hypercalcemia of malignancy, PTH levels are suppressed by the high

TABLE 7-1

CAUSES OF HYPERCALCEMIA

- Excessive PTH production
  - Primary hyperparathyroidism (adenoma, hyperplasia, rarely carcinoma)
  - Tertiary hyperparathyroidism (long-term stimulation of PTH secretion in renal insufficiency)
  - Ectopic PTH secretion (very rare)
  - Inactivating mutations in the CaSR (FHH)
  - Alterations in CaSR function (lithium therapy)
- Hypercalcemia of malignancy
  - Overproduction of PTHrP (many solid tumors)
  - Lytic skeletal metastases (breast, myeloma)
- Excessive $1,25(OH)_2D$ production
  - Granulomatous diseases (sarcoidosis, tuberculosis, silicosis)
  - Lymphomas
  - Vitamin D intoxication
- Primary increase in bone resorption
  - Hyperthyroidism
  - Immobilization
- Excessive calcium intake
  - Milk-alkali syndrome
  - Total parenteral nutrition
- Other causes
  - Endocrine disorders (adrenal insufficiency, pheochromocytoma, VIPoma)
  - Medications (thiazides, vitamin A, antiestrogens)

Abbreviations: CaSR, calcium sensor receptor; FHH, familial hypocalciuric hypercalcemia; PTH, parathyroid hormone; PTHrP, PTH-related peptide.

serum calcium levels. Hypercalcemia associated with granulomatous disease (e.g., sarcoidosis) or lymphomas is caused by enhanced conversion of 25(OH)D to the potent $1,25(OH)_2D$. In these disorders, $1,25(OH)_2D$ enhances intestinal calcium absorption, resulting in hypercalcemia and suppressed PTH. Disorders that directly increase calcium mobilization from bone, such as hyperthyroidism or osteolytic metastases, also lead to hypercalcemia with suppressed PTH secretion as does exogenous calcium overload, as in milk-alkali syndrome, or total parenteral nutrition with excessive calcium supplementation.

CLINICAL MANIFESTATIONS

Mild hypercalcemia (up to 11–11.5 mg/dL) is usually asymptomatic and recognized only on routine calcium measurements. Some patients may complain of vague neuropsychiatric symptoms, including trouble concentrating, personality changes, or depression. Other presenting symptoms may include peptic ulcer disease or nephrolithiasis, and fracture risk may be increased. More severe hypercalcemia (>12–13 mg/dL), particularly if it develops acutely, may result in lethargy, stupor, or coma, as well as gastrointestinal symptoms (nausea, anorexia, constipation, or pancreatitis). Hypercalcemia decreases renal concentrating ability, which may cause polyuria and polydipsia. With long-standing hyperparathyroidism, patients may present with bone pain or pathologic fractures. Finally, hypercalcemia can result in significant electrocardiographic changes, including bradycardia, AV block, and short QT interval; changes in serum calcium can be monitored by following the QT interval.

DIAGNOSTIC APPROACH

The first step in the diagnostic evaluation of hyper- or hypocalcemia is to ensure that the alteration in serum calcium levels is not due to abnormal albumin concentrations. About 50% of total calcium is ionized, and the rest is bound principally to albumin. Although direct measurements of ionized calcium are possible, they are easily influenced by collection methods and other artifacts; thus, it is generally preferable to measure total calcium and albumin to "correct" the serum calcium. When serum albumin concentrations are reduced, a corrected calcium concentration is calculated by adding 0.2 m*M* (0.8 mg/dL) to the total calcium level for every decrement in serum albumin of 1.0 g/dL below the reference value of 4.1 g/dL for albumin, and, conversely, for elevations in serum albumin.

A detailed history may provide important clues regarding the etiology of the hypercalcemia (Table 7-1). Chronic hypercalcemia is most commonly caused by primary hyperparathyroidism, as opposed to the second most common etiology of hypercalcemia, an underlying malignancy. The history should include medication use, previous neck surgery, and systemic symptoms suggestive of sarcoidosis or lymphoma.

Once true hypercalcemia is established, the second most important laboratory test in the diagnostic evaluation is a PTH level using a two-site assay for the intact hormone. Increases in PTH are often accompanied by hypophosphatemia. In addition, serum creatinine should be measured to assess renal function; hypercalcemia may impair renal function, and renal clearance of PTH may be altered depending on the fragments detected by the assay. If the PTH level is increased (or "inappropriately normal") in the setting of elevated calcium and low phosphorus, the diagnosis is almost always primary hyperparathyroidism. Because individuals with familial hypocalciuric hypercalcemia (FHH) may also present with mildly elevated PTH levels and hypercalcemia, this diagnosis should be considered and excluded because parathyroid surgery is ineffective in this condition. A calcium/creatinine clearance ratio (calculated as urine calcium/serum calcium divided by urine creatinine/serum creatinine) of <0.01 is suggestive of FHH, particularly when there is a family history of mild, asymptomatic hypercalcemia. In addition, a number of

laboratories are now offering sequence analysis of the CaSR gene for the definitive diagnosis of FHH. Ectopic PTH secretion is extremely rare.

A suppressed PTH level in the face of hypercalcemia is consistent with non-parathyroid-mediated hypercalcemia, most often due to underlying malignancy. Although a tumor that causes hypercalcemia is generally overt, a PTHrP level may be needed to establish the diagnosis of hypercalcemia of malignancy. Serum $1,25(OH)_2D$ levels are increased in granulomatous disorders, and clinical evaluation in combination with laboratory testing will generally provide a diagnosis for the various disorders listed in Table 7-1.

TREATMENT Hypercalcemia

Mild, asymptomatic hypercalcemia does not require immediate therapy, and management should be dictated by the underlying diagnosis. By contrast, significant, symptomatic hypercalcemia usually requires therapeutic intervention independent of the etiology of hypercalcemia. Initial therapy of significant hypercalcemia begins with volume expansion because hypercalcemia invariably leads to dehydration; 4–6 L of intravenous saline may be required over the first 24 h, keeping in mind that underlying comorbidities (e.g., congestive heart failure) may require the use of loop diuretics to enhance sodium and calcium excretion. However, loop diuretics should not be initiated until the volume status has been restored to normal. If there is increased calcium mobilization from bone (as in malignancy or severe hyperparathyroidism), drugs that inhibit bone resorption should be considered. Zoledronic acid (e.g., 4 mg intravenously over ~30 min), pamidronate (e.g., 60–90 mg intravenously over 2–4 h), and etidronate (e.g., 7.5 mg/kg per day for 3–7 consecutive days) are approved by the U.S. Food and Drug Administration for the treatment of hypercalcemia of malignancy in adults. Onset of action is within 1–3 days, with normalization of serum calcium levels occurring in 60–90% of patients. Bisphosphonate infusions may need to be repeated if hypercalcemia relapses. Because of their effectiveness, bisphosphonates have replaced calcitonin or plicamycin, which are rarely used in current practice for the management of hypercalcemia. In rare instances, dialysis may be necessary. Finally, while intravenous phosphate chelates calcium and decreases serum calcium levels, this therapy can be toxic because calcium-phosphate complexes may deposit in tissues and cause extensive organ damage.

In patients with $1,25(OH)_2D$-mediated hypercalcemia, glucocorticoids are the preferred therapy, as they decrease $1,25(OH)_2D$ production. Intravenous hydrocortisone (100–300 mg daily) or oral prednisone (40–60 mg daily) for 3–7 days are used most often. Other drugs, such as ketoconazole, chloroquine, and hydroxychloroquine, may also decrease $1,25(OH)_2D$ production and are used occasionally.

HYPOCALCEMIA

ETIOLOGY

The causes of hypocalcemia can be differentiated according to whether serum PTH levels are low (hypoparathyroidism) or high (secondary hyperparathyroidism). Although there are many potential causes of hypocalcemia, impaired PTH or vitamin D production are the most common etiologies **(Table 7-2)**. Because PTH is the main defense against hypocalcemia, disorders associated with deficient PTH production or secretion may be

TABLE 7-2
CAUSES OF HYPOCALCEMIA

Low Parathyroid Hormone Levels (Hypoparathyroidism)
Parathyroid agenesis
Isolated
DiGeorge syndrome
Parathyroid destruction
Surgical
Radiation
Infiltration by metastases or systemic diseases
Autoimmune
Reduced parathyroid function
Hypomagnesemia
Activating CaSR mutations
High Parathyroid Hormone Levels (Secondary Hyperparathyroidism)
Vitamin D deficiency or impaired $1,25(OH)_2D$ production/action
Nutritional vitamin D deficiency (poor intake or absorption)
Renal insufficiency with impaired $1,25(OH)_2D$ production
Vitamin D resistance, including receptor defects
Parathyroid hormone resistance syndromes
PTH receptor mutations
Pseudohypoparathyroidism (G protein mutations)
Drugs
Calcium chelators
Inhibitors of bone resorption (bisphosphonates, plicamycin)
Altered vitamin D metabolism (phenytoin, ketoconazole)
Miscellaneous causes
Acute pancreatitis
Acute rhabdomyolysis
Hungry bone syndrome after parathyroidectomy
Osteoblastic metastases with marked stimulation of bone formation (prostate cancer)

Abbreviations: CaSR, calcium sensor receptor; PTH, parathyroid hormone.

associated with profound, life-threatening hypocalcemia. In adults, hypoparathyroidism most commonly results from inadvertent damage to all four glands during thyroid or parathyroid gland surgery. Hypoparathyroidism is a cardinal feature of autoimmune endocrinopathies; rarely, it may be associated with infiltrative diseases such as sarcoidosis. Impaired PTH secretion may be secondary to magnesium deficiency or to activating mutations in the CaSR, which suppress PTH, leading to effects that are opposite to those that occur in FHH.

Vitamin D deficiency, impaired $1,25(OH)_2D$ production (primarily secondary to renal insufficiency), or vitamin D resistance also cause hypocalcemia. However, the degree of hypocalcemia in these disorders is generally not as severe as that seen with hypoparathyroidism because the parathyroids are capable of mounting a compensatory increase in PTH secretion. Hypocalcemia may also occur in conditions associated with severe tissue injury such as burns, rhabdomyolysis, tumor lysis, or pancreatitis. The cause of hypocalcemia in these settings may include a combination of low albumin, hyperphosphatemia, tissue deposition of calcium, and impaired PTH secretion.

CLINICAL MANIFESTATIONS

Patients with hypocalcemia may be asymptomatic if the decreases in serum calcium are relatively mild and chronic, or they may present with life-threatening complications. Moderate to severe hypocalcemia is associated with paresthesias, usually of the fingers, toes, and circumoral regions, and is caused by increased neuromuscular irritability. On physical examination, a Chvostek's sign (twitching of the circumoral muscles in response to gentle tapping of the facial nerve just anterior to the ear) may be elicited, although it is also present in ~10% of normal individuals. Carpal spasm may be induced by inflation of a blood pressure cuff to 20 mmHg above the patient's systolic blood pressure for 3 min (Trousseau's sign). Severe hypocalcemia can induce seizures, carpopedal spasm, bronchospasm, laryngospasm, and prolongation of the QT interval.

DIAGNOSTIC APPROACH

In addition to measuring serum calcium, it is useful to determine albumin, phosphorus, and magnesium levels. As for the evaluation of hypercalcemia, determining the PTH level is central to the evaluation of hypocalcemia. A suppressed (or "inappropriately low") PTH level in the setting of hypocalcemia establishes absent or reduced PTH secretion (hypoparathyroidism) as the cause of the hypocalcemia. Further history will often elicit the underlying cause (i.e., parathyroid agenesis vs. destruction). By contrast, an elevated PTH level (secondary hyperparathyroidism) should direct attention to the vitamin D axis as the cause of the hypocalcemia. Nutritional vitamin D deficiency is best assessed by obtaining serum 25-hydroxyvitamin D levels, which reflect vitamin D stores. In the setting of renal insufficiency or suspected vitamin D resistance, serum $1,25(OH)_2D$ levels are informative.

TREATMENT Hypocalcemia

The approach to treatment depends on the severity of the hypocalcemia, the rapidity with which it develops, and the accompanying complications (e.g., seizures, laryngospasm). Acute, symptomatic hypocalcemia is initially managed with calcium gluconate, 10 mL 10% wt/vol (90 mg or 2.2 mmol) intravenously, diluted in 50 mL of 5% dextrose or 0.9% sodium chloride, given intravenously over 5 min. Continuing hypocalcemia often requires a constant intravenous infusion (typically 10 ampuls of calcium gluconate or 900 mg of calcium in 1 L of 5% dextrose or 0.9% sodium chloride administered over 24 h). Accompanying hypomagnesemia, if present, should be treated with appropriate magnesium supplementation.

Chronic hypocalcemia due to hypoparathyroidism is treated with calcium supplements (1000–1500 mg/d elemental calcium in divided doses) and either vitamin D_2 or D_3 (25,000–100,000 U daily) or calcitriol [$1,25(OH)_2D$, 0.25–2 μg/d]. Other vitamin D metabolites (dihydrotachysterol, alfacalcidiol) are now used less frequently. Vitamin D deficiency, however, is best treated using vitamin D supplementation, with the dose depending on the severity of the deficit and the underlying cause. Thus, nutritional vitamin D deficiency generally responds to relatively low doses of vitamin D (50,000 U, 2–3 times per week for several months), while vitamin D deficiency due to malabsorption may require much higher doses (100,000 U/d or more). The treatment goal is to bring serum calcium into the low normal range and to avoid hypercalciuria, which may lead to nephrolithiasis.

CHAPTER 8

HYPERURICEMIA AND GOUT

Christopher M. Burns ■ Robert L. Wortmann ■ H. Ralph Schumacher ■ Lan X. Chen

Purines (adenine and guanine) and pyrimidines (cytosine, thymine, uracil) serve fundamental roles in the replication of genetic material, gene transcription, protein synthesis, and cellular metabolism. Disorders that involve abnormalities of nucleotide metabolism range from relatively common diseases such as hyperuricemia and gout, in which there is increased production or impaired excretion of a metabolic end product of purine metabolism (uric acid), to rare enzyme deficiencies that affect purine and pyrimidine synthesis or degradation. Understanding these biochemical pathways has led, in some instances, to the development of specific forms of treatment, such as the use of allopurinol, to reduce uric acid production.

URIC ACID METABOLISM

Uric acid is the final breakdown product of purine degradation in humans. It is a weak acid with pK_as of 5.75 and 10.3. Urates, the ionized forms of uric acid, predominate in plasma extracellular fluid and synovial fluid, with ~98% existing as monosodium urate at pH 7.4.

Plasma is saturated with monosodium urate at a concentration of 405 µmol/L (6.8 mg/dL) at 37°C. At higher concentrations, plasma is therefore supersaturated, creating the potential for urate crystal precipitation. However, plasma urate concentrations can reach 4800 µmol/L (80 mg/dL) without precipitation, perhaps because of the presence of solubilizing substances.

The pH of urine greatly influences the solubility of uric acid. At pH 5.0, urine is saturated with uric acid at concentrations ranging from 360 to 900 µmol/L (6–15 mg/dL). At pH 7, saturation is reached at concentrations between 9480 and 12,000 µmol/L (158 and 200 mg/dL). Ionized forms of uric acid in urine include mono- and disodium, potassium, ammonium, and calcium urates.

Although purine nucleotides are synthesized and degraded in all tissues, urate is produced only in tissues that contain xanthine oxidase, primarily the liver and small intestine. Urate production varies with the purine content of the diet and the rates of purine biosynthesis, degradation, and salvage **(Fig. 8-1)**. Normally, two-thirds to three-fourths of urate is excreted by the kidneys, and most of the remainder is eliminated through the intestines.

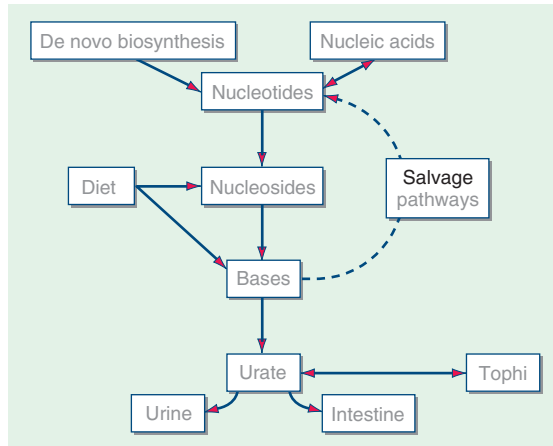


FIGURE 8-1
The total-body urate pool is the net result between urate production and excretion. Urate production is influenced by dietary intake of purines and the rates of de novo biosynthesis of purines from nonpurine precursors, nucleic acid turnover, and salvage by phosphoribosyltransferase activities. The formed urate is normally excreted by urinary and intestinal routes. Hyperuricemia can result from increased production, decreased excretion, or a combination of both mechanisms. When hyperuricemia exists, urate can precipitate and deposit in tissues as tophi.

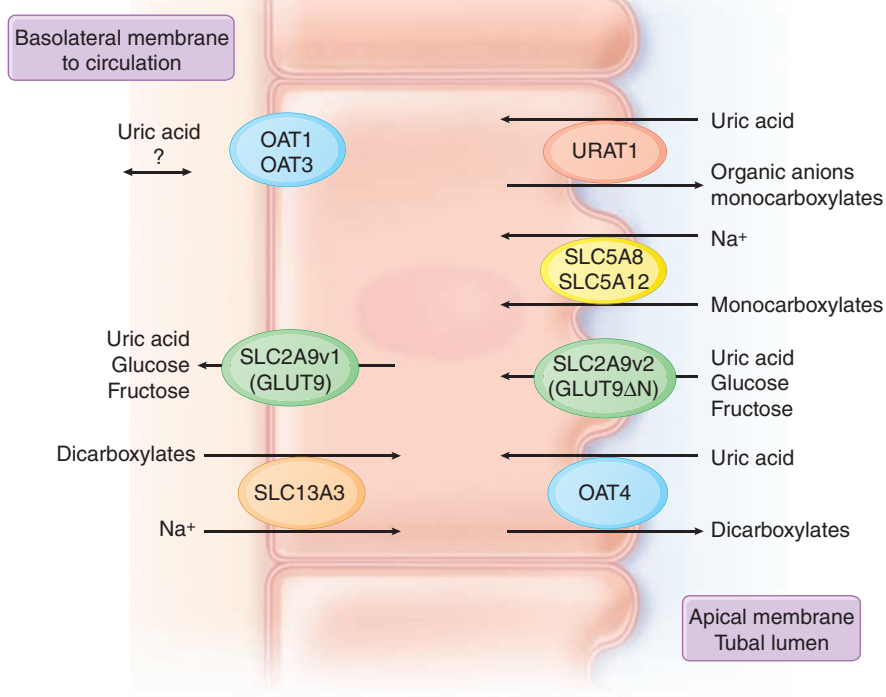


FIGURE 8-2
Schematic for handling of uric acid by the kidney. A complex interplay of transporters on both the apical and basolateral aspects of the renal tubule epithelial cell is involved in the reabsorption of uric acid. Please see text for details. Most uricosuric compounds inhibit URAT1 on the apical side, as well as OAT1, OAT3, and GLUT9 on the basolateral side.

The kidneys clear urate from the plasma and maintain physiologic balance by utilizing specific organic anion transporters (OATs), including urate transporter 1 (URAT1) and human uric acid transporter (hUAT) **(Fig. 8-2)**. URAT1 and other OATs carry urate into the tubular cells from the apical side of the lumen. Once inside the cell, urate must pass to the basolateral side of the lumen in a process controlled by the voltage-dependent carrier hUAT. Until recently, a four-component model has been used to describe the renal handling of urate/uric acid: (1) glomerular filtration, (2) tubular reabsorption, (3) secretion, and (4) postsecretory reabsorption. Although these processes have been considered sequential, it is now apparent that they are carried out in parallel by these transporters. URAT1 is a novel transporter expressed at the apical brush border of the proximal nephron. Uricosuric compounds **(Table 8-1)** directly inhibit URAT1 on the apical side of the tubular cell (so-called *cis*-inhibition). In contrast, antiuricosuric compounds (those that promote hyperuricemia), such as nicotinate, pyrazinoate, lactate, and other aromatic organic acids, serve as the exchange anion inside the cell, thereby stimulating anion exchange and urate reabsorption (*trans*-stimulation). The activities of URAT1, other OATs, and sodium anion transporter result in 8–12% of the filtered urate being excreted as uric acid.

Most children have serum urate concentrations of 180–240 μmol/L (3–4 mg/dL). Levels begin to rise in males during puberty but remain low in females until menopause. Mean serum urate values of adult men and premenopausal women are 415 and 360 μmol/L (6.8 and 6 mg/dL), respectively. After menopause, values for

TABLE 8-1

MEDICATIONS WITH URICOSURIC ACTIVITY	
Acetohexamide	Glyceryl guaiacolate
ACTH	Glycopyrrolate
Ascorbic acid	Halofenate
Azauridine	Losartan
Benzbromarone	Meclofenamate
Calcitonin	Phenolsulfonphthalein
Chlorprothixene	Phenylbutazone
Citrate	Probenecid
Dicumarol	Radiographic contrast agents
Diflunisal	Salicylates (>2 g/d)
Estrogens	Sulfinpyrazone
Fenofibrate	Tetracycline that is outdated
Glucocorticoids	Zoxazolamine

women increase to approximate those of men. In adulthood, concentrations rise steadily over time and vary with height, body weight, blood pressure, renal function, and alcohol intake.

HYPERURICEMIA

Hyperuricemia can result from increased production or decreased excretion of uric acid or from a combination of the two processes. Sustained hyperuricemia predisposes some individuals to develop clinical manifestations including gouty arthritis, urolithiasis, and renal dysfunction (see below).

Hyperuricemia is defined as a plasma (or serum) urate concentration >405 μmol/L (6.8 mg/dL). The risk of developing gouty arthritis or urolithiasis increases with higher urate levels and escalates in proportion to the degree of elevation. Hyperuricemia is present in between 2 and 13.2% of ambulatory adults and is even more frequent in hospitalized individuals.

CAUSES OF HYPERURICEMIA

Hyperuricemia may be classified as primary or secondary depending on whether the cause is innate or is the result of an acquired disorder. However, it is more useful to classify hyperuricemia in relation to the underlying pathophysiology, i.e., whether it results from increased production, decreased excretion, or a combination of the two (Fig. 8-1, **Table 8-2**).

TABLE 8-2
CLASSIFICATION OF HYPERURICEMIA BY PATHOPHYSIOLOGY

Urate Overproduction		
Primary idiopathic	Myeloproliferative diseases	Rhabdomyolysis
HPRT deficiency	Polycythemia vera	Exercise
PRPP synthetase overactivity	Psoriasis	Alcohol
Hemolytic processes	Paget's disease	Obesity
Lymphoproliferative diseases	Glycogenosis III, V, and VII	Purine-rich diet
Decreased Uric Acid Excretion		
Primary idiopathic	Starvation ketosis	Drug ingestion
Renal insufficiency	Beryllosis	Salicylates (>2 g/d)
Polycystic kidney disease	Sarcoidosis	Diuretics
Diabetes insipidus	Lead intoxication	Alcohol
Hypertension	Hyperparathyroidism	Levodopa
Acidosis	Hypothyroidism	Ethambutol
Lactic acidosis	Toxemia of pregnancy	Pyrazinamide
Diabetic etoacidosis	Bartter's syndrome	Nicotinic acid
	Down syndrome	Cyclosporine
Combined Mechanism		
Glucose-6-phosphatase deficiency	Fructose-1-phosphate aldolase deficiency	Alcohol
		Shock

Abbreviations: HPRT, hypoxanthine phosphoribosyltransferase; PRPP, phosphoribosylpyrophosphate.

Increased urate production

Diet contributes to the serum urate in proportion to its purine content. Strict restriction of purine intake reduces the mean serum urate level by about 60 μmol/L (1 mg/dL) and urinary uric acid excretion by ~1.2 mmol/d (200 mg/d). Foods high in nucleic acid content include liver, "sweetbreads" (i.e., thymus and pancreas), kidney, and anchovy.

Endogenous sources of purine production also influence the serum urate level **(Fig. 8-3)**. De novo purine biosynthesis is an 11-step process that forms inosine monophosphate (IMP). The rates of purine biosynthesis and urate production are determined, for the most part, by amidophosphoribosyltransferase (amidoPRT), which combines phosphoribosylpyrophosphate (PRPP) and glutamine. A secondary regulatory pathway is the salvage of purine bases by hypoxanthine phosphoribosyltransferase (HPRT). HPRT catalyzes the combination of the purine bases hypoxanthine and guanine with PRPP to form the respective ribonucleotides IMP and guanosine monophosphate (GMP).

Serum urate levels are closely coupled to the rates of de novo purine biosynthesis, which is driven in part by the level of PRPP, as evidenced by two X-linked inborn errors of purine metabolism. Both increased PRPP synthetase activity and HPRT deficiency are associated with overproduction of purines, hyperuricemia, and hyperuricaciduria (see below for clinical descriptions).

Accelerated purine nucleotide degradation can also cause hyperuricemia, i.e., with conditions of rapid cell turnover, proliferation, or cell death, as in leukemic blast crises, cytotoxic therapy for malignancy, hemolysis, or rhabdomyolysis. Hyperuricemia can result from excessive degradation of skeletal muscle ATP after strenuous physical exercise or status epilepticus and in glycogen storage diseases types III, V, and VII. The hyperuricemia of myocardial infarction, smoke inhalation, and acute respiratory failure may also be related to accelerated breakdown of ATP.

Decreased uric acid excretion

More than 90% of individuals with sustained hyperuricemia have a defect in the renal handling of uric acid.

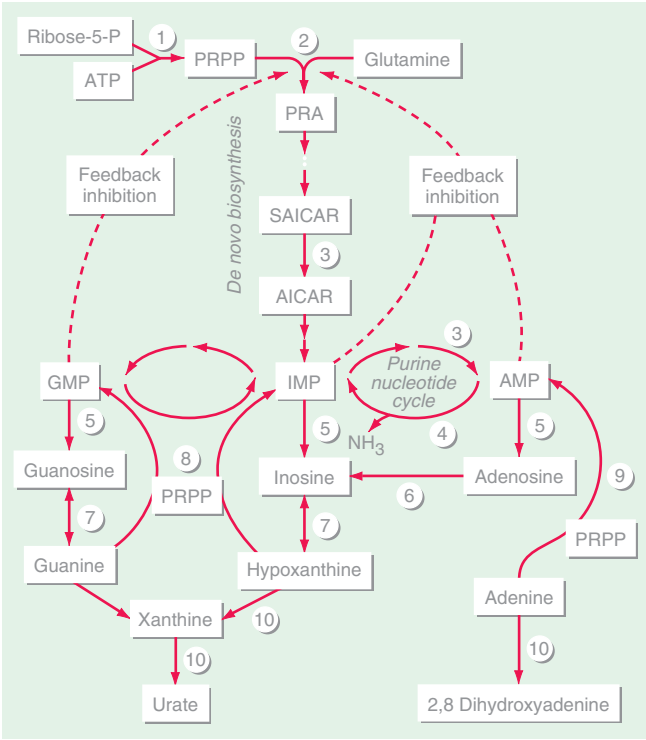


FIGURE 8-3
Abbreviated scheme of purine metabolism. (1) Phosphoribosylpyrophosphate (PRPP) synthetase, (2) amidophosphoribosyltransferase (amidoPRT), (3) adenylosuccinate lyase, (4) (myo-)adenylate (AMP) deaminase, (5) 5′-nucleotidase, (6) adenosine deaminase, (7) purine nucleoside phosphorylase, (8) hypoxanthine phosphoribosyltransferase (HPRT), (9) adenine phosphoribosyltransferase (APRT), and (10) xanthine oxidase. AICAR, aminoimidazole carboxamide ribotide; ATP, adenosine triphosphate; GMP, guanylate; IMP, inosine monophosphate; PRA, phosphoribosylamine; SAICAR, succinylaminoimidazole carboxamide ribotide.

Gouty individuals excrete ~40% less uric acid than nongouty individuals for any given plasma urate concentration. Uric acid excretion increases in gouty and nongouty individuals when plasma urate levels are raised by purine ingestion or infusion, but in those with gout, plasma urate concentrations must be 60–120 μmol/L (1–2 mg/dL) higher than normal to achieve equivalent uric acid excretion rates.

Altered uric acid excretion could theoretically result from decreased glomerular filtration, decreased tubular secretion, or enhanced tubular reabsorption. Decreased urate filtration does not appear to cause primary hyperuricemia but does contribute to the hyperuricemia of renal insufficiency. Although hyperuricemia is invariably present in chronic renal disease, the correlation between serum creatinine, urea nitrogen, and urate concentration is poor. Uric acid excretion per unit of glomerular filtration rate increases progressively with chronic renal insufficiency, but tubular secretory capacity tends to be preserved, tubular reabsorptive capacity is reduced, and extrarenal clearance of uric acid increases as renal damage becomes more severe.

Many agents that cause hyperuricemia exert their effects by stimulating reabsorption rather than inhibiting secretion. This appears to occur through a process of "priming" renal urate reabsorption through the sodium-dependent loading of proximal tubular epithelial cells with anions capable of *trans*-stimulating urate reabsorption. The sodium-coupled monocarboxyl transporters SMCT1 and 2 (SLC5A8, SLC5A12) in the brush border of the proximal tubular cells mediate sodium-dependent loading of these cells with monocarboxylates. A similar transporter, SLC13A3, mediates sodium-dependent influx of dicarboxylates into the epithelial cell from the basolateral membrane. Some of these carboxylates are well known to cause hyperuricemia, including pyrazinoate (from pyrazinamide treatment), nicotinate (from niacin therapy), and the organic acids lactate, β-hydroxybutyrate, and acetoacetate. The mono- and divalent anions then become substrates for URAT1 and organic anion transporter (OAT4), respectively, and are exchanged for uric acid from the proximal tubule. Increased blood levels of these anions result in their increased glomerular filtration and greater reabsorption by proximal tubular cells. The increased intraepithelial cell concentrations lead to increased uric acid reabsorption by promoting URAT1- and OAT4-dependent anion exchange. Low doses of salicylates also promote hyperuricemia by this mechanism. Sodium loading of proximal tubular cells also provokes urate retention by reducing extracellular fluid volume and increasing angiotensin II, insulin, and parathyroid hormone release. Additional organic anion transporters OAT1 and OAT3 are involved in the movement of uric acid through the basolateral membrane, although the detailed mechanisms are still being elucidated.

Glucose transporter 9 (GLUT9, SLC2A9) is an electrogenic hexose transporter with splicing variants that mediate co-reabsorption of uric acid along with glucose and fructose at the apical membrane (GLUT9&DELTA;N/SLC2A9v2), as well as through the basolateral membrane, and thus into the circulation (SLC2A9v1). This might be a mechanism for the observed association of the consumption of fructose-sweetened soft drinks with an increased risk of hyperuricemia and gout. Genomewide association scanning (GWAS) suggests that polymorphisms in SLC2A9 may play an important role in susceptibility to gout in the white population. The presence of one predisposing variant allele increases the relative risk of developing gout by 30–70%, most likely by increasing expression of the shorter isoform, SLC2A9v2 (GLUT9ΔN). Notably, these polymorphisms explain <5% of the variation in serum uric acid levels in whites.

Alcohol promotes hyperuricemia because of increased urate production and decreased uric acid excretion.

Excessive alcohol consumption accelerates hepatic breakdown of ATP to increase urate production. Alcohol consumption can also induce hyperlacticacidemia, which blocks uric acid secretion. The higher purine content in some alcoholic beverages such as beer may also be a factor.

EVALUATION

Hyperuricemia does not necessarily represent a disease, nor is it a specific indication for therapy. The decision to treat depends on the cause and the potential consequences of the hyperuricemia in each individual.

Quantification of uric acid excretion can be used to determine whether hyperuricemia is caused by overproduction or decreased excretion. On a purine-free diet, men with normal renal function excrete <3.6 mmol/d (600 mg/d). Thus, the hyperuricemia of individuals who excrete uric acid above this level while on a purine-free diet is due to purine overproduction; for those who excrete lower amounts on the purine-free diet, it is due to decreased excretion. If the assessment is performed while the patient is on a regular diet, the level of 4.2 mmol/d (800 mg/d) can be used as the discriminating value.

GOUT

The use of polarizing light microscopy during synovial fluid analysis in 1961 by McCarty and Hollander and the subsequent application of other crystallographic techniques, such as electron microscopy, energy-dispersive elemental analysis, and x-ray diffraction, have allowed investigators to identify the roles of different microcrystals, including monosodium urate (MSU), calcium pyrophosphate dihydrate (CPPD), calcium apatite (apatite), and calcium oxalate (CaOx), in inducing acute or chronic arthritis or periarthritis. The clinical events that result from deposition of MSU, CPPD, apatite, and CaOx have many similarities but also have important differences. Before the use of crystallographic techniques in rheumatology, much of what was considered to be gouty arthritis in fact was not. Because of often similar clinical presentations, the need to perform synovial fluid analysis to distinguish the type of crystal involved must be emphasized. Polarized light microscopy alone can identify most typical crystals; apatite, however, is an exception. Aspiration and analysis of effusions are also important to assess the possibility of infection. Apart from the identification of specific microcrystalline materials or organisms, synovial fluid characteristics in crystal-associated diseases are nonspecific, and synovial fluid can be inflammatory or noninflammatory. A list of possible musculoskeletal manifestations of crystal-associated arthritis is shown in Table 8-3.

TABLE 8-3

MUSCULOSKELETAL MANIFESTATIONS OF CRYSTAL-INDUCED ARTHRITIS

Acute mono- or polyarthritis	Destructive arthropathies
Bursitis	Pseudo-rheumatoid arthritis
Tendinitis	Pseudo-ankylosing spondylitis
Enthesitis	Spinal stenosis
Tophaceous deposits	Crowned dens syndrome
Peculiar type of osteoarthritis	Carpal tunnel syndrome
Synovial osteochondromatosis	Tendon rupture

Gout is a metabolic disease that most often affects middle-aged to elderly men and postmenopausal women. It results from an increased body pool of urate with hyperuricemia. It typically is characterized by episodic acute and chronic arthritis caused by deposition of MSU crystals in joints and connective tissue tophi and the risk for deposition in kidney interstitium or uric acid nephrolithiasis.

ACUTE AND CHRONIC ARTHRITIS

Acute arthritis is the most common early clinical manifestation of gout. Usually, only one joint is affected initially, but polyarticular acute gout can occur in subsequent episodes. The metatarsophalangeal joint of the first toe often is involved, but tarsal joints, ankles, and knees also are affected commonly. Especially in elderly patients or in advanced disease, finger joints may be involved. Inflamed Heberden's or Bouchard's nodes may be a first manifestation of gouty arthritis. The first episode of acute gouty arthritis frequently begins at night with dramatic joint pain and swelling. Joints rapidly become warm, red, and tender, with a clinical appearance that often mimics that of cellulitis. Early attacks tend to subside spontaneously within 3–10 days, and most patients have intervals of varying length with no residual symptoms until the next episode. Several events may precipitate acute gouty arthritis: dietary excess, trauma, surgery, excessive ethanol ingestion, hypouricemic therapy, and serious medical illnesses such as myocardial infarction and stroke.

After many acute mono- or oligoarticular attacks, a proportion of gouty patients may present with a chronic nonsymmetric synovitis, causing potential confusion with rheumatoid arthritis. Less commonly, chronic gouty arthritis will be the only manifestation, and, more rarely, the disease will manifest only as periarticular tophaceous deposits in the absence of synovitis. Women represent only 5–20% of all patients with gout. Premenopausal gout is rare; it is seen mostly in individuals with a strong family history of gout. Kindreds of

precocious gout in young females caused by decreased renal urate clearance and renal insufficiency have been described. Most women with gouty arthritis are postmenopausal and elderly, have osteoarthritis and arterial hypertension that cause mild renal insufficiency, and usually are receiving diuretics.

LABORATORY DIAGNOSIS

Even if the clinical appearance strongly suggests gout, the presumptive diagnosis ideally should be confirmed by needle aspiration of acutely or chronically involved joints or tophaceous deposits. Acute septic arthritis, several of the other crystalline-associated arthropathies, palindromic rheumatism, and psoriatic arthritis may present with similar clinical features. During acute gouty attacks, needle-shaped MSU crystals typically are seen both intracellularly and extracellularly **(Fig. 8-4)**. With compensated polarized light these crystals are brightly birefringent with negative elongation. Synovial fluid leukocyte counts are elevated from 2000 to 60,000/μL. Effusions appear cloudy due to the increased numbers of leukocytes. Large amounts of crystals occasionally produce a thick pasty or chalky joint fluid. Bacterial infection can coexist with urate crystals in synovial fluid; if there is any suspicion of septic arthritis, joint fluid must be cultured.

MSU crystals also can often be demonstrated in the first metatarsophalangeal joint and in knees not acutely involved with gout. Arthrocentesis of these joints is a useful technique to establish the diagnosis of gout between attacks.

Serum uric acid levels can be normal or low at the time of an acute attack, as inflammatory cytokines can be uricosuric and effective initiation of hypouricemic therapy can precipitate attacks. This limits the value of serum uric acid determinations for the diagnosis of gout.

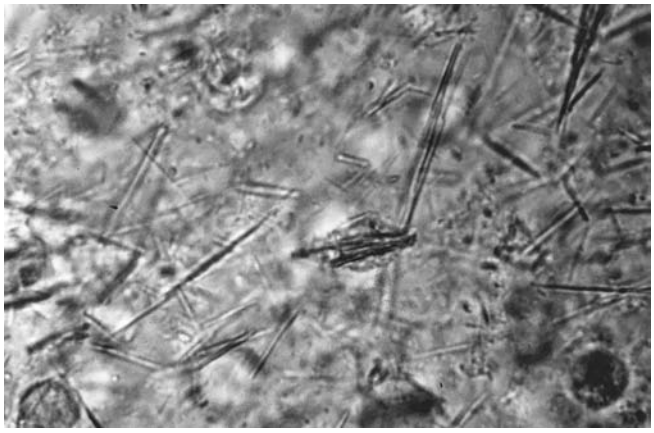


FIGURE 8-4
Extracellular and intracellular monosodium urate crystals, as seen in a fresh preparation of synovial fluid, illustrate needle- and rod-shaped crystals. These crystals are strongly negative birefringent crystals under compensated polarized light microscopy; 400×.

Nevertheless, serum urate levels are almost always elevated at some time and are important to use to follow the course of hypouricemic therapy. A 24-h urine collection for uric acid can, in some cases, be useful in assessing the risk of stones, elucidating overproduction or underexcretion of uric acid, and deciding whether it may be appropriate to use a uricosuric therapy. Excretion of >800 mg of uric acid per 24 h on a regular diet suggests that causes of overproduction of purine should be considered. Urinalysis, serum creatinine, hemoglobin, white blood cell (WBC) count, liver function tests, and serum lipids should be obtained because of possible pathologic sequelae of gout and other associated diseases requiring treatment and as baselines because of possible adverse effects of gout treatment.

RADIOGRAPHIC FEATURES

Early in the disease radiographic studies may only confirm clinically evident swelling. Cystic changes, well-defined erosions with sclerotic margins (often with overhanging bony edges), and soft tissue masses are characteristic features of advanced chronic tophaceous gout. Ultrasound, CT, and MRI are being studied and are likely to become more sensitive for early changes.

TREATMENT Gout

ACUTE GOUTY ARTHRITIS The mainstay of treatment during an acute attack is the administration of anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or glucocorticoids. NSAIDs are used most often in individuals without complicating comorbid conditions. Both colchicine and NSAIDs may be poorly tolerated and dangerous in the elderly and in the presence of renal insufficiency and gastrointestinal disorders. This was repeated later. Ice pack applications and rest of the involved joints can be helpful. Colchicine given orally is a traditional and effective treatment if used early in an attack. One useful regimen is one 0.6-mg tablet given every 8 h with subsequent tapering. This is generally better tolerated than the formerly advised hourly regimen. The drug must be stopped promptly at the first sign of loose stools, and symptomatic treatment must be given for the diarrhea. Intravenous colchicine has been taken off the market. NSAIDs given in full anti-inflammatory doses are effective in ~90% of patients, and the resolution of signs and symptoms usually occurs in 5–8 days. The most effective drugs are any of those with a short half-life and include indomethacin, 25–50 mg tid; naproxen, 500 mg bid; ibuprofen, 800 mg tid; and diclofenac, 50 mg tid. Glucocorticoids given IM or orally, for example, prednisone, 30–50 mg/d as the initial dose and gradually

tapered with the resolution of the attack, can be effective in polyarticular gout. For a single joint or a few involved joints intraarticular triamcinolone acetonide, 20–40 mg, or methylprednisolone, 25–50 mg, have been effective and well tolerated. Based on recent evidence on the essential role of the inflammasome and interleukin 1 β (IL-1β) in acute gout, anakinra has been used and other inhibitors of IL-1β are under investigation.

HYPOURICEMIC THERAPY Ultimate control of gout requires correction of the basic underlying defect: the hyperuricemia. Attempts to normalize serum uric acid to <300–360 μmol/L (5.0–6.0 mg/dL) to prevent recurrent gouty attacks and eliminate tophaceous deposits entail a commitment to long-term hypouricemic regimens and medications that generally are required for life. Hypouricemic therapy should be considered when, as in most patients, the hyperuricemia cannot be corrected by simple means (control of body weight, low-purine diet, increase in liquid intake, limitation of ethanol use, decreased use of fructose-containing foods and beverages, and avoidance of diuretics). The decision to initiate hypouricemic therapy usually is made taking into consideration the number of acute attacks (urate lowering may be cost-effective after two attacks), serum uric acid levels [progression is more rapid in patients with serum uric acid >535 μmol/L (>9.0 mg/dL)], the patient's willingness to commit to lifelong therapy, or the presence of uric acid stones. Urate-lowering therapy should be initiated in any patient who already has tophi or chronic gouty arthritis. Uricosuric agents such as probenecid can be used in patients with good renal function who underexcrete uric acid, with <600 mg in a 24-h urine sample. Urine volume must be maintained by ingestion of 1500 mL of water every day. Probenecid can be started at a dose of 250 mg twice daily and increased gradually as needed up to 3 g per day to maintain a serum uric acid level <360 μmol/L (6 mg/dL). Probenecid is generally not effective in patients with serum creatinine levels >177 μmol/L (2 mg/dL). These patients may require allopurinol or benzbromarone (not available in the United States). Benzbromarone is another uricosuric drug that is more effective in patients with renal failure. Some agents used to treat common comorbidities, including losartan, fenofibrate, and amlodipine, have some mild uricosuric effects.

The xanthine oxidase inhibitor allopurinol is by far the most commonly used hypouricemic agent and is the best drug to lower serum urate in overproducers, urate stone formers, and patients with renal disease. It can be given in a single morning dose, 100–300 mg initially and increasing up to 800 mg if needed. In patients with chronic renal disease, the initial allopurinol dose should be lower and adjusted depending on the serum creatinine concentration; for example, with a creatinine clearance of 10 mL/min, one generally would use 100 mg every other day. Doses can be increased gradually to reach the target urate level of 6 mg/dL; however, more studies are needed to provide exact guidance. Toxicity of allopurinol has been recognized increasingly in patients who use thiazide diuretics and patients allergic to penicillin and ampicillin. The most serious side effects include life-threatening toxic epidermal necrolysis, systemic vasculitis, bone marrow suppression, granulomatous hepatitis, and renal failure. Patients with mild cutaneous reactions to allopurinol can reconsider the use of a uricosuric agent, undergo an attempt at desensitization to allopurinol, or take febuxostat, a new, chemically unrelated specific xanthine oxidase inhibitor. Febuxostat is approved at 40 or 80 mg once a day and does not require dose adjustment in mild to moderate renal disease. Patients can also pay increased attention to diet and should be aware of new alternative agents (see below). Urate-lowering drugs are generally not initiated during acute attacks but after the patient is stable and low-dose colchicine has been initiated to decrease the risk of the flares that often occur with urate lowering. Colchicine anti-inflammatory prophylaxis in doses of 0.6 mg one to two times daily should be given along with the hypouricemic therapy until the patient is normouricemic and without gouty attacks for 6 months or as long as tophi are present. Colchicine should not be used in dialysis patients and is given in lower doses in patients with renal disease or with P glycoprotein or CYP3A4 inhibitors such as clarithromycin that can increase toxicity of colchicine. Peglotricase is a new urate-lowering biologic agent that can be effective in patients allergic to or failing xanthine oxidase inhibitors. New uricosurics are undergoing investigation.

COMPLICATIONS

The most recognized complication of hyperuricemia is *gouty arthritis*. In the general population, the prevalence of hyperuricemia ranges between 2.0 and 13.2%, and the prevalence of gout is between 1.3 and 3.7%. The higher the serum urate level, the more likely an individual is to develop gout. In one study, the incidence of gout was 4.9% for individuals with serum urate concentrations >540 μmol/L (9.0 mg/dL) compared with 0.5% for those with values between 415 and 535 μmol/L (7.0 and 8.9 mg/dL). The complications of gout correlate with both the duration and severity of hyperuricemia.

Hyperuricemia also causes several renal problems: (1) nephrolithiasis; (2) urate nephropathy, a rare cause of renal insufficiency attributed to monosodium urate crystal deposition in the renal interstitium; and (3) uric acid nephropathy, a reversible cause of acute renal failure resulting from deposition of large amounts of uric acid crystals in the renal collecting ducts, pelvis, and ureters.

NEPHROLITHIASIS

Uric acid nephrolithiasis occurs most commonly, but not exclusively, in individuals with gout. In gout, the prevalence of nephrolithiasis correlates with the serum and urinary uric acid levels, reaching ~50% with serum urate levels of 770 μmol/L (13 mg/dL) or urinary uric acid excretion >6.5 mmol/d (1100 mg/d).

Uric acid stones can develop in individuals with no evidence of arthritis, only 20% of whom are hyperuricemic. Uric acid can also play a role in other types of kidney stones. Some nongouty individuals with calcium oxalate or calcium phosphate stones have hyperuricemia or hyperuricaciduria. Uric acid may act as a nidus on which calcium oxalate can precipitate or lower the formation product for calcium oxalate crystallization.

URATE NEPHROPATHY

Urate nephropathy, sometimes referred to as *urate nephrosis*, is a late manifestation of severe gout and is characterized histologically by deposits of monosodium urate crystals surrounded by a giant cell inflammatory reaction in the medullary interstitium and pyramids. The disorder is now rare and cannot be diagnosed in the absence of gouty arthritis. The lesions may be clinically silent or cause proteinuria, hypertension, and renal insufficiency.

URIC ACID NEPHROPATHY

This reversible cause of acute renal failure is due to precipitation of uric acid in renal tubules and collecting ducts that causes obstruction to urine flow. Uric acid nephropathy develops following sudden urate overproduction and marked hyperuricaciduria. Factors that favor uric acid crystal formation include dehydration and acidosis. This form of acute renal failure occurs most often during an aggressive "blastic" phase of leukemia or lymphoma prior to or coincident with cytolytic therapy but has also been observed in individuals with other neoplasms, following epileptic seizures, and after vigorous exercise with heat stress. Autopsy studies have demonstrated intraluminal precipitates of uric acid, dilated proximal tubules, and normal glomeruli. The initial pathogenic events are believed to include obstruction of collecting ducts with uric acid and obstruction of distal renal vasculature.

If recognized, uric acid nephropathy is potentially reversible. Appropriate therapy has reduced the mortality from about 50% to practically nil. Serum levels cannot be relied on for diagnosis because this condition has developed in the presence of urate concentrations varying from 720 to 4800 μmol/L (12–80 mg/dL). The distinctive feature is the urinary uric acid concentration. In most forms of acute renal failure with decreased urine output, urinary uric acid content is either normal or reduced, and the ratio of uric acid to creatinine is <1. In acute uric acid nephropathy the ratio of uric acid to creatinine in a random urine sample or 24-h specimen is >1, and a value that high is essentially diagnostic.

HYPERURICEMIA AND METABOLIC SYNDROME

Metabolic syndrome is characterized by abdominal obesity with visceral adiposity, impaired glucose tolerance due to insulin resistance with hyperinsulinemia, hypertriglyceridemia, increased low-density lipoprotein cholesterol, decreased high-density lipoprotein cholesterol, and hyperuricemia. Hyperinsulinemia reduces the renal excretion of uric acid and sodium. Not surprisingly, hyperuricemia resulting from euglycemic hyperinsulinemia may precede the onset of type 2 diabetes, hypertension, coronary artery disease, and gout in individuals with metabolic syndrome.

TREATMENT Hyperuricemia

ASYMPTOMATIC HYPERURICEMIA Hyperuricemia is present in ~5% of the population and in up to 25% of hospitalized individuals. The vast majority are at no clinical risk. In the past, the association of hyperuricemia with cardiovascular disease and renal failure led to the use of urate-lowering agents for patients with asymptomatic hyperuricemia. This practice is no longer recommended except for individuals receiving cytolytic therapy for neoplastic disease, in which treatment is given in an effort to prevent uric acid nephropathy. Because hyperuricemia can be a component of the metabolic syndrome, its presence is an indication to screen for and aggressively treat any accompanying obesity, hyperlipidemia, diabetes mellitus, or hypertension.

Hyperuricemic individuals are at risk to develop gouty arthritis, especially those with higher serum urate levels. However, most hyperuricemic persons never develop gout, and prophylactic treatment is not indicated. Furthermore, neither structural kidney damage nor tophi are identifiable before the first attack. Reduced renal function cannot be attributed to asymptomatic hyperuricemia, and treatment of asymptomatic hyperuricemia does not alter the progression of renal dysfunction in patients with renal disease. Increased risk of stone formation in those with asymptomatic hyperuricemia is not established.

Thus, because treatment with specific antihyperuricemic agents entails inconvenience, cost, and potential toxicity, routine treatment of asymptomatic hyperuricemia cannot be justified other than for prevention of acute uric acid nephropathy. In addition, routine screening for asymptomatic hyperuricemia is not recommended. If hyperuricemia is diagnosed, however, the cause should be determined. Causal factors should be

corrected if the condition is secondary, and associated problems such as hypertension, hypercholesterolemia, diabetes mellitus, and obesity should be treated.

SYMPTOMATIC HYPERURICEMIA

Nephrolithiasis Antihyperuricemic therapy is recommended for the individual who has both gouty arthritis and either uric acid– or calcium-containing stones, both of which may occur in association with hyperuricaciduria. Regardless of the nature of the calculi, fluid ingestion should be sufficient to produce a daily urine volume >2 L. Alkalinization of the urine with sodium bicarbonate or acetazolamide may be justified to increase the solubility of uric acid. Specific treatment of uric acid calculi requires reducing the urine uric acid concentration with a xanthine oxidase inhibitor, such as allopurinol or febuxostat. These agents decrease the serum urate concentration and the urinary excretion of uric acid in the first 24 h, with a maximum reduction occurring within 2 weeks. The average effective dose of allopurinol is 300–400 mg/d. Allopurinol can be given once a day because of the long half-life (18 h) of its active metabolite, oxypurinol. The drug is effective in patients with renal insufficiency, but the dose should be reduced. Allopurinol is also useful in reducing the recurrence of calcium oxalate stones in gouty patients and in nongouty individuals with hyperuricemia or hyperuricaciduria. Febuxostat (40–80 mg/d) is also taken once daily, and doses do not need to be adjusted in the presence of mild to moderate renal dysfunction. Potassium citrate (30–80 mmol/d orally in divided doses) is an alternative therapy for patients with uric acid stones alone or mixed calcium/uric acid stones. A xanthine oxidase inhibitor is also indicated for the treatment of 2,8-dihydroxyadenine kidney stones.

Uric Acid Nephropathy Uric acid nephropathy is often preventable, and immediate, appropriate therapy has greatly reduced the mortality rate. Vigorous IV hydration and diuresis with furosemide dilute the uric acid in the tubules and promote urine flow to ≥100 mL/h. The administration of acetazolamide, 240–500 mg every 6–8 h, and sodium bicarbonate, 89 mmol/L, IV enhances urine alkalinity and thereby solubilizes more uric acid. It is important to ensure that the urine pH remains >7.0 and to watch for circulatory overload. In addition, antihyperuricemic therapy in the form of allopurinol in a single dose of 8 mg/kg is administered to reduce the amount of urate that reaches the kidney. If renal insufficiency persists, subsequent daily doses should be reduced to 100–200 mg because oxypurinol, the active metabolite of allopurinol, accumulates in renal failure. Despite these measures, hemodialysis may be required. Urate oxidase (Rasburicase) can also be administered IV to prevent or to treat tumor lysis syndrome.

HYPOURICEMIA

Hypouricemia, defined as a serum urate concentration <120 μmol/L (2.0 mg/dL) can result from decreased production of urate, increased excretion of uric acid, or a combination of both mechanisms. It occurs in <0.2% of the general population and <0.8% of hospitalized individuals. Hypouricemia causes no symptoms or pathology and therefore requires no therapy.

Most hypouricemia results from increased renal uric acid excretion. The finding of normal amounts of uric acid in a 24-h urine collection in an individual with hypouricemia is evidence for a renal cause. Medications with uricosuric properties (Table 8-1) include aspirin (at doses >2.0 g/d), losartan, fenofibrate, x-ray contrast materials, and glyceryl guaiacolate. Total parenteral hyperalimentation can also cause hypouricemia, possibly a result of the high glycine content of the infusion formula. Other causes of increased urate clearance include conditions such as neoplastic disease, hepatic cirrhosis, diabetes mellitus, and inappropriate secretion of vasopressin; defects in renal tubular transport such as primary Fanconi syndrome and Fanconi syndromes caused by Wilson's disease, cystinosis, multiple myeloma, and heavy metal toxicity; and isolated congenital defects in the bidirectional transport of uric acid. Hypouricemia can be familial, generally inherited in an autosomal recessive manner. Most cases are caused by a loss of function mutation in *SLC12A12*, the gene that encodes URAT-1, resulting in increased renal urate clearance. Individuals with normal *SLC12A12* most likely have a defect in other urate transporters. Although usually asymptomatic, some patients suffer from urate nephrolithiasis or exercise-induced renal failure.

SELECTED INBORN ERRORS OF PURINE METABOLISM

(**Table 8-4**; see also Fig. 8-3.) More than 30 defects in human purine and pyrimidine metabolic pathways have been identified thus far. Many are benign, but about half are associated with clinical manifestations, some causing major morbidity and mortality. Advances in genetics, as well as high-performance liquid chromatography and tandem mass spectrometry, have allowed for better diagnosis.

PURINE DISORDERS

HPRT DEFICIENCY

The HPRT gene is located on the X chromosome. Affected males are hemizygous for the mutant gene; carrier females are asymptomatic. A complete deficiency of HPRT, the Lesch-Nyhan syndrome, is characterized

TABLE 8-4

INBORN ERRORS OF PURINE METABOLISM

ENZYME	ACTIVITY	INHERITANCE	CLINICAL FEATURES	LABORATORY FEATURES
Hypoxanthine phosphoribosyltransferase	Complete deficiency	X-linked	Self-mutilation, choreoathetosis, gout, and uric acid lithiasis	Hyperuricemia, hyperuricosuria
	Partial deficiency	X-linked	Gout and uric acid lithiasis	Hyperuricemia, hyperuricosuria
Phosphoribosylpyrophosphate synthetase	Overactivity	X-linked	Gout, uric acid lithiasis, and deafness	Hyperuricemia, hyperuricosuria
Adenine phosphoribosyltransferase	Deficiency	Autosomal recessive	2,8-Dihydroxyadenine lithiasis	—
Xanthine oxidase	Deficiency	Autosomal recessive	Xanthinuria and xanthine lithiasis	Hypouricemia, hypouricosuria
Adenylosuccinate lyase	Deficiency	Autosomal recessive	Autism and psychomotor retardation	—
Myoadenylate deaminase	Deficiency	Autosomal recessive	Myopathy with exercise intolerance or asymptomatic	—
Adenosine deaminase	Deficiency	Autosomal recessive	Severe combined immunodeficiency disease and chondroosseous dysplasia	—
Purine nucleoside phosphorylase	Deficiency	Autosomal recessive	T cell–mediated immunodeficiency	—

by hyperuricemia, self-mutilative behavior, choreoathetosis, spasticity, and mental retardation. A partial deficiency of HPRT, the Kelley-Seegmiller syndrome, is associated with hyperuricemia but no central nervous system manifestations. In both disorders, the hyperuricemia results from urate overproduction and can cause uric acid crystalluria, nephrolithiasis, obstructive uropathy, and gouty arthritis. Early diagnosis and appropriate therapy with allopurinol can prevent or eliminate all the problems attributable to hyperuricemia but have no effect on the behavioral or neurologic abnormalities.

INCREASED PRPP SYNTHETASE ACTIVITY

Like the HPRT deficiency states, PRPP synthetase overactivity is X-linked and results in gouty arthritis and uric acid nephrolithiasis. Nerve deafness occurs in some families.

ADENINE PHOSPHORIBOSYLTRANSFERASE (APRT) DEFICIENCY

APRT deficiency is inherited as an autosomal recessive trait. Affected individuals develop kidney stones composed of 2,8-dihydroxyadenine. Whites with the disorder have a complete deficiency (type I), whereas Japanese subjects have some measurable enzyme activity (type II). Expression of the defect is similar in the two populations, as is the frequency of the heterozygous state (0.4–1.1 per 100). Allopurinol treatment prevents stone formation.

HEREDITARY XANTHINURIA

A deficiency of xanthine oxidase causes all purine in the urine to occur in the form of hypoxanthine and xanthine. About two-thirds of deficient individuals are asymptomatic. The remainder develop kidney stones composed of xanthine.

MYOADENYLATE DEAMINASE DEFICIENCY

Primary (inherited) and secondary (acquired) forms of myoadenylate deaminase deficiency have been described. The primary form is inherited as an autosomal recessive trait. Clinically, some may have relatively mild myopathic symptoms with exercise or other triggers, but most individuals with this defect are asymptomatic. Therefore, another explanation for the myopathy should be sought in symptomatic patients with this deficiency. The acquired deficiency occurs in association with a wide variety of neuromuscular disease, including muscular dystrophies, neuropathies, inflammatory myopathies, and collagen vascular diseases.

ADENYLOSUCCINATE LYASE DEFICIENCY

Deficiency of this enzyme is due to an autosomal recessive trait and causes profound psychomotor retardation, seizures, and other movement disorders. All individuals with this deficiency are mentally retarded, and most are autistic.

CHAPTER 9

NEPHROLITHIASIS

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Kidney stones are one of the most common urologic problems. In the United States, ~13% of men and 7% of women will develop a kidney stone during their lifetimes, and the prevalence is increasing throughout the industrialized world.

TYPES OF STONES

Calcium salts, uric acid, cystine, and struvite are the constituents of most kidney stones in the western hemisphere (Chap. 4). Calcium oxalate and calcium phosphate stones make up 75–85% of the total **(Table 9-1)** and those constituents may be admixed in the same stone. Calcium phosphate in stones is usually hydroxyapatite [$Ca_5(PO_4)_3OH$] or, less commonly, brushite ($CaHPO_4H_2O$), although the incidence of brushite stones is increasing.

Calcium stones are more common in men; the average age of onset is the third to fourth decade. Approximately 50% of people who form a single calcium stone form another within the next 10 years, and some form multiple recurrent stones. The average rate of new stone formation in recurrent stone formers is about one stone every 3 years. *Uric acid stones* account for 5–10% of kidney stones and are also more common in men. Five percent of stones are *struvite*, whereas *cystine stones* are uncommon, accounting for ~1% of cases in most series of nephrolithiasis.

MANIFESTATIONS OF STONES

As stones grow on the surfaces of the renal papillae or within the collecting system, they do not necessarily produce symptoms. Asymptomatic stones may be discovered during the course of radiographic studies undertaken for unrelated reasons. Stones are a common cause of isolated hematuria. Stones become symptomatic when they enter the ureter or occlude the ureteropelvic junction, causing pain and obstruction.

Stone passage

A stone can traverse the ureter without symptoms, but passage usually produces pain and bleeding. The pain begins gradually, usually in the flank, but increases over the next 20–60 min to become so severe that narcotics may be needed for its control. The pain may remain in the flank or spread downward and anteriorly toward the ipsilateral loin, testis, or vulva. A stone in the portion of the ureter within the bladder wall causes frequency, urgency, and dysuria that may be confused with urinary tract infection. The vast majority of ureteral stones <0.5 cm in diameter pass spontaneously.

Helical computed tomography (CT) scanning without radiocontrast enhancement is now the standard radiologic procedure for diagnosis of nephrolithiasis. The advantages of CT include detection of uric acid stones in addition to the traditional radiopaque stones, no exposure to the risk of radiocontrast agents, and possible diagnosis of other causes of abdominal pain in a patient suspected of having renal colic from stones. Ultrasound is not as sensitive as CT in detecting renal or ureteral stones. Standard abdominal x-rays may be used to monitor patients for formation and growth of kidney stones, as they are less expensive and provide less radiation exposure than CT scans. Calcium, cystine, and struvite stones are all radiopaque on standard x-rays, whereas uric acid stones are radiolucent.

Other syndromes

Staghorn calculi

Struvite, cystine, and uric acid stones often grow too large to enter the ureter. They gradually fill the renal pelvis and may extend outward through the infundibula to the calyces themselves. Very large staghorn stones can have surprisingly few symptoms and may lead to the eventual loss of kidney function.

TABLE 9-1

MAJOR CAUSES OF RENAL STONES

STONE TYPE AND CAUSES	PERCENT OF ALL STONES[a]	PERCENT OCCURRENCE OF SPECIFIC CAUSES[a]	RATIO OF MALES TO FEMALES	ETIOLOGY	DIAGNOSIS	TREATMENT
Calcium stones	75–85		2:1 to 3:1			
Idiopathic hypercalciuria		50–55	2:1	? Hereditary	Normocalcemia, unexplained hypercalciuria[b]	Low-sodium, low-protein diet; thiazide diuretics
Hyperuricosuria		20	4:1	Diet	Urine uric acid >750 mg per 24 h (women), >800 mg per 24 h (men)	Allopurinol or low-purine diet
Primary hyperparathyroidism		3–5	3:10	Neoplasia	Hypercalcemia with nonsuppressed parathyroid hormone	Surgery
Distal renal tubular acidosis		Rare	1:1	Hereditary or acquired	Hyperchloremic acidosis, minimum urine pH >5.5	Alkali replacement
Dietary hyperoxaluria		10–30	1:1	High-oxalate diet or low-calcium diet	Urine oxalate >40 mg per 24 h	Low-oxalate, normal-calcium diet
Enteric hyperoxaluria		~1–2	1:1	Bowel surgery	Urine oxalate >75 mg per 24 h	Low-oxalate diet and oral calcium pills
Primary hyperoxaluria		Rare	1:1	Hereditary	Urine oxalate and glycolic or l-glyceric acid increased	Fluids, pyridoxine, citrate, and neutral phosphate
Hypocitraturia		20–40	1:1 to 2:1	? Hereditary, diet	Urine citrate <320 mg per 24 h	Alkali supplements
Idiopathic stone disease		20	2:1	Unknown	None of the above present	Oral phosphate, fluids
Uric acid stones	5–10					
Metabolic syndrome		~30	1:1	Diet	Glucose intolerance, obesity, hyperlipidemia	Alkali and allopurinol if daily urine uric acid >1000 mg
Gout		~30	3:1 to 4:1	Hereditary	Clinical diagnosis	Alkali and allopurinol
Idiopathic		~30	1:1	? Hereditary	Uric acid stones, no gout	Alkali and allopurinol if daily urine uric acid >1000 mg
Dehydration		?	1:1	Intestinal, habit	History, intestinal fluid loss	Alkali, fluids, reversal of cause
Lesch-Nyhan syndrome		Rare	Males only	Hereditary	Reduced hypoxanthine-guanine phosphoribosyltransferase level	Allopurinol
Cystine stones	1		1:1	Hereditary	Stone type; elevated cystine excretion	Massive fluids, alkali, D-penicillamine if needed
Struvite stones	5		1:3	Infection	Stone type	Antimicrobial agents and judicious surgery

[a]Values are percentages of patients who form a particular type of stone and who display each specific cause of stones.
[b]Urine calcium >300 mg/24 h (men), 250 mg/24 h (women), or 4 mg/kg per 24 h either sex. Hyperthyroidism, Cushing's syndrome, sarcoidosis, malignant tumors, immobilization, vitamin D intoxication, rapidly progressive bone disease, and Paget's disease all cause hypercalciuria and must be excluded in diagnosis of idiopathic hypercalciuria.

Nephrocalcinosis

Calcium stones grow on the papillae. Most break loose and cause colic, but they may remain in place so that multiple papillary calcifications are found by x-ray, a condition termed *nephrocalcinosis*. Papillary nephrocalcinosis is common in hereditary distal renal tubular acidosis (RTA) and in other types of severe hypercalciuria. In medullary sponge kidney disease (Chap. 16), calcification may occur in dilated distal collecting ducts.

Infection

Although urinary tract infection is not a direct consequence of stone disease, it can occur after instrumentation and surgery of the urinary tract, which are used frequently in the treatment of stone disease. Stone disease and urinary tract infection can enhance their respective seriousness and interfere with treatment. Obstruction of an infected kidney by a stone may lead to sepsis and extensive damage of renal tissue, since it converts the urinary tract proximal to the obstruction into a closed space that can become an abscess. Stones may harbor bacteria in the stone matrix, leading to recurrent urinary tract infection, and infection due to bacteria that have the enzyme urease can cause stones composed of struvite.

Activity of stone disease

In active disease, new stones are forming or preformed stones are growing. Sequential radiographs are needed to document the growth or appearance of new stones and ensure that passed stones are actually newly formed, not preexistent.

PATHOGENESIS OF STONES

Urinary stones usually arise because of the breakdown of a delicate balance between solubility and precipitation of salts. The kidneys must conserve water, but they must excrete materials that have low solubility. These two opposing requirements must be balanced during adaptation to diet, climate, and activity. The problem is mitigated to some extent by the fact that urine contains substances such as pyrophosphate, citrate, and glycoproteins that inhibit crystallization. These protective mechanisms are less than perfect. When urine becomes supersaturated with insoluble materials, because excretion rates are excessive and/or because water conservation is extreme, crystals form and may grow and aggregate to form a stone.

Supersaturation

A solution in equilibrium with a solid phase is said to be saturated with respect to that substance. If the concentration of a substance in a solution is above the saturation point, the solution is said to be supersaturated and can support the growth of crystals, and if supersaturation is excessive, new crystals can begin to develop spontaneously. Excessive supersaturation is common in stone formation.

Calcium, oxalate, and phosphate form many soluble complexes among themselves and with other substances in urine, such as citrate. As a result, their free ion activities are below their chemical concentrations. Reduction in ligands such as citrate can increase ion activity and therefore supersaturation. Urine supersaturation can be increased by dehydration or by overexcretion of calcium, oxalate, phosphate, cystine, or uric acid. Urine pH is also important; phosphate and uric acid are acids that dissociate readily over the physiologic range of urine pH. Alkaline urine contains more dibasic phosphate, favoring deposits of brushite and apatite. Below a urine pH of 5.5, uric acid crystals predominate, whereas phosphate crystals are rare. The solubility of calcium oxalate is not influenced by changes in urine pH. Measurements of supersaturation in a 24-h urine sample probably underestimate the risk of precipitation. Transient dehydration, variation of urine pH, and postprandial bursts of overexcretion may cause spikes in supersaturation.

Crystallization

When urine supersaturation is excessive, crystals begin to nucleate. Once formed, crystal nuclei will grow in size if urine is supersaturated with respect to that crystal phase. Multiple crystals can then aggregate to form a kidney stone. For a kidney stone to form, crystals must be retained in the renal pelvis long enough to grow and aggregate to a clinically significant size. Recent studies have shown that common calcium oxalate kidney stones form as overgrowths on apatite plaques in the renal papillae. These plaques, called Randall's plaques, provide an excellent surface for heterogeneous nucleation of calcium oxalate salts. The Randall's plaques begin in the deep medulla in the basement membrane of the thin limb of the loop of Henle and then spread through the interstitium to the basement membrane of the papillary urothelium. If the urothelium becomes damaged, the plaque is exposed to the urine, and calcium oxalate crystals form on the plaque, accumulating a clinically significant mass to form a stone. Calcium phosphate stone formers, particularly formers of brushite, do not follow this pattern. Inner medullary collecting ducts are plugged with apatite crystals, and stones form as extensions of those plugs. Unlike in calcium oxalate stone formers, renal papillae are often fibrotic and deformed.

EVALUATION AND TREATMENT OF PATIENTS WITH NEPHROLITHIASIS

Most patients with nephrolithiasis have remediable metabolic disorders that cause stones and can be detected by

chemical analyses of serum and urine. Adults with recurrent kidney stones and children with even a single kidney stone should be evaluated. A practical outpatient evaluation consists of two 24-h urine collections, with a corresponding blood sample; measurements of serum and urine calcium, uric acid, electrolytes, and creatinine, along with urine pH, volume, oxalate, and citrate should be made. Since stone risks vary with diet, activity, and environment, at least one urine collection should be made on a weekend when the patient is at home and another on a workday. When possible, the composition of kidney stones should be determined because treatment depends on stone type (Table 9-1). No matter what disorders are found, every patient should be counseled to avoid dehydration and drink copious amounts of water. The efficacy of high fluid intake was confirmed in a prospective study of first-time stone formers. Increasing urine volume to 2.5 L per day resulted in a 50% reduction of stone recurrence compared with the control group.

TREATMENT **Nephrolithiasis**

The management of stones already present in the kidneys or urinary tract requires a combined medical and surgical approach. The specific treatment depends on the location of the stone, the extent of obstruction, the nature of the stone, the function of the affected and unaffected kidneys, the presence or absence of urinary tract infection, the progress of stone passage, and the risks of operation or anesthesia in light of the clinical state of the patient. Medical therapy can enhance passage of ureteral stones. Oral α_1-adrenergic blockers relax ureteral muscle and have been shown to reduce time to stone passage and the need for surgical removal of small stones. Severe obstruction, infection, intractable pain, and serious bleeding are indications for removal of a stone.

Advances in urologic technology have rendered open surgery for stones a rare event. There are now three alternatives for stone removal. *Extracorporeal lithotripsy* causes the in situ fragmentation of stones in the kidney, renal pelvis, or ureter by exposing them to shock waves. After multiple shock waves, most stones are reduced to powder that moves through the ureter into the bladder. *Percutaneous nephrolithotomy* requires the passage of a nephroscope into the renal pelvis through a small incision in the flank. Stones are then disrupted by a small ultrasound transducer or holmium laser. The third method is *ureteroscopy* with stone disruption using a holmium laser. Ureteroscopy generally is used for stones in the ureter, but some surgeons are now using ureteroscopy for stones in the renal pelvis as well.

Calcium stones

Idiopathic hypercalciuria

This condition is the most common metabolic abnormality found in patients with nephrolithiasis (Table 9-1). It is familial and is probably a polygenic trait, although there are some rare monogenic causes of hypercalciuria and kidney stones such as Dent's disease, which is an X-linked disorder characterized by hypercalciuria, nephrocalcinosis, and progressive kidney failure. Idiopathic hypercalciuria is diagnosed by the presence of hypercalciuria without hypercalcemia and the absence of other systemic disorders known to affect mineral metabolism. Vitamin D overactivity through either high calcitriol levels or excess vitamin D receptor is a likely explanation for the hypercalciuria in many patients. Recent studies have shown that a polymorphism (Arg990Gly) of the calcium-sensing receptor, which leads to activation of the receptor, is more common in hypercalciuric subjects and probably contributes to higher urine calcium excretion. Hypercalciuria contributes to stone formation by raising urine saturation with respect to calcium oxalate and calcium phosphate.

TREATMENT **Hypercalciuria**

For many years the standard therapy for hypercalciuria was dietary calcium restriction. However, studies have shown that low-calcium diets increase the risk of incident stone formation, perhaps by reducing the amount of calcium in the intestine to bind oxalate, thereby increasing urine oxalate levels. A 5-year prospective trial compared the efficacy of a low-calcium diet to a low-protein, low-sodium, normal-calcium diet in preventing stone recurrence in male calcium stone formers. The group on the low-calcium diet had a significantly greater rate of stone relapse. In addition, hypercalciuric stone formers have reduced bone mineral density and an increased risk of fracture compared with the non-stone-forming population. Low calcium intake probably contributes to the low bone mineral density. In sum, low-calcium diets are of unknown efficacy in preventing stone formation and carry a long-term risk of bone disease, making low-sodium and low-protein diets a superior treatment option. If diet therapy is not sufficient to prevent stones, thiazide diuretics may be used. Thiazide diuretics lower urine calcium and are effective in preventing the formation of stones. Three 3-year randomized trials have shown a 50% decrease in stone formation in the thiazide-treated groups compared with the placebo-treated controls. The drug effect requires slight contraction of the extracellular fluid volume, and high dietary NaCl intake reduces its therapeutic effect. Thiazide-induced hypokalemia should be treated aggressively since hypokalemia will reduce urine citrate, an important inhibitor of calcium crystallization.

Hyperuricosuria

About 20% of calcium oxalate stone formers are hyperuricosuric, primarily because of an excessive intake of purine from meat and fish. The mechanism of stone formation probably involves salting out calcium oxalate by urate. A low-purine diet is desirable but difficult for many patients to achieve. The alternative is allopurinol, which has been shown to be effective in a randomized, controlled trial.

Primary hyperparathyroidism

The diagnosis of this condition is established by documenting that hypercalcemia that cannot be otherwise explained is accompanied by inappropriately elevated serum concentrations of parathyroid hormone. Hypercalciuria, which usually is present, raises the urine supersaturation of calcium phosphate and/or calcium oxalate (Table 9-1). Calcium oxalate stones form on interstitial apatite plaque, whereas calcium phosphate stones form on apatite crystals, obstructing collecting ducts. In patients who have hyperparathyroidism, the Arg990Gly polymorphism of the calcium-sensing receptor leads to higher urine calcium excretion and an increased risk of nephrolithiasis. Prompt diagnosis of hyperparathyroidism is important because parathyroidectomy should be carried out before recurrent stones or renal damage occurs.

Distal renal tubular acidosis

(See also Chap. 16) The defect in this condition seems to reside in the distal nephron, which cannot establish a normal pH gradient between urine and blood, leading to hyperchloremic acidosis. The diagnosis is suggested by a minimum urine pH >5.5 in the presence of systemic acidosis. Hypercalciuria, an alkaline urine, and a low urine citrate level increase urine saturation with respect to calcium phosphate. Calcium phosphate stones form, nephrocalcinosis is common, and osteomalacia or rickets may occur. Apatite deposits form in inner medullary collecting ducts and cause extensive medullary tubular interstitial nephropathy, which can lead to reduced kidney function. Renal tubular acidosis may be genetic, secondary to a systemic disease, or caused by a medication. Topiramate, a drug commonly used for seizures and migraines, inhibits the enzyme carbonic anhydrase and may cause calcium nephrolithiasis.

Treatment with supplemental alkali reduces hypercalciuria and limits the production of new stones. The preferred form of alkali is potassium citrate, which is given at a dose of 0.5–2.0 meq/kg body weight in two to three divided doses per day. In incomplete distal renal tubular acidosis, systemic acidosis is absent, but urine pH cannot be lowered below 5.5 after an exogenous acid load. Incomplete RTA may develop in some patients who form calcium oxalate stones because of idiopathic hypercalciuria; the importance of RTA in producing stones in this situation is uncertain, and thiazide treatment is a reasonable alternative. Alkali also can be used in incomplete RTA. In treating patients with alkali, it is prudent to monitor changes in urine citrate and pH. If urine pH increases without an increase in citrate, calcium phosphate supersaturation will increase and stone disease may worsen.

Hyperoxaluria

Oxalate is a metabolic end product in humans. Urine oxalate comes from diet and endogenous metabolic production, with ~40–50% originating from dietary sources. The upper limit of normal for oxalate excretion is generally considered to be 40–50 mg per day. Mild hyperoxaluria (50–80 mg/d) usually is caused by excessive intake of high-oxalate foods such as spinach, nuts, and chocolate. In addition, low-calcium diets may promote hyperoxaluria as there is less calcium available to bind oxalate in the intestine. Enteric hyperoxaluria is a consequence of small-bowel disease, resulting in fat malabsorption. Oxalate excretion is often >100 mg per day. Enteric hyperoxaluria may be caused by jejunoileal bypass for obesity, pancreatic insufficiency, or extensive small-intestine involvement from Crohn's disease. With fat malabsorption, calcium in the bowel lumen is bound by fatty acids instead of oxalate, which is left free for absorption in the colon. Delivery of unabsorbed fatty acids and bile salts to the colon injures the colonic mucosa and enhances oxalate absorption. Recent studies have shown that modern bariatric surgery for obesity that involves bypassing intestinal segments, such as Roux-en-Y gastric bypass and biliopancreatic diversions, may lead to hyperoxaluria that can cause kidney failure as well as kidney stones. The mechanism of hyperoxaluria has not been well studied.

Primary hyperoxaluria is a rare autosomal recessive disease that causes severe hyperoxaluria. Patients usually present with recurrent calcium oxalate stones during childhood. Primary hyperoxaluria type 1 is due to a deficiency in the peroxisomal enzyme alanine:glyoxylate aminotransferase. Type 2 is due to a deficiency of D-glyceric dehydrogenase. Severe hyperoxaluria from any cause can lead to stone formation and produce tubulointerstitial nephropathy (Chap. 17).

TREATMENT **Hyperoxaluria**

Patients with mild to moderate hyperoxaluria should be treated with a diet low in oxalate and with a normal intake of calcium and magnesium to reduce oxalate absorption. Enteric hyperoxaluria can be treated with a low-fat, low-oxalate diet and calcium supplements, given with meals, to bind oxalate in the gut lumen. The oxalate-binding resin cholestyramine provides an

additional form of therapy. Treatment for primary hyperoxaluria includes a high fluid intake, neutral phosphate, potassium citrate, and pyridoxine (25–200 mg/d). Even with aggressive therapy, irreversible renal failure may occur. Liver transplantation to correct the enzyme defect, combined with kidney transplantation, has been successfully utilized in patients with primary hyperoxaluria.

Hypocitraturia

Urine citrate prevents calcium stone formation by creating a soluble complex with calcium, effectively reducing free urine calcium. Hypocitraturia is found in 20–40% of stone formers either as a single disorder or in combination with other metabolic abnormalities. It can be secondary to systemic disorders such as RTA, chronic diarrheal illness, and hypokalemia, or it may be a primary disorder, in which case it is called *idiopathic hypocitraturia*.

TREATMENT **Hypocitraturia**

Treatment is with alkali, which increases urine citrate excretion; generally, bicarbonate or citrate salts are used. Potassium salts are preferred as sodium loading increases urinary excretion of calcium, reducing the effectiveness of treatment. Two randomized, placebo-controlled trials have demonstrated the effectiveness of citrate supplements in calcium oxalate stone formers. Lemonade and other citrate-rich beverages have been used to treat hypocitraturia, although the increase in urine citrate is not as great as that seen with pharmacologic dosing of citrate salts.

Idiopathic calcium lithiasis

Some patients have no metabolic cause for stones despite a thorough metabolic evaluation (Table 9-1). The best treatment appears to be high fluid intake so that the urine specific gravity remains at ≤1.005 throughout the day and night. Thiazide diuretics and citrate therapy may help reduce crystallization of calcium salts, but there have been no prospective trials in this patient population. Oral phosphate at a dose of 2 g phosphorus daily may lower urine calcium and increase urine pyrophosphate, thereby reducing the rate of recurrence. Orthophosphate causes mild nausea and diarrhea, but tolerance may improve with continued intake.

Uric acid stones

Persistently acidic urine is the major risk factor for uric acid stone formation. When urine pH is low, the protonated form of uric acid predominates and is soluble in urine at concentrations of 100 mg/L. Concentrations above this level represent supersaturation that causes crystals and stones to form. Common causes of acidic urine and uric acid stones include metabolic syndrome, chronic diarrheal states, gout, and idiopathic uric acid lithiasis. As the prevalence of obesity increases, metabolic syndrome is becoming an increasingly important cause of uric acid stone formation, as insulin resistance leads to a decrease in ammoniagenesis, requiring that the metabolic acid load be excreted as titratable acid. Hyperuricosuria, when present, increases supersaturation, but urine of low pH can be supersaturated with uric acid even though the daily excretion rate is normal. Myeloproliferative syndromes, chemotherapy for malignant tumors, and Lesch-Nyhan syndrome cause such massive production of uric acid and consequent hyperuricosuria that stones and uric acid sludge form even at a normal urine pH. Obstruction of the renal tubules by uric acid crystals can cause acute renal failure.

TREATMENT **Uric Acid Lithiasis**

The two goals of treatment are to raise urine pH and lower excessive urine uric acid excretion to <1 g/d. Supplemental alkali, 1–3 meq/kg of body weight per day, should be given in three or four divided doses, one of which should be given at bedtime. The goal of treatment should be a urine pH between 6 and 6.5 in a 24-h urine collection. Increasing urine pH above 6.5 will not provide additional benefit in preventing uric acid crystallization but increases the risk of calcium phosphate stone formation. The form of the alkali may be important. Potassium citrate may reduce the risk of calcium salts crystallizing when urine pH is increased, whereas sodium alkali salts may increase the risk. A low-purine diet should be instituted in uric acid stone formers with hyperuricosuria. Patients who continue to form uric acid stones despite treatment with fluids, alkali, and a low-purine diet should have allopurinol added to their regimen.

Cystinuria and cystine stones

In this inherited disorder, proximal tubular and jejunal transport of the dibasic amino acids cystine, lysine, arginine, and ornithine is defective, and excessive amounts are lost in the urine. Clinical disease is due solely to the insolubility of cystine. Cystine crystals plug terminal collecting ducts, and stones may grow as an extension of those plugs. Damage to the papillae and medulla from crystal obstruction is the probable reason why kidney function is reduced in cystinuria compared with routine stone disease.

Pathogenesis

Cystinuria occurs because of defective transport of dibasic amino acids by the brush borders of renal tubule and intestinal epithelial cells. Disease-causing mutations

have been identified in both the heavy and light chains of a heteromeric amino acid transporter found in the proximal tubule of the kidney. Cystinuria is classified into two main types, based on the urinary excretion of cystine in obligate heterozygotes. In type I cystinuria, heterozygotes have normal urine cystine excretion; thus, type I has an autosomal recessive pattern of inheritance. A gene on chromosome 2 that has been designated *SLC3A1* encodes the heavy chain of the transporter and has been found to be abnormal in type I. In non-type I cystinuria, heterozygotes have moderately elevated urine cystine excretion, with homozygotes having a much higher urine cystine excretion. Non-type I is inherited as a dominant trait with incomplete penetrance. Non-type I is due to mutations in the *SLC7A9* gene on chromosome 19, which encodes the light chain of the heteromeric transporter. In rare cases, mutations of the *SLC7A9* gene can lead to a type I phenotype.

Diagnosis

Cystine stones are formed only by patients with cystinuria, but 10% of stones in cystinuric patients do not contain cystine; therefore, every stone former should be screened for the disease. The sediment from a first morning urine specimen in many patients with homozygous cystinuria reveals typical hexagonal, platelike cystine crystals. Cystinuria can also be detected by using the urine sodium nitroprusside test. Because the test is sensitive, it is positive for cystinuria in many asymptomatic heterozygotes. A positive nitroprusside test or the finding of cystine crystals in the urine sediment should be evaluated by measurement of daily cystine excretion. Cystine stones seldom form in adults unless urine excretion is at least 300 mg/d.

TREATMENT **Cystinuria and Cystine Stones**

High fluid intake, even at night, is the cornerstone of therapy. Daily urine volume should exceed 3 L. Raising urine pH with alkali is helpful provided that the urine pH exceeds 7.5. A low-salt diet (100 mmol/d) can reduce cystine excretion up to 40%. Because side effects are common, drugs such as penicillamine and tiopronin, which form mixed soluble disulfide cysteine-drug complexes, should be used only when fluid loading, salt reduction, and alkali therapy are ineffective. Low-methionine diets have not proved to be practical for clinical use, but patients should avoid protein gluttony.

Struvite stones

These stones are a result of urinary infection with bacteria, usually *Proteus* species, which possess urease, an enzyme that degrades urea to NH_3 and CO_2. The NH_3 hydrolyzes to NH_4^+ and raises urine pH to 8 or 9. The NH_4^+ precipitates PO_4^{3-} and Mg^{2+} to form $MgNH_4PO_4$ (struvite). Struvite does not form in urine in the absence of infection, because NH_4^+ concentration is low in urine that is alkaline in response to physiologic stimuli. Chronic *Proteus* infection can occur because of impaired urinary drainage, or urologic instrumentation or surgery, and especially with chronic antibiotic treatment, which can favor the dominance of *Proteus* in the urinary tract. The presence of struvite crystals in urine, rectangular prisms that resemble coffin lids, indicates infection with urease-producing organisms.

TREATMENT **Struvite Stones**

Complete removal of the stone with subsequent sterilization of the urinary tract is the treatment of choice for patients who can tolerate the procedures. Percutaneous nephrolithotomy is the preferred surgical approach for most patients. At times, extracorporeal lithotripsy may be used in combination with a percutaneous approach. Open surgery is rarely required. Irrigation of the renal pelvis and calyces with hemiacidrin, a solution that dissolves struvite, can reduce recurrence after surgery. Stone-free rates of 50–90% have been reported after surgical intervention. Antimicrobial treatment is best reserved for dealing with acute infection and for maintenance of a sterile urine after surgery. Urine cultures and culture of stone fragments removed at surgery should guide the choice of antibiotic. For patients who are not candidates for surgical removal of a stone, acetohydroxamic acid, an inhibitor of urease, can be used. Unfortunately, acetohydroxamic acid has many side effects, such as headache, tremor, and thrombophlebitis, that limit its use.

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SECTION III

ACUTE KIDNEY INJURY AND CHRONIC RENAL FAILURE

CHAPTER 10

ACUTE KIDNEY INJURY

Sushrut S. Waikar ■ Joseph V. Bonventre

Acute kidney injury (AKI), previously known as acute renal failure, is characterized by the sudden impairment of kidney function resulting in the retention of nitrogenous and other waste products normally cleared by the kidneys. AKI is not a single disease but, rather, a designation for a heterogeneous group of conditions that share common diagnostic features: specifically, an increase in the blood urea nitrogen (BUN) concentration and/or an increase in the plasma or serum creatinine (SCr) concentration, often associated with a reduction in urine volume. AKI can range in severity from asymptomatic and transient changes in laboratory parameters of glomerular filtration rate (GFR) to overwhelming and rapidly fatal derangements in effective circulating volume regulation and electrolyte and acid-base composition of the plasma.

Changing the name of a syndrome as well known as "acute renal failure" does not occur frequently. We will summarize some of the reasons why the name was changed to "acute kidney injury." The term *failure* reflects only part of the spectrum of damage to the kidney that occurs clinically. In most cases of damage, the reduction in kidney function is modest. Nevertheless, this modest change has been documented to be associated with negative effects on outcome, albeit not nearly as ominous as those seen with large decreases in kidney function associated with frank kidney failure that often requires acute dialysis therapies. Furthermore, the term *renal* is not well understood in the general population and this makes communication with patients and family more challenging; hence "kidney" has replaced "renal."

EPIDEMIOLOGY

AKI complicates 5–7% of acute care hospital admissions and up to 30% of admissions to the intensive care unit. AKI is also a major medical complication in the developing world, particularly in the setting of diarrheal illnesses, infectious diseases like malaria and leptospirosis, and natural disasters such as earthquakes. The incidence of AKI has grown by more than fourfold in the United States since 1988 and is estimated to have a yearly incidence of 500 per 100,000 population, higher than the yearly incidence of stroke. AKI is associated with a markedly increased risk of death in hospitalized individuals, particularly in those admitted to the ICU where in-hospital mortality rates may exceed 50%.

AKI IN THE DEVELOPING WORLD

The epidemiology of AKI differs tremendously between developed and developing countries, owing to differences in demographics, economics, geography, and comorbid disease burden. While certain features of AKI are common to both—particularly since urban centers of some developing countries increasingly resemble those in the developed world—many etiologies for AKI are region specific such as envenomations from snakes, spiders, caterpillars, and bees; infectious causes such as malaria and leptospirosis; and crush injuries and resultant rhabdomyolysis from earthquakes.

ETIOLOGY AND PATHOPHYSIOLOGY

The causes of AKI have traditionally been divided into three broad categories: prerenal azotemia, intrinsic renal parenchymal disease, and postrenal obstruction **(Fig. 10-1)**.

PRERENAL AZOTEMIA

Prerenal azotemia (from "azo," meaning nitrogen, and "-emia") is the most common form of AKI. It is the designation for a rise in SCr or BUN concentration due to inadequate renal plasma flow and intraglomerular hydrostatic pressure to support normal glomerular filtration. The most common clinical conditions associated with

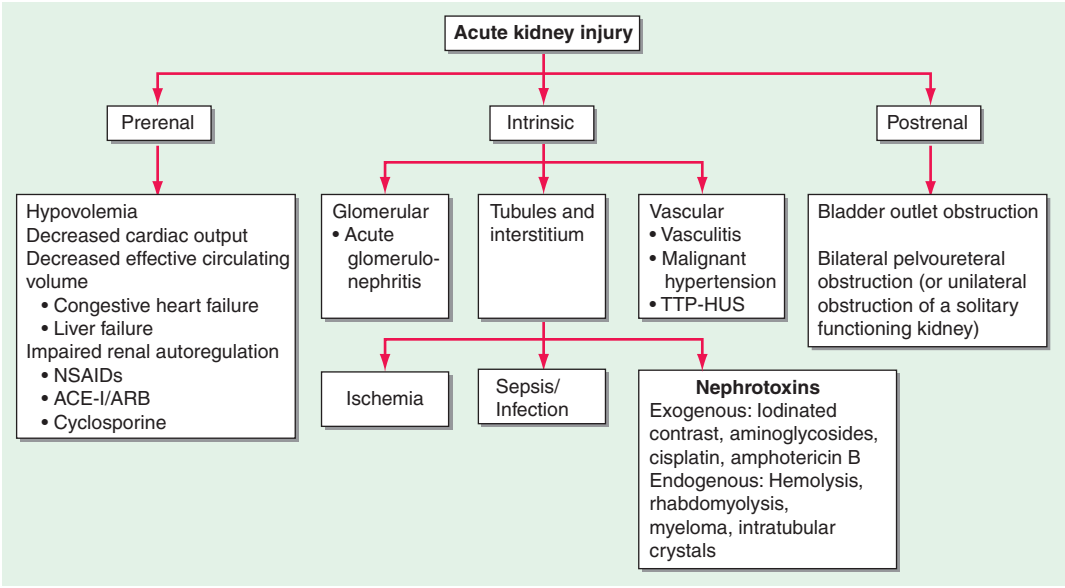

FIGURE 10-1

Classification of the major causes of acute kidney injury. ACE-1, angiotensin-converting enzyme 1; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs; TTP-HUS, thrombotic thrombocytopenic purpura–hemolytic uremic syndrome.

prerenal azotemia are hypovolemia, decreased cardiac output, and medications that interfere with renal autoregulatory responses such as nonsteroidal anti-inflammatory drugs (NSAIDs) and inhibitors of angiotensin II (Fig. 10-2). Prerenal azotemia may coexist with other forms of intrinsic AKI. Prolonged periods of prerenal azotemia may lead to ischemic injury, often termed acute tubular necrosis, or ATN. By definition, prerenal azotemia involves no parenchymal damage to the kidney and is rapidly reversible once intraglomerular hemodynamics are restored.

Normal GFR is maintained in part by the relative resistances of the afferent and efferent renal arterioles, which determine the glomerular plasma flow and the transcapillary hydraulic pressure gradient that drive glomerular ultrafiltration. Mild degrees of hypovolemia and reductions in cardiac output elicit compensatory renal physiologic changes. Because renal blood flow accounts for 20% of the cardiac output, renal vasoconstriction and salt and water reabsorption occur as a homeostatic response to decreased effective circulating volume or cardiac output in order to maintain blood pressure and increase intravascular volume to sustain perfusion to the cerebral and coronary vessels. Mediators of this response include angiotensin II, norepinephrine, and vasopressin (also termed antidiuretic hormone). Glomerular filtration can be maintained despite reduced renal blood flow by angiotensin II–mediated renal efferent vasoconstriction, which maintains glomerular capillary hydrostatic pressure closer to normal and thereby prevents marked reductions in GFR if renal blood flow reduction is not excessive.

In addition, a myogenic reflex within the afferent arteriole leads to dilation in the setting of low perfusion pressure, thereby maintaining glomerular perfusion. Intrarenal biosynthesis of vasodilator prostaglandins (prostacyclin, prostaglandin E_2), kallikrein and kinins, and possibly nitric oxide (NO) also increase in response to low renal perfusion pressure. Autoregulation is also accomplished by tubuloglomerular feedback, in which decreases in solute delivery to the macula densa (specialized cells within the distal tubule) elicit dilation of the juxtaposed afferent arteriole in order to maintain glomerular perfusion, a mechanism mediated, in part, by NO. There is a limit, however, to the ability of these counterregulatory mechanisms to maintain GFR in the face of systemic hypotension. Even in healthy adults, renal autoregulation usually fails once the systolic blood pressure falls below 80 mmHg.

A number of factors determine the robustness of the autoregulatory response and, thereby, the risk of prerenal azotemia. Atherosclerosis, long-standing hypertension, and older age can lead to hyalinosis and myointimal hyperplasia, causing structural narrowing of the intrarenal arterioles and impaired capacity for renal afferent vasodilation. In chronic kidney disease, renal afferent vasodilation may be operating at maximal capacity in order to maximize GFR in response to reduced functional renal mass. Drugs can affect the compensatory changes evoked to maintain GFR. NSAIDs inhibit renal prostaglandin production, limiting renal afferent vasodilation. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) limit renal efferent vasoconstriction; this effect is particularly pronounced in patients with bilateral renal artery stenosis or unilateral renal artery stenosis (in the case of a solitary functioning kidney) because renal efferent vasoconstriction is

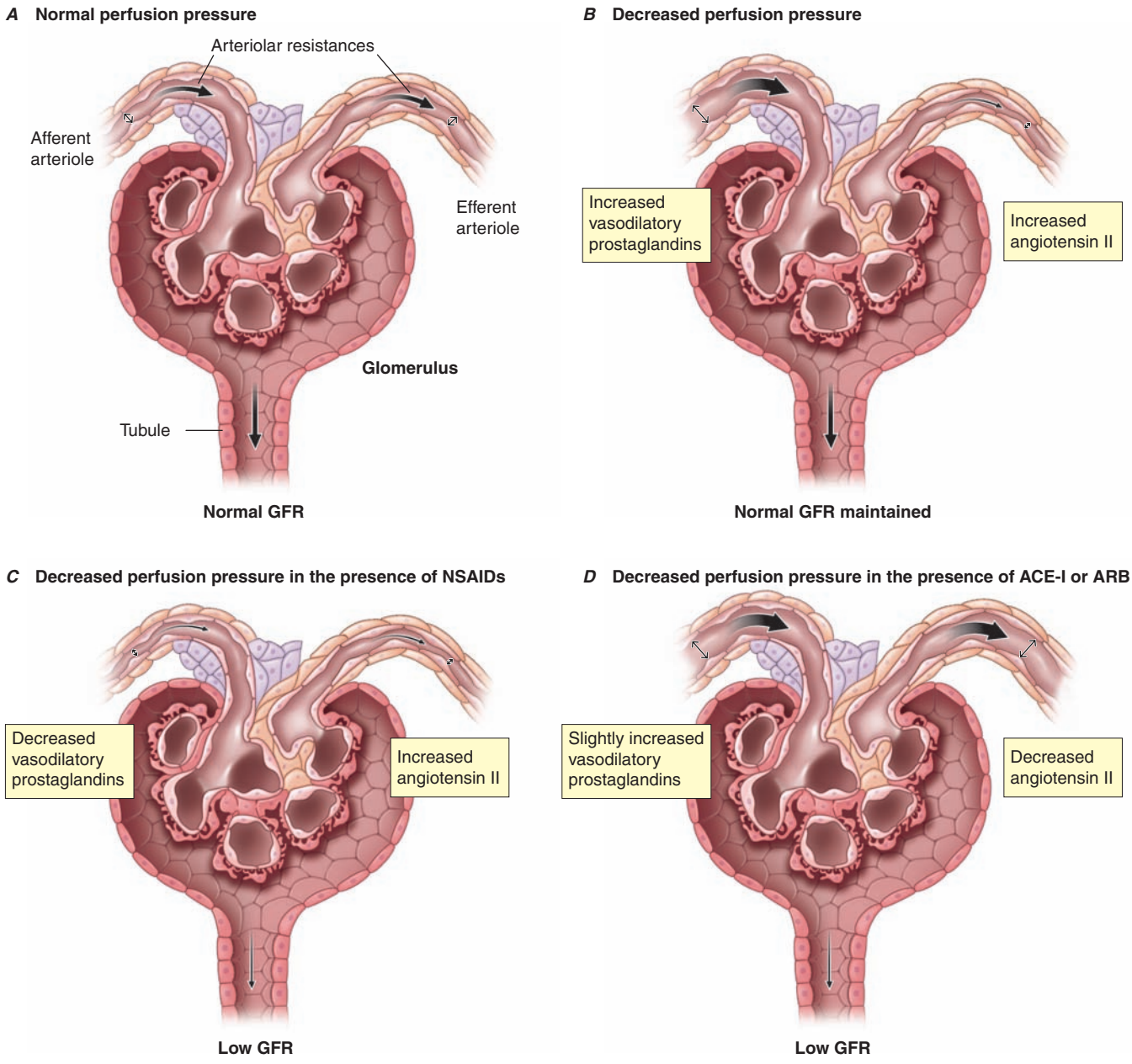

FIGURE 10-2

Intrarenal mechanisms for autoregulation of the glomerular filtration rate (GFR) under decreased perfusion pressure and reduction of the GFR by drugs. Panel ***A*** shows normal conditions and a normal GFR. Panel ***B*** shows reduced perfusion pressure within the autoregulatory range. Normal glomerular capillary pressure is maintained by afferent vasodilatation and efferent vasoconstriction. Panel ***C*** shows reduced perfusion pressure with a nonsteroidal anti-inflammatory drug (NSAID). Loss of vasodilatory prostaglandins increases afferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease. Panel ***D*** shows reduced perfusion pressure with an angiotensin-converting enzyme (ACE-I) inhibitor or an angiotensin receptor blocker (ARB). Loss of angiotensin II action reduces efferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease. (*From JG Abuelo: N Engl J Med 2007;357:797-805; with permission.*)

needed to maintain GFR due to low renal perfusion. The combined use of nonsteroidal anti-inflammatory agents with ACE inhibitors or ARBs poses a particularly high risk for developing prerenal azotemia.

Many individuals with advanced cirrhosis exhibit a unique hemodynamic profile that resembles prerenal azotemia despite total body volume overload. Systemic vascular resistance is markedly reduced due to primary arterial vasodilation in the splanchnic circulation, resulting ultimately in activation of vasoconstrictor responses similar to those seen in hypovolemia. AKI is a common complication in this setting, and it can be triggered by volume depletion and spontaneous bacterial peritonitis. A particularly poor prognosis is seen in the case of

type 1 hepatorenal syndrome, in which AKI without an alternate cause (e.g., infection, shock, nephrotoxic drugs) persists despite volume administration and withholding of diuretics. Type 2 hepatorenal syndrome is a less severe form characterized mainly by refractory ascites.

INTRINSIC AKI

The most common causes of intrinsic AKI are sepsis, ischemia, and nephrotoxins, both endogenous and exogenous **(Fig. 10-3)**. In many cases, prerenal azotemia advances to tubular injury. Although classically termed "acute tubular necrosis," human biopsy confirmation of tubular necrosis is, in general, lacking in cases of sepsis and ischemia; indeed, processes such as inflammation, apoptosis, and altered regional perfusion may be more relevant pathophysiologically. Other causes of intrinsic AKI are less common and can be conceptualized anatomically according to the major site of renal parenchymal damage: glomeruli, tubulointerstitium, and vessels.

SEPSIS-ASSOCIATED AKI

In the United States, more than 700,000 cases of sepsis occur each year. AKI complicates more than 50% of cases of severe sepsis, and greatly increases the risk of death. Sepsis is also a very important cause of AKI in the developing world. Decreases in GFR with sepsis

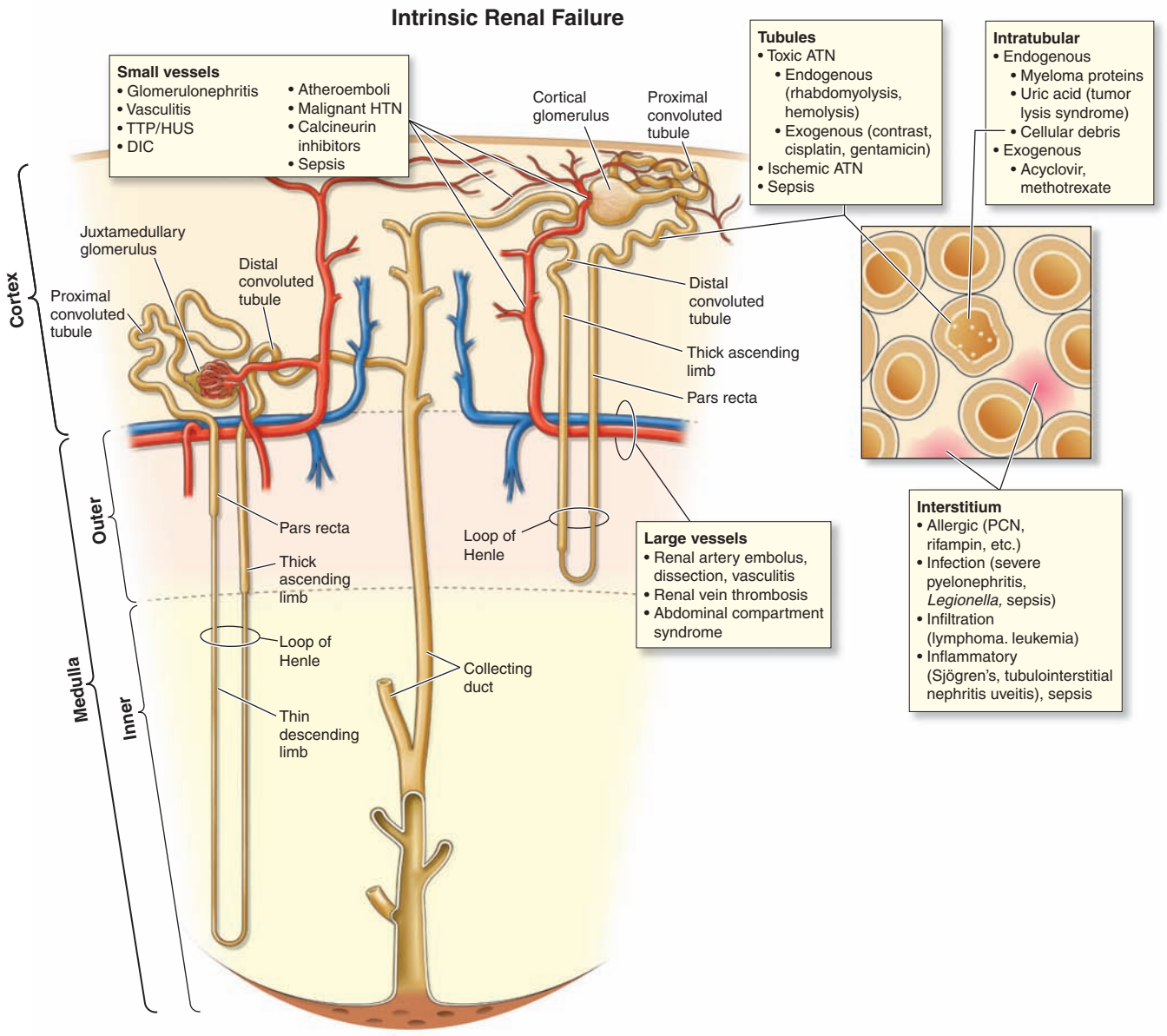

FIGURE 10-3

Major causes of intrinsic acute kidney injury. ATN, acute tubular necrosis; DIC, disseminated intravascular coagulation; HTN, hypertensive nephropathy; MTX, methotrexate; PCN, penicillin; TINU, tubulointerstitial nephritis-uveitis; TTP/HUS, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome.

can occur even in the absence of overt hypotension, although most cases of severe AKI typically occur in the setting of hemodynamic collapse requiring vasopressor support. While there is clearly tubular injury associated with AKI in sepsis as manifest by the presence of tubular debris and casts in the urine, postmortem examinations of kidneys from individuals with severe sepsis suggest that other factors, perhaps related to inflammation and interstitial edema, must be considered in the pathophysiology of sepsis-induced AKI.

The hemodynamic effects of sepsis—arising from generalized arterial vasodilation, mediated in part by cytokines that upregulate the expression of inducible NO synthase in the vasculature—can lead to a reduction in GFR. The operative mechanisms may be excessive efferent arteriole vasodilation, particularly early in the course of sepsis, or renal vasoconstriction from activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, vasopressin, and endothelin. Sepsis may lead to endothelial damage, which results in microvascular thrombosis, activation of reactive oxygen species, and leukocyte adhesion and migration, all of which may injure renal tubular cells.

ISCHEMIA-ASSOCIATED AKI

Healthy kidneys receive 20% of the cardiac output and account for 10% of resting oxygen consumption, despite constituting only 0.5% of the human body mass. The kidneys are also the site of one of the most hypoxic regions in the body, the renal medulla. The outer medulla is particularly vulnerable to ischemic damage because of the architecture of the blood vessels that supply oxygen and nutrients to the tubules. Enhanced leukocyte-endothelial interactions in the small vessels lead to inflammation and reduced local blood flow to the metabolically very active S3 segment of the proximal tubule, which depends on oxidative metabolism for survival. Ischemia alone in a normal kidney is usually not sufficient to cause severe AKI, as evidenced by the relatively low risk of severe AKI even after total interruption of renal blood flow during suprarenal aortic clamping or cardiac arrest. Clinically, AKI more commonly develops when ischemia occurs in the context of limited renal reserve (e.g., chronic kidney disease or older age) or coexisting insults such as sepsis, vasoactive or nephrotoxic drugs, rhabdomyolysis, and the systemic inflammatory states associated with burns and pancreatitis. Prerenal azotemia and ischemia-associated AKI represent a continuum of the manifestations of renal hypoperfusion. Persistent preglomerular vasoconstriction may be a common underlying cause of the reduction in GFR seen in AKI; implicated factors for vasoconstriction include activation of tubuloglomerular feedback from enhanced delivery of solute to the macula densa following proximal tubule injury, increased basal vascular tone and reactivity to vasoconstrictive agents, and decreased vasodilator responsiveness. Other contributors to low GFR include backleak of filtrate across ischemic and denuded tubular epithelium and mechanical obstruction of tubules from necrotic debris **(Fig. 10-4)**.

Postoperative AKI

Ischemia-associated AKI is a serious complication in the postoperative period, especially after major operations

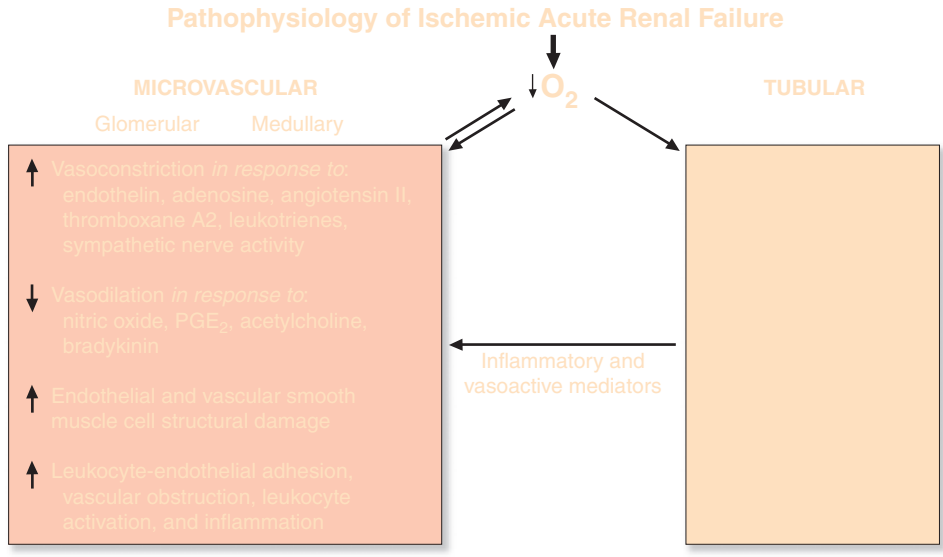

FIGURE 10-4
Interacting microvascular and tubular events contributing to the pathophysiology of ischemic acute kidney injury. PGE_2, prostaglandin E_2. (*From JV Bonventre, JM Weinberg: J Am Soc Nephrol 14:2199, 2003.*)

involving significant blood loss and intraoperative hypotension. The procedures most commonly associated with AKI are cardiac surgery with cardiopulmonary bypass (particularly for combined valve and bypass procedures), vascular procedures with aortic cross clamping, and intraperitoneal procedures. Severe AKI requiring dialysis occurs in approximately 1% of cardiac and vascular surgery procedures. The risk of severe AKI has been less well studied for major intraperitoneal procedures, but appears to be of comparable magnitude. Common risk factors for postoperative AKI include underlying chronic kidney disease, older age, diabetes mellitus, congestive heart failure, and emergency procedures. The pathophysiology of AKI following cardiac surgery is multifactorial. Major AKI risk factors are common in the population undergoing cardiac surgery. The use of nephrotoxic agents including iodinated contrast for cardiac imaging prior to surgery may increase the risk of AKI. Cardiopulmonary bypass is a unique hemodynamic state characterized by nonpulsatile flow and exposure of the circulation to extracorporeal circuits. Longer duration of cardiopulmonary bypass is a risk factor for AKI. In addition to ischemic injury from sustained hypoperfusion, cardiopulmonary bypass may cause AKI through a number of mechanisms including extracorporeal circuit activation of leukocytes and inflammatory processes, hemolysis with resultant pigment nephropathy (see later in the chapter), and aortic injury with resultant atheroemboli. AKI from atheroembolic disease, which can also occur following percutaneous catheterization of the aorta, or spontaneously, is due to cholesterol crystal embolization resulting in partial or total occlusion of multiple small arteries within the kidney. Over time, a foreign body reaction can result in intimal proliferation, giant cell formation, and further narrowing of the vascular lumen, accounting for the generally subacute (over a period of weeks rather than days) decline in renal function.

Burns and acute pancreatitis

Extensive fluid losses into the extravascular compartments of the body frequently accompany severe burns and acute pancreatitis. AKI is an ominous complication of burns, affecting 25% of individuals with more than 10% total body surface area involvement. In addition to severe hypovolemia resulting in decreased cardiac output and increased neurohormonal activation, burns and acute pancreatitis both lead to dysregulated inflammation and an increased risk of sepsis and acute lung injury, all of which may facilitate the development and progression of AKI. Individuals undergoing massive fluid resuscitation for trauma, burns, and acute pancreatitis can also develop the abdominal compartment syndrome, where markedly elevated intraabdominal pressures, usually higher than 20 mmHg, lead to renal vein compression and reduced GFR.

Diseases of the microvasculature leading to ischemia

Microvascular causes of AKI include the thrombotic microangiopathies [antiphospholipid antibody syndrome, radiation nephritis, malignant nephrosclerosis, and thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP-HUS)], scleroderma, and atheroembolic disease. Large vessel diseases associated with AKI include renal artery dissection, thromboembolism, thrombosis, and renal vein compression or thrombosis.

NEPHROTOXIN-ASSOCIATED AKI

The kidney has very high susceptibility to nephrotoxicity due to extremely high blood perfusion and concentration of circulating substances along the nephron where water is reabsorbed and in the medullary interstitium; this results in high-concentration exposure of toxins to tubular, interstitial, and endothelial cells. Nephrotoxic injury occurs in response to a number of pharmacologic compounds with diverse structures, endogenous substances, and environmental exposures. All structures of the kidney are vulnerable to toxic injury, including the tubules, interstitium, vasculature, and collecting system. As with other forms of AKI, risk factors for nephrotoxicity include older age, chronic kidney disease (CKD), and prerenal azotemia. Hypoalbuminemia may increase the risk of some forms of nephrotoxin-associated AKI due to increased free-circulating drug concentrations.

Contrast agents

Iodinated contrast agents used for cardiovascular and CT imaging are a leading cause of AKI. The risk of AKI, or "contrast nephropathy," is negligible in those with normal renal function but increases markedly in the setting of chronic kidney disease, particularly diabetic nephropathy. The most common clinical course of contrast nephropathy is characterized by a rise in SCr beginning 24–48 hours following exposure, peaking within 3–5 days, and resolving within 1 week. More severe, dialysis-requiring AKI is uncommon except in the setting of significant preexisting chronic kidney disease, often in association with congestive heart failure or other coexisting causes for ischemia-associated AKI. Patients with multiple myeloma and renal disease are particularly susceptible. Low fractional excretion of sodium and relatively benign urinary sediment without features of tubular necrosis (see later in the chapter) are common findings. Contrast nephropathy is thought to occur from a combination of factors, including (1) hypoxia in the renal outer medulla due to perturbations in renal microcirculation and occlusion of small vessels; (2) cytotoxic damage to the tubules directly or via the generation of oxygen free radicals, especially since the concentration of the agent within

the tubule is markedly increased; and (3) transient tubule obstruction with precipitated contrast material. Other diagnostic agents implicated as a cause of AKI are high-dose gadolinium used for MRI and oral sodium phosphate solutions used as bowel purgatives.

Antibiotics

Several antimicrobial agents are commonly associated with AKI. *Aminoglycosides and amphotericin B* both cause tubular necrosis. Nonoliguric AKI (i.e., without a significant reduction in urine volume) accompanies 10–30% of courses of aminoglycoside antibiotics, even when plasma levels are in the therapeutic range. Aminoglycosides are freely filtered across the glomerulus and then accumulate within the renal cortex, where concentrations can greatly exceed those of the plasma. AKI typically manifests after 5–7 days of therapy and can present even after the drug has been discontinued. Hypomagnesemia is a common finding.

Amphotericin B causes renal vasoconstriction from an increase in tubuloglomerular feedback as well as direct tubular toxicity mediated by reactive oxygen species. Nephrotoxicity from amphotericin B is dose and duration dependent. This drug binds to tubular membrane cholesterol and introduces pores. Clinical features of amphotericin B nephrotoxicity include polyuria, hypomagnesemia, hypocalcemia, and nongap metabolic acidosis.

Vancomycin may be associated with AKI, particularly when trough levels are high, but a causal relationship with AKI has not been definitively established. *Acyclovir* can precipitate in tubules and cause AKI by tubular obstruction, particularly when given as an intravenous bolus at high doses (500 mg/m^2) or in the setting of hypovolemia. *Foscarnet*, *pentamidine*, and *cidofovir* (less commonly prescribed antimicrobials) are also frequently associated with AKI due to tubular toxicity. AKI secondary to acute interstitial nephritis can occur as a consequence of a number of antibiotics, including *penicillins*, *cephalosporins*, *quinolones*, *sulfonamides*, and *rifampin*.

Chemotherapeutic agents

Cisplatin and *carboplatin* are accumulated by proximal tubular cells and cause necrosis and apoptosis. Intensive hydration regimens have reduced the incidence of cisplatin nephrotoxicity, but it remains a dose-limiting toxicity. *Ifosfamide* may cause hemorrhagic cystitis and tubular toxicity, manifested as Type II renal tubular acidosis (Fanconi's syndrome), polyuria, hypokalemia, and a modest decline in GFR. Antiangiogenesis agents such as *bevacizumab*, can cause proteinuria and hypertension via injury to the glomerular microvasculature (thrombotic microangiopathy). Other antineoplastic agents such as mitomycin C and gemcitabine may cause thrombotic microangiopathy with resultant AKI.

Toxic ingestions

Ethylene glycol, present in automobile antifreeze, is metabolized to oxalic acid, glycolaldehyde, and glyoxylate, which may cause AKI through direct tubular injury. Diethylene glycol is an industrial agent that has been the cause of outbreaks of severe AKI around the world due to adulteration of pharmaceutical preparations. The metabolite 2-hydroxyethoxyacetic acid (HEAA) is thought to be responsible for tubular injury. Melamine contamination of foodstuffs has led to nephrolithiasis and AKI, either through intratubular obstruction or possibly direct tubular toxicity. Aristolochic acid was found to be the cause of "Chinese herb nephropathy" and "Balkan nephropathy" due to contamination of medicinal herbs or farming. The list of environmental toxins is likely to grow and contribute to a better understanding of previously catalogued "idiopathic" chronic tubular interstitial disease, a common diagnosis in both the developed and developing world.

Endogenous toxins

AKI may be caused by a number of endogenous compounds, including myoglobin, hemoglobin, uric acid, and myeloma light chains. Myoglobin can be released by injured muscle cells, and hemoglobin can be released during massive hemolysis leading to pigment nephropathy. Rhabdomyolysis may result from traumatic crush injuries, muscle ischemia during vascular or orthopedic surgery, compression during coma or immobilization, prolonged seizure activity, excessive exercise, heat stroke or malignant hyperthermia, infections, metabolic disorders (e.g., hypophosphatemia, severe hypothyroidism), and myopathies (drug induced, metabolic, or inflammatory). Pathogenic factors for AKI include intrarenal vasoconstriction, direct proximal tubular toxicity, and mechanical obstruction of the distal nephron lumen when myoglobin or hemoglobin precipitates with Tamm-Horsfall protein (uromodulin, the most common protein in urine and produced in the thick ascending limb of the loop of Henle), a process favored by acidic urine. Tumor lysis syndrome may follow initiation of cytotoxic therapy in patients with high-grade lymphomas and acute lymphoblastic leukemia; massive release of uric acid (with serum levels often exceeding 15 mg/dL) leads to precipitation of uric acid in the renal tubules and AKI. Other features of tumor lysis syndrome include hyperkalemia and hyperphosphatemia. The tumor lysis syndrome can also occasionally occur spontaneously or with treatment for solid tumors or multiple myeloma. Myeloma light chains can also cause AKI by direct tubular toxicity and by binding to Tamm-Horsfall protein to form obstructing intratubular casts. Hypercalcemia, which can also be seen in multiple myeloma, may cause AKI by intense renal vasoconstriction and volume depletion.

Allergic acute tubulointerstitial disease and other causes of intrinsic AKI

While many of the ischemic and toxic causes of AKI previously described result in tubulointerstitial disease, many drugs are also associated with the development of an allergic response characterized by an inflammatory infiltrate and often peripheral and urinary eosinophilia. AKI may be caused by severe infections and infiltrative diseases. Diseases of the glomeruli or vasculature can lead to AKI by compromising blood flow within the renal circulation. Glomerulonephritis or vasculitis are relatively uncommon but potentially severe causes of AKI that may necessitate timely treatment with immunosuppressive agents or therapeutic plasma exchange.

POSTRENAL ACUTE KIDNEY INJURY

(See also Chap. 21) Postrenal AKI occurs when the normally unidirectional flow of urine is acutely blocked either partially or totally, leading to increased retrograde hydrostatic pressure and interference with glomerular filtration. Obstruction to urinary flow may be caused by functional or structural derangements anywhere from the renal pelvis to the tip of the urethra **(Fig. 10-5)**. Normal urinary flow rate does not rule out the presence of partial obstruction, since the GFR is normally two orders of magnitude higher than the urinary flow rate. For AKI to occur in healthy individuals, obstruction must affect both kidneys unless only one kidney is functional, in which case unilateral obstruction can cause AKI. Unilateral obstruction may cause AKI in the setting of significant underlying CKD or in rare cases from reflex vasospasm of the contralateral kidney. Bladder neck obstruction is a common cause of postrenal AKI and can be due to prostate disease (benign prostatic hypertrophy or prostate cancer), neurogenic bladder, or therapy with anticholinergic drugs. Obstructed Foley catheters can cause postrenal AKI if not recognized and relieved. Other causes of lower tract obstruction are blood clots, calculi, and urethral strictures. Ureteric obstruction can occur from intraluminal obstruction (e.g., calculi, blood clots, sloughed renal papillae), infiltration of the ureteric wall (e.g., neoplasia), or external compression (e.g., retroperitoneal fibrosis, neoplasia, abscess, or inadvertent surgical damage). The pathophysiology of postrenal AKI involves hemodynamic alterations triggered by an abrupt increase in intratubular pressures. An initial period of hyperemia from afferent arteriolar dilation is followed by intrarenal vasoconstriction from the generation of angiotensin II, thromboxane A2, and vasopressin, and a reduction in NO production. Reduced GFR is due to underperfusion of glomeruli and, possibly, changes in the glomerular ultrafiltration coefficient.

DIAGNOSTIC EVALUATION (TABLE 10-1)

The presence of AKI is usually inferred by an elevation in the SCr concentration. AKI is currently defined by a rise of at least 0.3 mg/dL or 50% higher than baseline within a 24- to 48-hour period or a reduction in urine output to

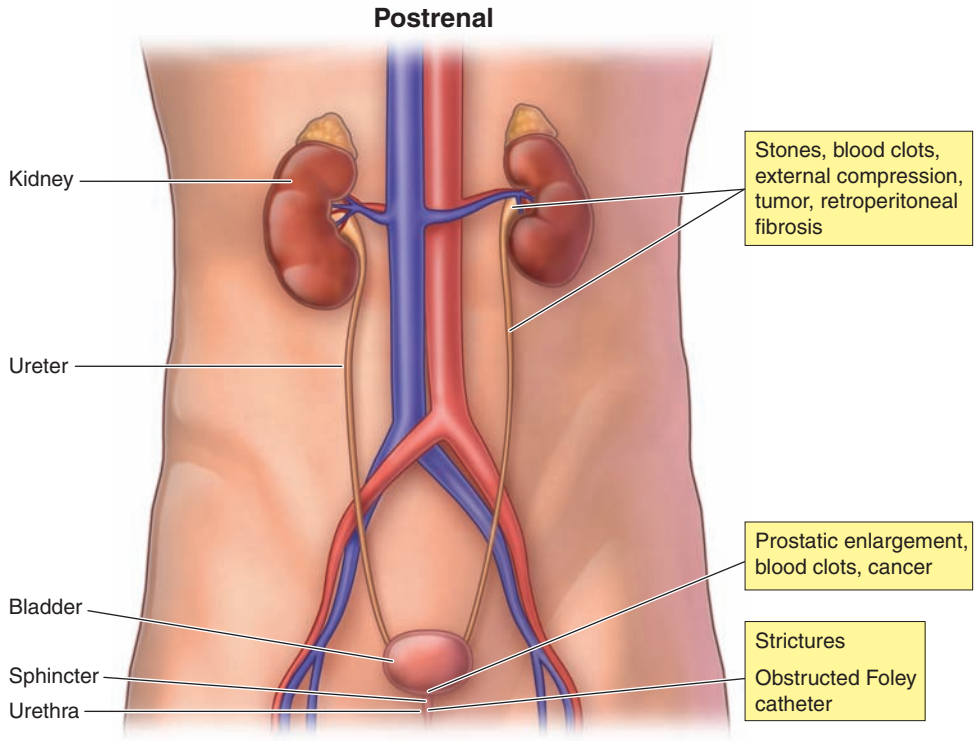

FIGURE 10-5
Anatomic sites and causes of obstruction leading to postrenal acute kidney injury.

TABLE 10-1

MAJOR CAUSES, CLINICAL FEATURES, AND DIAGNOSTIC STUDIES FOR ACUTE KIDNEY INJURY

ETIOLOGY	CLINICAL FEATURES	LABORATORY FEATURES	COMMENTS
Prerenal azotemia	History of poor fluid intake or fluid loss (hemorrhage, diarrhea, vomiting, sequestration into extravascular space); NSAID/ACE-I/ARB; heart failure; evidence of volume depletion (tachycardia, absolute or postural hypotension, low jugular venous pressure, dry mucous membranes), decreased effective circulatory volume (cirrhosis, heart failure)	BUN/creatinine ratio above 20, FeNa <1%, hyaline casts in urine sediment, urine specific gravity >1.018, urine osmolality >500 mosmol/kg.	Low FeNa, high specific gravity and osmolality may not be seen in the setting of CKD, diuretic use; BUN elevation out of proportion to creatinine may alternatively indicate upper GI bleed or increased catabolism. Response to restoration of hemodynamics is most diagnostic.
Sepsis-associated AKI	Sepsis, sepsis syndrome, or septic shock. Overt hypotension not always seen in mild to moderate AKI	Positive culture from normally sterile body fluid; urine sediment often contains granular casts, renal tubular epithelial cell casts.	FeNa may be low (<1%), particularly early in the course, but is usually >1% and osmolality <500 mosmol/kg.
Ischemia-associated AKI	Systemic hypotension, often superimposed upon sepsis and/or reasons for limited renal reserve such as older age, CKD	Urine sediment often contains granular casts, renal tubular epithelial cell casts. FeNa typically >1%.	
Nephrotoxin-Associated AKI: Endogenous			
Rhabdomyolysis	Traumatic crush injuries, seizures, immobilization	Elevated myoglobin, creatine kinase; urinalysis heme positive with few red blood cells.	FeNa may be low (<1%).
Hemolysis	Recent blood transfusion with transfusion reaction	Anemia, elevated LDH, low haptoglobin.	FeNa may be low (<1%); evaluation for transfusion reaction.
Tumor lysis	Recent chemotherapy	Hyperphosphatemia, hypocalcemia, hyperuricemia.	
Multiple myeloma	Age >60 years, constitutional symptoms, bone pain	Monoclonal spike in urine or serum electrophoresis; low anion gap.	Bone marrow or renal biopsy can be diagnostic.
Nephrotoxin-Associated AKI: Exogenous			
Contrast nephropathy	Exposure to iodinated contrast	Characteristic course is rise in SCr within 1–2 d, peak within 3–5 d, recovery within 7 d.	FeNa may be low (<1%).
Tubular injury	Aminoglycoside antibiotics, cisplatin, tenofovir, zoledronate	Urine sediment often contains granular casts, renal tubular epithelial cell casts. FeNa typically >1%.	
Interstitial nephritis	Recent medication exposure; can have fever, rash arthralgias	Eosinophilia, sterile pyuria; often nonoliguric.	Urine eosinophils have limited diagnostic accuracy; systemic signs of drug reaction often absent; kidney biopsy may be helpful.
Other Causes of Intrinsic AKI			
Glomerulonephritis/vasculitis	Variable (Chap. 15) features include skin rash, arthralgias, sinusitis (AGBM disease), lung hemorrhage (AGBM, ANCA, lupus), recent skin infection or pharyngitis (poststreptococcal)	ANA, ANCA, AGBM antibody, hepatitis serologies, cryoglobulins, blood culture, decreased complement levels, ASO titer (abnormalities of these tests depending on etiology).	Kidney biopsy may be necessary.

(*continued*)

TABLE 10-1

MAJOR CAUSES, CLINICAL FEATURES, AND DIAGNOSTIC STUDIES FOR ACUTE KIDNEY INJURY (*CONTINUED*)

ETIOLOGY	CLINICAL FEATURES	LABORATORY FEATURES	COMMENTS
Interstitial nephritis	Nondrug-related causes include tubulointerstitial nephritis-uveitis (TINU) syndrome, *Legionella* infection	Eosinophilia, sterile pyuria; often nonoliguric.	Urine eosinophils have limited diagnostic accuracy; kidney biopsy may be necessary.
TTP-HUS	Recent GI infection or use of calcineurin inhibitors	Schistocytes on peripheral blood smear, elevated LDH, anemia, thrombocytopenia.	Kidney biopsy may be necessary.
Atheroembolic disease	Recent manipulation of the aorta or other large vessels; may occur spontaneously or after anticoagulation; retinal plaques, palpable purpura, livedo reticularis, GI bleed	Hypocomplementemia, eosinophiluria (variable), variable amounts of proteinuria.	Skin or kidney biopsy can be diagnostic.
Postrenal AKI	History of kidney stones, prostate disease, obstructed bladder catheter, retroperitoneal or pelvic neoplasm	No specific findings other than AKI; may have pyuria or hematuria.	Imaging with computed tomography or ultrasound.

Abbreviations: ACE-1, angiotensin-converting enzyme-1; AGBM, antiglomerular basement membrane; AKI, acute kidney injury; ANA, antinuclear antibody; ANCA, antineutrophilic cytoplasmic antibody; ARB, angiotensin receptor blocker; ASO, antistreptolysin O; BUN, blood urea nitrogen; CKD, chronic kidney disease; FeNa, fractional excretion of sodium; GI, gastrointestinal; LDH, lactate dehydrogenase; NSAID, nonsteroidal anti-inflammatory drug. TTP-HUS, thrombotic thrombocytopenic purpura–hemolytic uremic syndrome.

0.5 mL/kg per hour for longer than 6 hours. It is important to recognize that given this definition, some patients with AKI will not have tubular or glomerular damage (e.g., prerenal azotemia). The distinction between AKI and chronic kidney disease is important for proper diagnosis and treatment. The distinction is straightforward when a recent baseline SCr concentration is available, but more difficult in the many instances in which the baseline is unknown. In such cases, clues suggestive of chronic kidney disease can come from radiologic studies (e.g., small, shrunken kidneys with cortical thinning on renal ultrasound, or evidence of renal osteodystrophy) or laboratory tests such as normocytic anemia or secondary hyperparathyroidism with hyperphosphatemia and hypocalcemia, consistent with CKD. No set of tests, however, can rule out AKI superimposed on CKD since AKI is a frequent complication in patients with CKD, further complicating the distinction. Serial blood tests showing continued substantial rise of SCr is clear evidence of AKI. Once the diagnosis of AKI is established, its cause needs to be determined.

HISTORY AND PHYSICAL EXAMINATION

The clinical context, careful history taking, and physical examination often narrow the differential diagnosis for the cause of AKI. Prerenal azotemia should be suspected in the setting of vomiting, diarrhea, glycosuria causing polyuria, and several medications including diuretics, NSAIDs, ACE inhibitors, and ARBs. Physical signs of orthostatic hypotension, tachycardia, reduced jugular venous pressure, decreased skin turgor, and dry mucous membranes are often present in prerenal azotemia. A history of prostatic disease, nephrolithiasis, or pelvic or paraaortic malignancy would suggest the possibility of postrenal AKI. Whether or not symptoms are present early during obstruction of the urinary tract depends on the location of obstruction. Colicky flank pain radiating to the groin suggests acute ureteric obstruction. Nocturia and urinary frequency or hesitancy can be seen in prostatic disease. Abdominal fullness and suprapubic pain can accompany massive bladder enlargement. Definitive diagnosis of obstruction requires radiologic investigations.

A careful review of all medications is imperative in the evaluation of an individual with AKI. Not only are medications frequently a cause of AKI, but doses of administered medications must be adjusted for estimated GFR. Idiosyncratic reactions to a wide variety of medications can lead to allergic interstitial nephritis, which may be accompanied by fever, arthralgias, and a pruritic erythematous rash. The absence of systemic features of hypersensitivity, however, does not exclude the diagnosis of interstitial nephritis.

AKI accompanied by palpable purpura, pulmonary hemorrhage, or sinusitis raises the possibility of systemic vasculitis with glomerulonephritis. Atheroembolic disease can be associated with livedo reticularis and other signs of emboli to the legs. A tense abdomen should prompt consideration of acute abdominal compartment

syndrome, which requires measurement of bladder pressure. Signs of limb ischemia may be clues to the diagnosis of rhabdomyolysis.

URINE FINDINGS

Complete anuria early in the course of AKI is uncommon except in the following situations: complete urinary tract obstruction, renal artery occlusion, overwhelming septic shock, severe ischemia (often with cortical necrosis), or severe proliferative glomerulonephritis or vasculitis. A reduction in urine output (oliguria, defined as <400 mL/24 h) usually denotes more significant AKI (i.e., lower GFR) than when urine output is preserved. Oliguria is associated with worse clinical outcomes. Preserved urine output can be seen in nephrogenic diabetes insipidus characteristic of long-standing urinary tract obstruction, tubulointerstitial disease, or nephrotoxicity from cisplatin or aminoglycosides, among other causes. Red or brown urine may be seen with or without gross hematuria; if the color persists in the supernatant after centrifugation, then pigment nephropathy from rhabdomyolysis or hemolysis should be suspected.

The urinalysis and urine sediment examination are invaluable tools, but they require clinical correlation because of generally limited sensitivity and specificity **(Fig. 10-6)** (Chap. 4). In the absence of preexisting proteinuria from CKD, AKI from ischemia or nephrotoxins leads to mild proteinuria (<1 g/d). Greater proteinuria in AKI suggests damage to the glomerular ultrafiltration barrier or excretion of myeloma light chains; the latter are not detected with conventional urine dipsticks (which detect albumin) and require the sulfosalicylic acid test or immunoelectrophoresis. Atheroemboli can cause a variable degree of proteinuria. Extremely heavy proteinuria ("nephrotic range," >3.5 g/d) can occasionally be seen in glomerulonephritis, vasculitis, or interstitial nephritis (particularly from NSAIDs). AKI can also complicate cases of minimal-change disease, a cause of the nephrotic syndrome (Chap. 1). If the dipstick is positive for hemoglobin but few red blood cells are evident in the urine sediment, then rhabdomyolysis or hemolysis should be suspected.

Prerenal azotemia may present with hyaline casts or an unremarkable urine sediment exam. Postrenal AKI may also lead to an unremarkable sediment, but hematuria and pyuria may be seen depending on the cause of obstruction. AKI from ATN due to ischemic injury, sepsis, or certain nephrotoxins has characteristic urine sediment findings: pigmented "muddy brown" granular casts and tubular epithelial cell casts. These findings may be absent in more than 20% of cases, however. Glomerulonephritis may lead to dysmorphic red blood cells or red blood cell casts. Interstitial nephritis may lead to white blood cell casts. The urine sediment findings overlap somewhat in glomerulonephritis and interstitial nephritis, and a diagnosis is not always possible on the basis of the urine sediment alone. Urine eosinophils

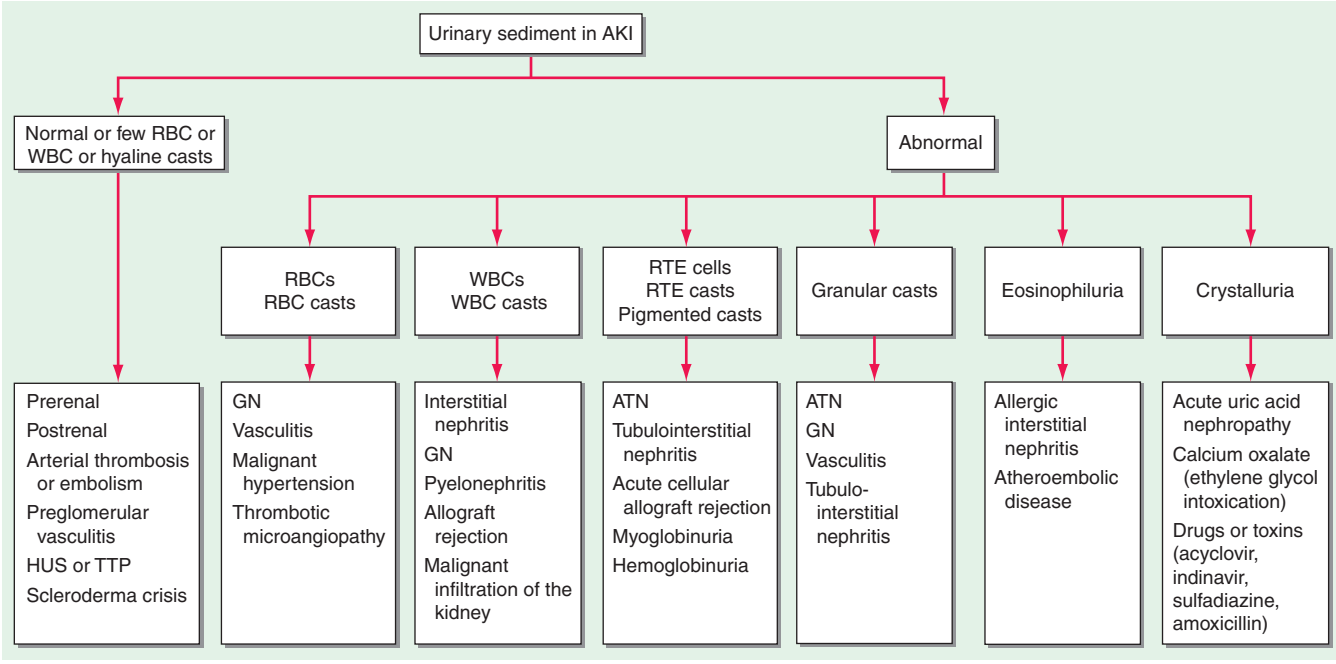

FIGURE 10-6

Interpretation of urinary sediment findings in acute kidney injury. ATN, acute tubular necrosis; GN, glomerulonephritis; HUS, hemolytic uremic syndrome; RTE, renal tubular epithelial; TTP, thrombotic thrombocytopenic purpura. (*Adapted from L Yang, JV Bonventre: Diagnosis and clinical evaluation of acute kidney injury. In Comprehensive Nephrology, 4th ed. J Floege et al [eds]. Philadelphia, Elsevier, 2010.*)

have a limited role in differential diagnosis; they can be seen in interstitial nephritis, pyelonephritis, cystitis, atheroembolic disease, or glomerulonephritis. Crystalluria may be important diagnostically. The finding of oxalate crystals in AKI should prompt an evaluation for ethylene glycol toxicity. Abundant uric acid crystals may be seen in the tumor lysis syndrome.

BLOOD LABORATORY FINDINGS

Certain forms of AKI are associated with characteristic patterns in the rise and fall of SCr. Prerenal azotemia typically leads to modest rises in SCr that return to baseline with improvement in hemodynamic status. Contrast nephropathy leads to a rise in SCr within 24–48 hours, peak within 3–5 days, and resolution within 5–7 days. In comparison, atheroembolic disease usually manifests with more subacute rises in SCr, although severe AKI with rapid increases in SCr can occur in this setting. With many of the epithelial cell toxins such as aminoglycoside antibiotics and cisplatin, the rise in SCr is characteristically delayed for 4–5 days to 2 weeks after initial exposure.

A complete blood count may provide diagnostic clues. Anemia is common in AKI and is usually multifactorial in origin. It is not related to an effect of AKI solely on production of red blood cells since this effect in isolation takes longer to manifest. Severe anemia in the absence of bleeding may reflect hemolysis, multiple myeloma, or thrombotic microangiopathy (e.g., HUS or TTP). Other laboratory findings of thrombotic microangiopathy include thrombocytopenia, schistocytes on peripheral blood smear, elevated lactate dehydrogenase level, and low haptoglobin content. Peripheral eosinophilia can accompany interstitial nephritis, atheroembolic disease, polyarteritis nodosa, and Churg-Strauss vasculitis.

AKI often leads to hyperkalemia, hyperphosphatemia, and hypocalcemia. Marked hyperphosphatemia with accompanying hypocalcemia, however, suggests rhabdomyolysis or the tumor lysis syndrome. Creatinine phosphokinase levels and serum uric acid are elevated in rhabdomyolysis, while tumor lysis syndrome shows normal or marginally elevated creatine kinase and markedly elevated serum uric acid. The anion gap may be increased with any cause of uremia due to retention of anions such as phosphate, hippurate, sulfate, and urate. The co-occurrence of an increased anion gap and an osmolal gap may suggest ethylene glycol poisoning, which may also cause oxalate crystalluria. Low anion gap may provide a clue to the diagnosis of multiple myeloma due to the presence of unmeasured cationic proteins. Laboratory blood tests helpful for the diagnosis of glomerulonephritis and vasculitis include depressed complement levels and high titers of antinuclear antibodies (ANAs), antineutrophilic cytoplasmic antibodies (ANCAs), antiglomerular basement membrane (AGBM) antibodies, and cryoglobulins.

RADIOLOGIC EVALUATION

Postrenal AKI should always be considered in the differential diagnosis of AKI because treatment is usually successful if instituted early. Simple bladder catheterization can rule out urethral obstruction. Imaging of the urinary tract with renal ultrasound or CT should be undertaken to investigate obstruction in individuals with AKI unless an alternate diagnosis is apparent. Findings of obstruction include dilation of the collecting system and hydroureteronephrosis. Obstruction can be present without radiologic abnormalities in the setting of volume depletion, retroperitoneal fibrosis, encasement with tumor, and also early in the course of obstruction. If a high clinical index of suspicion for obstruction persists despite normal imaging, antegrade or retrograde pyelography should be performed. Imaging may also provide additional helpful information about kidney size and echogenicity to assist in the distinction between acute versus CKD. Large kidneys observed in these studies suggest the possibility of diabetic nephropathy, HIV-associated nephropathy, infiltrative diseases, or occasionally acute interstitial nephritis. Vascular imaging may be useful if venous or arterial obstruction is suspected, but the risks of contrast administration should be kept in mind. MRI with gadolinium-based contrast agents should be avoided if possible in severe AKI due to the possibility of inducing nephrogenic system fibrosis, a rare but serious complication seen most commonly in patients with end-stage renal disease.

RENAL FAILURE INDICES

Several indices have been used to help differentiate prerenal azotemia from intrinsic AKI when the tubules are malfunctioning. The low tubular flow rate and increased recycling of urea seen in prerenal azotemia may cause a disproportionate elevation of the BUN compared to creatinine. Other causes of disproportionate BUN elevation need to be kept in mind, however, including upper gastrointestinal bleeding, hyperalimentation, increased tissue catabolism, and glucocorticoid use.

The fractional excretion of sodium (FeNa) is the fraction of the filtered sodium load that is reabsorbed by the tubules and is a measure of both the kidney's ability to reabsorb sodium as well as endogenously and exogenously administered factors that affect tubular reabsorption. As such, it depends on sodium intake, effective intravascular volume, GFR, and intact tubular reabsorptive mechanisms. With prerenal azotemia, the FeNa may be below 1%, suggesting avid tubular sodium reabsorption. In patients with CKD, a FeNa significantly

above 1% can still be present despite a prerenal state. The FeNa may also be above 1% despite hypovolemia due to treatment with diuretics. Low FeNa is often seen in glomerulonephritis (and other disorders), and, hence, should not be taken as prima facie evidence of prerenal azotemia. Low FeNa is therefore suggestive but not synonymous with effective intravascular volume depletion, and should not be used as the sole guide for volume management. The response of urine output to crystalloid or colloid fluid administration may be both diagnostic and therapeutic in prerenal azotemia. In ischemic AKI, the FeNa is frequently above 1% because of tubular injury and resultant inability to reabsorb sodium. Several causes of ischemia-associated and nephrotoxin-associated AKI can present with FeNa below 1%, however, including sepsis (often early in the course), rhabdomyolysis, and contrast nephropathy.

The ability of the kidneys to produce a concentrated urine is dependent upon many factors and reliant on good tubular function in multiple regions of the kidney. In the patient not taking diuretics and with good baseline kidney function, urine osmolality may be above 500 mosmol/kg in prerenal azotemia, consistent with an intact medullary gradient and elevated serum vasopressin levels causing water reabsorption, resulting in concentrated urine. In elderly patients and those with CKD, however, baseline concentrating defects may exist, making urinary osmolality unreliable in many instances. Loss of concentrating ability is common in septic or ischemic AKI, resulting in urine osmolality below 350 mosmol/kg, but the finding is not specific.

KIDNEY BIOPSY

If the cause of AKI is not apparent based on the clinical context, physical examination, and laboratory studies, kidney biopsy should be considered. The results of kidney biopsy can provide definitive diagnostic and prognostic information about acute and CKDs. The procedure is most often used in AKI when prerenal azotemia, postrenal AKI, and ischemic or nephrotoxic AKI have been deemed unlikely, and other possible diagnoses are being considered such as glomerulonephritis, vasculitis, interstitial nephritis, myeloma kidney, HUS and TTP, and allograft dysfunction. Kidney biopsy is associated with a risk of bleeding, which can be severe and organ or life threatening in patients with thrombocytopenia or coagulopathy.

NOVEL BIOMARKERS

BUN and creatinine are functional biomarkers of glomerular filtration rather than tissue injury biomarkers and therefore may be suboptimal for the diagnosis of actual parenchymal kidney damage. BUN and creatinine are also relatively slow to rise after kidney injury. Several novel kidney injury biomarkers have been investigated and show great promise for the early and accurate diagnosis of AKI. *Kidney injury molecule-1 (KIM-1)* is a type 1 transmembrane protein that is abundantly expressed in proximal tubular cells injured by ischemia or nephrotoxins such as cisplatin. KIM-1 is not expressed in appreciable quantities in the absence of tubular injury or in extrarenal tissues. KIM-1's functional role may be to confer phagocytic properties to tubular cells, enabling them to clear debris from the tubular lumen after kidney injury. KIM-1 can be detected shortly after ischemic or nephrotoxic injury in the urine and therefore may be an easily tested biomarker in the clinical setting. *Neutrophil gelatinase associated lipocalin* (*NGAL*, also known as lipocalin-2 or siderocalin) is another leading novel biomarker of AKI. NGAL was first discovered as a protein in granules of human neutrophils. NGAL can bind to iron siderophore complexes and may have tissue-protective effects in the proximal tubule. NGAL is highly upregulated after inflammation and kidney injury and can be detected in the plasma and urine within 2 hours of cardiopulmonary bypass–associated AKI. Other injury markers that are being studied in an attempt to increase the early recognition of injury and predict the outcome in AKI are listed in **Table 10-2**.

COMPLICATIONS

The kidney plays a central role in homeostatic control of volume status, blood pressure, plasma electrolyte composition, and acid-base balance, and for excretion of nitrogenous and other waste products. Complications associated with AKI are therefore protean and depend on the severity of AKI and other associated conditions. Mild to moderate AKI may be entirely asymptomatic, particularly early in the course.

UREMIA

Buildup of nitrogenous waste products, manifested as an elevated BUN concentration, is a hallmark of AKI. BUN itself poses little direct toxicity at levels below 100 mg/dL. At higher concentrations, mental status changes and bleeding complications can arise. Other toxins normally cleared by the kidney may be responsible for the symptom complex known as uremia. Few of the many possible uremic toxins have been definitively identified. The correlation of BUN and SCr concentrations with uremic symptoms is extremely variable, due in part to differences in urea and creatinine generation rates across individuals.

TABLE 10-2

BIOMARKERS OF ACUTE KIDNEY INJURY

BIOMARKER	COMMENTS	DETECTION	SPECIES
Alanine aminopeptidase (AAP)	1. Proximal tubule brush border enzyme 2. Instability may limit clinical utility	Colorimetry	Rat, dog, human
Alkaline phosphatase (AP)	1. Proximal tubule brush border enzyme. Human intestinal alkaline phosphatase is specific for proximal tubular S3 segment; human tissue nonspecific alkaline phosphatase is specific for S1 and S2 segments 2. Levels may not correlate with extent of functional injury 3. Instability may limit clinical utility	Colorimetry	Rat, human
α-Glutathione-*S*-transferase (α-GST)	1. Proximal tubule cytosolic enzyme 2. Requires stabilization buffer for specimen storage and processing 3. Upregulated in AKI and renal cell carcinoma	ELISA	Mouse, rat, human
γ-Glutamyl transpeptidase (γGT)	1. Proximal tubule brush border enzyme 2. Instability requires samples to be analyzed quickly after collection, limiting clinical utility	Colorimetry	Rat, human
N-Acetyl-β-(D) glucosaminidase (NAG)	1. Proximal tubule lysosomal enzyme 2. More stable than other urinary enzymes 3. Extensive preclinical and clinical data in a variety of conditions (nephrotoxicant exposure, cardiopulmonary bypass, delayed renal allograft function, etc.) 4. Endogenous urea may inhibit activity	Colorimetry	Mouse, rat, human
β_2-Microglobulin	1. Light chain of the MHC I molecule expressed on the cell surface of all nucleated cells 2. Monomeric form is filtered by the glomerulus and reabsorbed by the proximal tubule cells 3. Early marker of tubular dysfunction in a variety of conditions 4. Instability in acidic urine limits clinical utility	ELISA Nephelometry	Mouse, rat, human
α_1-Microglobulin	1. Synthesized by the liver 2. Filtered by the glomerulus and reabsorbed by proximal tubule cells 3. Early marker of tubular dysfunction; high levels may predict poorer outcome 4. Stable across physiologic urinary pH	ELISA Nephelometry	Mouse, rat, human
Retinol-binding protein	1. Synthesized by liver, involved in vitamin A transport 2. Filtered by glomerulus and reabsorbed by proximal tubule cells 3. Early marker of tubular dysfunction 4. Increased stability in acidic urine when compared to β_2-microglobulin	ELISA Nephelometry	Mouse, rat, human
Cystatin C	1. Important extracellular inhibitor of cysteine proteases 2. Filtered by the glomerulus and reabsorbed by proximal tubule cells 3. Elevated urinary levels reflect tubular dysfunction; high levels may predict poorer outcome	ELISA Nephelometry	Mouse, rat, human
Microalbumin	1. Established marker for monitoring progression of chronic kidney disease 2. Elevated urinary levels may be indicative of proximal tubular damage 3. Lack of specificity for AKI may limit its utility	ELISA Immunoturbidimetry	Mouse, rat, dog, monkey, human
Kidney injury molecule-1 (KIM-1)	1. Type-1 cell membrane glycoprotein upregulated in dedifferentiated proximal tubule epithelial cells 2. Ectodomain is shed and can be quantitated in urine following AKI in preclinical and clinical studies 3. Elevated urinary levels are highly sensitive and specific for AKI 4. Upregulated following various models of preclinical and clinical AKI, fibrosis, renal cell carcinoma, and polycystic kidney disease	ELISA, Luminex®-based assay	Zebrafish, mouse, rat, dog, monkey, human

(*continued*)

TABLE 10-2

BIOMARKERS OF ACUTE KIDNEY INJURY (*CONTINUED*)

BIOMARKER	COMMENTS	DETECTION	SPECIES
Clusterin	1. Expressed on dedifferentiated proximal tubular epithelial cells 2. Elevated kidney and urinary levels are very sensitive for AKI in preclinical models 3. Upregulated in various rodent models of AKI, fibrosis, renal cell carcinoma, and polycystic kidney disease 4. No clinical study demonstrating its use	ELISA	Mouse, rat, dog, monkey, human
Neutrophil gelatinase associated lipocalin (NGAL)	1. Initially identified bound to gelatinase in specific granules of the neutrophils, but also may be induced in epithelial cells in the setting of inflammation or malignancy 2. Expression upregulated in kidney proximal tubule cells and urine following ischemic or cisplatin induced renal injury 3. Found to be an early indicator of AKI following cardiopulmonary bypass 4. Specificity for AKI in setting of sepsis and pyuria need to be further established	ELISA Luminex®-based assay	Mouse, rat, human
Interleukin-18 (IL-18)	1. Cytokine with broad immunomodulatory properties, particularly in setting of ischemic injury 2. Constitutively expressed in distal tubules; strong immunoreactivity in proximal tubules with transplant rejection 3. Elevated urinary levels found to be early marker of AKI and independent predictor of mortality in critically ill patients	ELISA Luminex®-based assay	Mouse, rat, human
Cysteine-rich protein (CYR-61)	1. Induced in proximal straight tubules of kidney and secreted in the urine within 3–6 h following ischemic kidney injury 2. Urinary levels decrease rapidly in spite of progression of injury indicating stability issue 3. No clinical study demonstrating its use 4. No quantitative method established	Western blot	Mouse, rat, human
Osteopontin	1. Upregulated in various rodent models of AKI 2. The induction correlates with inflammation and tubulointerstitial fibrosis 3. No clinical study demonstrating its use	ELISA	Mouse, rat, monkey, human
Liver fatty acid–binding protein (L-FABP)	1. Expressed in proximal tubule epithelial cells 2. Current evidence suggests clinical utility as a biomarker in CKD and diabetic nephropathy 3. Additional studies necessary to determine utility in setting of preclinical and clinical AKI	ELISA	Mouse, rat, human
Sodium/hydrogen exchanger isoform (NHE3)	1. Most abundant sodium transporter in the renal tubule 2. Urinary levels found to discriminate between prerenal azotemia and AKI in ICU patients 3. Samples require considerable processing, limiting assay throughput	Immunoblotting	Mouse, rat, human
Exosomal fetuin-A	1. Acute phase protein synthesized in the liver and secreted into the circulation 2. Levels in proximal tubule cell cytoplasm correspond to degree of injury 3. Urinary levels found to be much higher in ICU patients with AKI compared to ICU patients without AKI and healthy volunteers 4. Samples require considerable processing, limiting assay throughput 5. Additional studies necessary to determine utility in setting of preclinical and clinical AKI	Immunoblotting	Rat, human

Abbreviations: AKI, acute kidney injury; ELISA, enzyme-linked immunosorbent assay; ICU, intensive care unit; RCC, renal cell carcinoma.

HYPERVOLEMIA AND HYPOVOLEMIA

Expansion of extracellular fluid volume is a major complication of oliguric and anuric AKI, due to impaired salt and water excretion. The result can be weight gain, dependent edema, increased jugular venous pressure, and pulmonary edema; the latter can be life threatening. Pulmonary edema can also occur from volume overload and hemorrhage in pulmonary renal syndromes. AKI may also induce or exacerbate acute lung injury characterized by increased vascular permeability and inflammatory cell infiltration in lung parenchyma. Recovery from AKI can sometimes be accompanied by polyuria, which, if untreated, can lead to significant volume depletion. The polyuric phase of recovery may be due to an osmotic diuresis from retained urea and other waste products, as well as delayed recovery of tubular reabsorptive functions.

HYPONATREMIA

Administration of excessive hypotonic crystalloid or isotonic dextrose solutions can result in hypoosmolality and hyponatremia, which, if severe, can cause neurologic abnormalities, including seizures.

HYPERKALEMIA

Abnormalities in plasma electrolyte composition can be mild or life threatening. Frequently the most concerning complication of AKI is hyperkalemia. Marked hyperkalemia is particularly common in rhabdomyolysis, hemolysis, and tumor lysis syndrome due to release of intracellular potassium from damaged cells. Potassium affects the cellular membrane potential of cardiac and neuromuscular tissues. Muscle weakness may be a symptom of hyperkalemia. The more serious complication of hyperkalemia is due to effects on cardiac conduction, leading to potentially fatal arrhythmias.

ACIDOSIS

Metabolic acidosis, usually accompanied by an elevation in the anion gap, is common in AKI, and can further complicate acid-base and potassium balance in individuals with other causes of acidosis, including sepsis, diabetic ketoacidosis, or respiratory acidosis.

HYPERPHOSPHATEMIA AND HYPOCALCEMIA

AKI can lead to hyperphosphatemia, particularly in highly catabolic patients or those with AKI from rhabdomyolysis, hemolysis, and tumor lysis syndrome. Metastatic deposition of calcium phosphate can lead to hypocalcemia. AKI-associated hypocalcemia may also arise from derangements in the vitamin D–parathyroid axis. Hypocalcemia is often asymptomatic but can lead to perioral paresthesias, muscle cramps, seizures, carpopedal spasms, and prolongation of the QT interval on electrocardiography. Calcium levels should be corrected for the degree of hypoalbuminemia, if present, or ionized calcium levels should be followed. Mild, asymptomatic hypocalcemia does not require treatment.

BLEEDING

Hematologic complications of AKI include anemia and bleeding, both of which are exacerbated by coexisting disease processes such as sepsis, liver disease, and disseminated intravascular coagulation. Direct hematologic effects from AKI-related uremia include decreased erythropoiesis and platelet dysfunction.

INFECTIONS

Infections are a common precipitant of AKI and also a dreaded complication of AKI. Impaired host immunity has been described in end-stage renal disease and may be operative in severe AKI.

CARDIAC COMPLICATIONS

The major cardiac complications of AKI are arrhythmias, pericarditis, and pericardial effusion.

MALNUTRITION

AKI is often a severely hypercatabolic state, and therefore malnutrition is a major complication.

TREATMENT Acute Kidney Injury

PREVENTION AND TREATMENT The management of individuals with and at risk for AKI varies according to the underlying cause (Table 10-3). Common to all are several principles. Optimization of hemodynamics, correction of fluid and electrolyte imbalances, discontinuation of nephrotoxic medications, and dose adjustment of administered medications are all critical. Common causes of AKI such as sepsis and ischemic ATN, do not yet have specific therapies once injury is established, but meticulous clinical attention is needed to support the patient until (if) AKI resolves. The kidney possesses a remarkable capacity to repair itself after even severe, dialysis-requiring AKI. However, some patients with AKI do not recover fully and may remain dialysis dependent.

TABLE 10-3

MANAGEMENT OF ISCHEMIA- AND NEPHROTOXIN-ASSOCIATED AKI

General Issues

1. Optimization of systemic and renal hemodynamics through volume resuscitation and judicious use of vasopressors
2. Elimination of nephrotoxic agents (e.g., ACE inhibitors, ARBs, NSAIDs, aminoglycosides) if possible
3. Initiation of renal replacement therapy when indicated

Specific Issues

1. Nephrotoxin specific
   a. Rhabdomyolysis: consider forced alkaline diuresis
   b. Tumor lysis syndrome: allopurinol or rasburicase
2. Volume overload
   a. Salt and water restriction
   b. Diuretics
   c. Ultrafiltration
3. Hyponatremia
   a. Restriction of enteral free water intake, minimization of hypotonic intravenous solutions including those containing dextrose
4. Hyperkalemia
   a. Restriction of dietary potassium intake
   b. Discontinuation of potassium-sparing diuretics, ACE inhibitors, ARBs, NSAIDs
   c. Loop diuretics to promote urinary potassium loss
   d. Potassium-binding ion-exchange resin (sodium polystyrene sulfonate)
   e. Insulin (10 units regular) and glucose (50 mL of 50% dextrose) to promote entry of potassium intracellularly
   f. Inhaled beta-agonist therapy to promote entry of potassium intracellularly
   g. Calcium gluconate or calcium chloride (1 g) to stabilize the myocardium
5. Metabolic acidosis
   a. Sodium bicarbonate (if pH <7.2 to keep serum bicarbonate >15 mmol/L)
   b. Administration of other bases, e.g., THAM
   c. Renal replacement therapy
6. Hyperphosphatemia
   a. Restriction of dietary phosphate intake
   b. Phosphate binding agents (calcium acetate, sevelamer hydrochloride, aluminum hydroxide—taken with meals)
7. Hypocalcemia
   a. Calcium carbonate or calcium gluconate if symptomatic
8. Hypermagnesemia
   a. Discontinue Mg^{2+}-containing antacids
9. Hyperuricemia
   a. Acute treatment is usually not required except in the setting of tumor lysis syndrome (see earlier in the chapter)
10. Nutrition
    a. Sufficient protein and calorie intake to avoid negative nitrogen balance
11. Drug dosing
    a. Careful attention to dosages and frequency of administration of drugs, adjustment for degree of renal failure

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs; TRAM, tris (hydroxymethyl) aminomethane.

Prerenal Azotemia Prevention and treatment of prerenal azotemia requires optimization of renal perfusion. The composition of replacement fluids should be targeted to the type of fluid lost. Severe acute blood loss should be treated with packed red blood cells. Isotonic crystalloid and/or colloid should be used for less severe acute hemorrhage or plasma loss in the case of burns and pancreatitis. Crystalloid solutions are less expensive and probably equally as efficacious as colloid solutions. Crystalloid has been reported to be preferable to albumin in the setting of traumatic brain injury. Isotonic crystalloid (e.g., 0.9% saline) or colloid should be used for volume resuscitation in severe hypovolemia, whereas hypotonic crystalloids (e.g., 0.45% saline) suffice for less severe hypovolemia. Excessive chloride administration from 0.9% saline may lead to hyperchloremic metabolic acidosis. Use of bicarbonate-containing solutions (e.g., dextrose water with 150 meq sodium bicarbonate) should be used if metabolic acidosis is a concern.

Optimization of cardiac function in the cardiorenal syndrome (i.e., renal hypoperfusion from poor cardiac output) may require use of inotropic agents, preload- and afterload-reducing agents, antiarrhythmic drugs, and mechanical aids such as an intraaortic balloon pump. Invasive hemodynamic monitoring to guide therapy may be necessary.

Cirrhosis and Hepatorenal Syndrome Fluid management in individuals with cirrhosis, ascites, and AKI is challenging because of the frequent difficulty in ascertaining intravascular volume status. Administration of intravenous fluids as a volume challenge may be required diagnostically as well as therapeutically. Excessive volume administration may, however, result in worsening ascites and pulmonary compromise in the setting of hepatorenal syndrome or AKI due to superimposed spontaneous bacterial peritonitis. Peritonitis should be ruled out by culture of ascitic fluid. Albumin may prevent AKI in those treated with antibiotics for spontaneous bacterial peritonitis. The definitive treatment of the hepatorenal syndrome is orthotopic liver transplantation. Bridge therapies that have shown promise include terlipressin (a vasopressin analog), combination therapy with octreotide (a somatostatin analog) and midodrine (an α_1-adrenergic agonist), and norepinephrine, all in combination with intravenous albumin (25–50 mg per day, maximum 100 g/d).

Intrinsic AKI Several agents have been tested and have failed to show benefit in the treatment of ischemic acute tubular injury. These include atrial natriuretic peptide, low-dose dopamine, endothelin antagonists, loop diuretics, calcium channel blockers, α-adrenergic receptor blockers, prostaglandin analogs, antioxidants, antibodies against leukocyte adhesion molecules, and

insulin-like growth factor and many others. Most studies have enrolled patients with severe and well-established AKI, and treatment may have been initiated too late. Novel kidney injury biomarkers may provide an opportunity to test agents earlier in the course of AKI.

AKI due to acute glomerulonephritis or vasculitis may respond to immunosuppressive agents and/or plasmapheresis (Chap. 1). Allergic interstitial nephritis due to medications requires discontinuation of the offending agent. Glucocorticoids have been used, but not tested in randomized trials, in cases where AKI persists or worsens despite discontinuation of the suspected medication. AKI due to scleroderma (scleroderma renal crisis) should be treated with ACE inhibitors.

Early and aggressive volume repletion is mandatory in patients with rhabdomyolysis, who may require 10 L of fluid per day. Alkaline fluids (e.g., 75 mmol sodium bicarbonate added to 0.45% saline) may be beneficial in preventing tubular injury and cast formation, but carry the risk of worsening hypocalcemia. Diuretics may be used if fluid repletion is adequate but unsuccessful in achieving urinary flow rates of 200–300 mL/h. There is no specific therapy for established AKI in rhabdomyolysis, other than dialysis in severe cases or general supportive care to maintain fluid and electrolyte balance and tissue perfusion. Careful attention must be focused on calcium and phosphate status because of precipitation in damaged tissue and released when the tissue heals.

Postrenal AKI Prompt recognition and relief of urinary tract obstruction can forestall the development of permanent structural damage induced by urinary stasis. The site of obstruction defines the treatment approach. Transurethral or suprapubic bladder catheterization may be all that is needed initially for urethral strictures or functional bladder impairment. Ureteric obstruction may be treated by percutaneous nephrostomy tube placement or ureteral stent placement. Relief of obstruction is usually followed by an appropriate diuresis for several days. In rare cases, severe polyuria persists due to tubular dysfunction and may require continued administration of intravenous fluids and electrolytes for a period of time.

SUPPORTIVE MEASURES

Volume Management Hypervolemia in oliguric or anuric AKI may be life threatening due to acute pulmonary edema, especially since many patients have coexisting pulmonary disease, and AKI likely increases pulmonary vascular permeability. Fluid and sodium should be restricted, and diuretics may be used to increase the urinary flow rate. There is no evidence that increasing urine output itself improves the natural history of AKI, but diuretics may help to avoid the need for dialysis in some cases. In severe cases of volume overload, furosemide may be given as a bolus (200 mg) followed by an intravenous drip (10–40 mg/h), with or without a thiazide diuretic. Diuretic therapy should be stopped if there is no response. Dopamine in low doses may transiently increase salt and water excretion by the kidney in prerenal states, but clinical trials have failed to show any benefit in patients with intrinsic AKI. Because of the risk of arrhythmias and potential bowel ischemia, it has been argued that the risks of dopamine may outweigh the benefits in the treatment or prevention of AKI.

Electrolyte and acid-base abnormalities The treatment of dysnatremias and hyperkalemia is described in Chap. 6. Metabolic acidosis is not treated unless severe (pH <7.20 and serum bicarbonate <15 mmol/L). Acidosis can be treated with oral or intravenous sodium bicarbonate (Chap. 5), but overcorrection should be avoided because of the possibility of metabolic alkalosis, hypocalcemia, hypokalemia, and volume overload. Hyperphosphatemia is common in AKI and can usually be treated by limiting intestinal absorption of phosphate using phosphate binders (calcium carbonate, calcium acetate, sevelamer, or aluminum hydroxide). Hypocalcemia does not usually require therapy unless symptoms are present.

Malnutrition Protein energy wasting is common in AKI, particularly in the setting of multisystem organ failure. Inadequate nutrition may lead to starvation ketoacidosis and protein catabolism. Excessive nutrition may increase the generation of nitrogenous waste and lead to worsening azotemia. Total parenteral nutrition requires large volumes of fluid administration and may complicate efforts at volume control.

Anemia The anemia seen in AKI is usually multifactorial and is not improved by erythropoiesis-stimulating agents, due to their delayed onset of action and the presence of bone marrow resistance in critically ill patients. Uremic bleeding may respond to desmopressin or estrogens, but may require dialysis in the case of long-standing or severe uremia. Gastrointestinal prophylaxis with proton pump inhibitors or histamine (H_2) receptor blockers is required. Venous thromboembolism prophylaxis is important and should be tailored to the clinical setting; low-molecular-weight heparins and factor Xa inhibitors have unpredictable pharmacokinetics in severe AKI and should be avoided.

Dialysis Indications and Modalities (See also Chap. 12) Dialysis is indicated when medical management fails to control volume overload, in hyperkalemia, in acidosis, in some toxic ingestions, and when there are severe complications of uremia (asterixis, pericardial rub or effusion, encephalopathy, uremic bleeding). The timing of dialysis is still a matter of debate. Late initiation of dialysis carries the risk of avoidable volume, electrolyte, and metabolic complications of AKI. On the other hand,

initiating dialysis too early may unnecessarily expose individuals to intravenous lines and invasive procedures, with the attendant risks of infection, bleeding, procedural complications, and hypotension. The initiation of dialysis should not await the development of a life-threatening complication of renal failure. Many nephrologists initiate dialysis for AKI empirically when the BUN exceeds 100 mg/dL in patients without clinical signs of recovery of kidney function.

The available modes for renal replacement therapy in AKI require either access to the peritoneal cavity (for peritoneal dialysis) or the large blood vessels (for hemodialysis, hemofiltration, and other hybrid procedures). Small solutes are removed across a semipermeable membrane down their concentration gradient ("diffusive" clearance) and/or along with the movement of plasma water ("convective" clearance). The choice of modality is often dictated by the immediate availability of technology and the expertise of medical staff. Peritoneal dialysis is performed through a temporary intraperitoneal catheter. It is rarely used in the United States for AKI in adults but has enjoyed widespread use internationally, particularly when hemodialysis technology is not available. Dialysate solution is instilled into and removed from the peritoneal cavity at regular intervals in order to achieve diffusive and convective clearance of solutes across the peritoneal membrane; ultrafiltration of water is achieved by the presence of an osmotic gradient across the peritoneal membrane, typically due to high concentrations of dextrose in the dialysate. Being a continuous procedure, it is often better tolerated than intermittent procedures like hemodialysis in hypotensive patients. Peritoneal dialysis may not be sufficient for hypercatabolic patients due to inherent limitations in dialysis efficacy.

Hemodialysis can be employed intermittently or continuously, and can be done through convective clearance, diffusive clearance, or a combination of the two. Vascular access is through the femoral, internal jugular, or subclavian veins. Hemodialysis is an intermittent procedure that removes solutes through diffusive and convective clearance. Hemodialysis is performed 3–4 h per d, three to four times per week, and is the most common form of renal replacement therapy for AKI. One of the major complications of hemodialysis is hypotension, particularly in the critically ill.

Continuous intravascular procedures were developed in the early 1980s to treat hemodynamically unstable patients without inducing the rapid shifts of volume, osmolarity, and electrolytes characteristic of intermittent hemodialysis. Continuous renal replacement therapy (CRRT) can be performed by convective clearance [continuous venovenous hemofiltration (CVVH)], in which large volumes of plasma water (and accompanying solutes) are forced across the semipermeable membrane by means of hydrostatic pressure; the plasma water is then replaced by a physiologic crystalloid solution. CRRT can also be performed by diffusive clearance [continuous venovenous hemodialysis (CVVHD)], a technology similar to hemodialysis except at lower blood flow and dialysate flow rates. A hybrid therapy combines both diffusive and convective clearance [continuous venovenous hemodiafiltration (CVVHDF)]. To achieve some of the advantages of CRRT without the need for 24-h staffing of the procedure, a newer form of therapy has been introduced, termed slow low-efficiency dialysis (SLED) or extended daily dialysis (EDD). In this therapy, blood flow and dialysate flow are higher than in CVVHD, but the treatment time is reduced to 12 h.

The optimal dose of dialysis for AKI is not clear. Daily intermittent hemodialysis and high-dose CRRT do not confer a demonstrable survival or renal recovery advantage, but care should be taken to avoid undertreatment. Studies have failed to show that continuous therapies are superior to intermittent therapies. If available, CRRT is often preferred in patients with severe hemodynamic instability, cerebral edema, or significant volume overload.

OUTCOME AND PROGNOSIS

The development of AKI is associated with a significantly increased risk of in-hospital and long-term mortality, longer length of stay, and increased costs. Prerenal azotemia, with the exception of the cardiorenal and hepatorenal syndromes, and postrenal azotemia carry a better prognosis than most cases of intrinsic AKI. The kidneys may recover even after severe, dialysis-requiring AKI. Survivors of an episode of AKI requiring temporary dialysis, however, are at extremely high risk for progressive CKD, and up to 10% may develop end-stage renal disease. Post-discharge care under the supervision of a nephrologist for aggressive secondary prevention of kidney disease is prudent. Patients with AKI are more likely to die prematurely after they leave the hospital even if their kidney function has recovered.

CHAPTER 11

CHRONIC KIDNEY DISEASE

Joanne M. Bargman ■ Karl Skorecki

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR). Table 11-1 provides a widely accepted classification, based on guidelines of the National Kidney Foundation [Kidney Dialysis Outcomes Quality Initiative (KDOQI)], in which stages of CKD are defined according to the estimated GFR.

The term *chronic renal failure* applies to the process of continuing significant irreversible reduction in nephron number and typically corresponds to CKD stages 3–5. The pathophysiologic processes and adaptations associated with chronic renal failure will be the focus of this chapter. The dispiriting term *end-stage renal disease* represents a stage of CKD where the accumulation of toxins, fluid, and electrolytes normally excreted by the kidneys results in the *uremic syndrome*. This syndrome leads to death unless the toxins are removed by renal replacement therapy using dialysis or kidney transplantation. These latter interventions are discussed in Chaps. 12 and 13. *End-stage renal disease* will be supplanted in this chapter by the term *stage 5 CKD*.

TABLE 11-1

CLASSIFICATION OF CHRONIC KIDNEY DISEASE (CKD)

STAGE	GFR, mL/min PER 1.73 m^2
0	>90[a]
1	≥90[b]
2	60–89
3	30–59
4	15–29
5	<15

[a]With risk factors for CKD (see text).
[b]With demonstrated kidney damage (e.g., persistent proteinuria, abnormal urine sediment, abnormal blood and urine chemistry, abnormal imaging studies).
Abbreviation: GFR, glomerular filtration rate.
Source: Modified from National Kidney Foundation. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, classification and stratification. Am J Kidney Dis 39:suppl 1, 2002.

PATHOPHYSIOLOGY OF CHRONIC KIDNEY DISEASE

The pathophysiology of CKD involves two broad sets of mechanisms of damage: (1) initiating mechanisms specific to the underlying etiology (e.g., genetically determined abnormalities in kidney development or integrity, immune complex deposition and inflammation in certain types of glomerulonephritis, or toxin exposure in certain diseases of the renal tubules and interstitium) and (2) a set of progressive mechanisms, involving hyperfiltration and hypertrophy of the remaining viable nephrons, that are a common consequence following long-term reduction of renal mass, irrespective of underlying etiology (Chap. 2). The responses to reduction in nephron number are mediated by vasoactive hormones, cytokines, and growth factors. Eventually, these short-term adaptations of hypertrophy and hyperfiltration become maladaptive as the increased pressure and flow predisposes to distortion of glomerular architecture, associated with sclerosis and dropout of the remaining nephrons (Fig. 11-1). Increased intrarenal activity of the renin-angiotensin axis appears to contribute both to the initial adaptive hyperfiltration and to the subsequent maladaptive hypertrophy and sclerosis, the latter, in part, owing to the stimulation of transforming growth factor β (TGF-β). This process explains why a reduction in renal mass from an isolated insult may lead to a progressive decline in renal function over many years (Fig. 11-2).

IDENTIFICATION OF RISK FACTORS AND STAGING OF CKD

It is important to identify factors that increase the risk for CKD, even in individuals with normal GFR. Risk factors include hypertension, diabetes mellitus, autoimmune disease, older age, African ancestry, a family history of renal disease, a previous episode of acute kidney

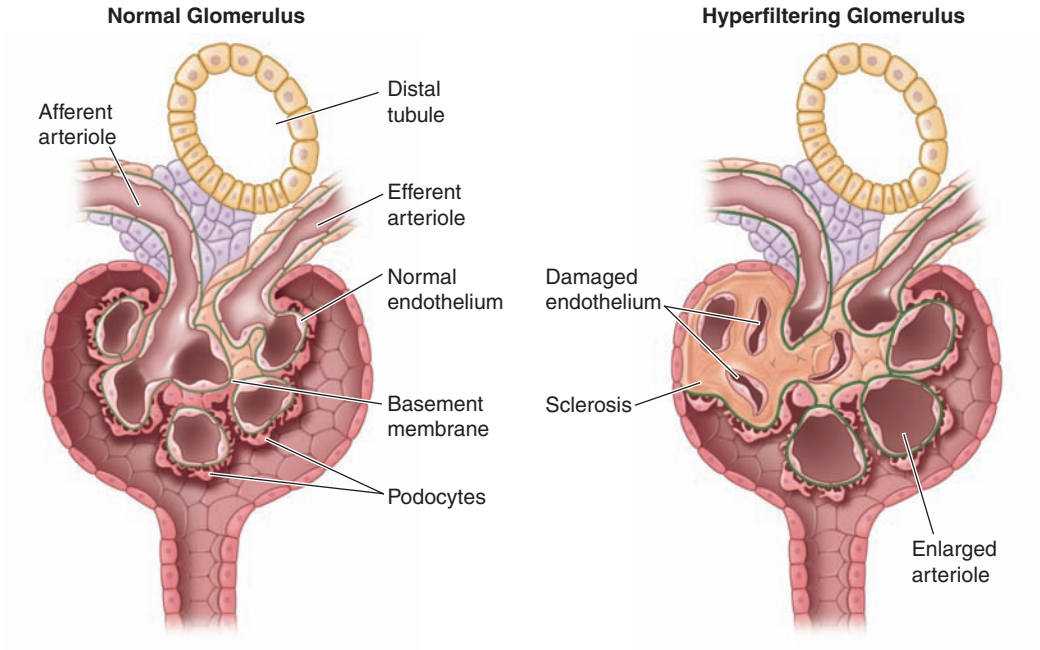

FIGURE 11-1

Left: Schema of the normal glomerular architecture. Right: Secondary glomerular changes associated with a reduction in nephron number, including enlargement of capillary lumens and focal adhesions, which are thought to occur consequent to compensatory hyperfiltration and hypertrophy in the remaining nephrons. (*Modified from JR Ingelfinger: N Engl J Med 348:99, 2003.*)

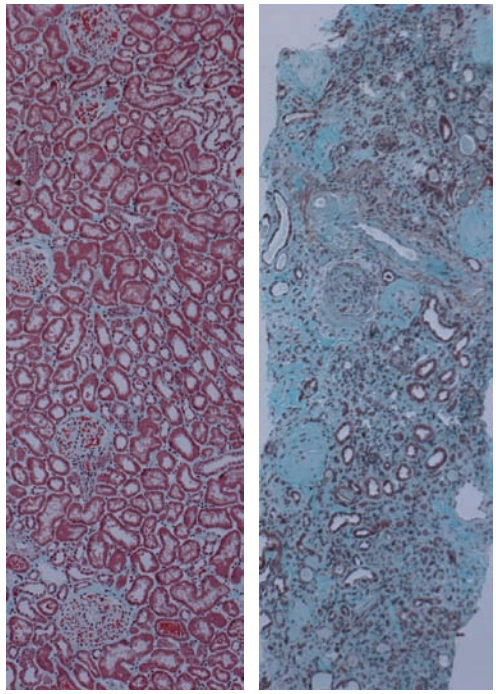

FIGURE 11-2

Left: Low-power photomicrograph of a normal kidney showing normal glomeruli and healthy tubulointerstitium without fibrosis. **Right:** Low-power photomicrograph of chronic kidney disease with sclerosis of many glomeruli and severe tubulointerstitial fibrosis (*Masson trichrome, ×40 magnification. Slides courtesy of the late Dr. Andrew Herzenberg.*)

injury, and the presence of proteinuria, abnormal urinary sediment, or structural abnormalities of the urinary tract.

Recent research in the genetics of predisposition to common complex diseases has revealed DNA sequence variants at a number of genetic loci that are associated with common forms of CKD. A striking example is the finding of allelic versions of the *APOL1* gene, of West African population ancestry, which contributes to the several-fold higher frequency of certain common etiologies of CKD (e.g., focal segmental glomerulosclerosis) observed among African and Hispanic Americans. The prevalence in West African populations seems to have an evolutionary basis, since these same variants offer protection from tropical pathogens.

In order to stage CKD, it is necessary to estimate the GFR. Two equations commonly used to estimate GFR are shown in **Table 11-2** and incorporate the measured plasma creatinine concentration, age, sex, and ethnic origin. Many laboratories now report an estimated GFR, or "eGFR," using one of these equations.

The normal annual mean decline in GFR with age from the peak GFR (~120 mL/min per 1.73 m^2) attained during the third decade of life is ~1 mL/min per year per 1.73 m^2, reaching a mean value of 70 mL/min per 1.73 m^2 at age 70. The mean GFR is lower in women than in men. For example, a woman in her 80s with a normal serum creatinine may have a GFR of just 50 mL/min per 1.73 m^2. Thus, even a mild elevation in serum creatinine concentration [e.g., 130 μmol/L (1.5 mg/dL)]

TABLE 11-2

RECOMMENDED EQUATIONS FOR ESTIMATION OF GLOMERULAR FILTRATION RATE (GFR) USING SERUM CREATININE CONCENTRATION (P_{Cr}), AGE, SEX, RACE, AND BODY WEIGHT

1. Equation from the Modification of Diet in Renal Disease study[a]

   Estimated GFR (mL/min per 1.73 m^2) =

   $$1.86 \times (P_{Cr})^{-1.154} \times (age)^{-0.203}$$

   Multiply by 0.742 for women

   Multiply by 1.21 for African Americans

2. Cockcroft-Gault equation

   Estimated creatinine clearance (mL/min) =

   $$\frac{(140 - age) \quad body\ weight\ (kg)}{72 \quad P_{Cr}\ (mg/dL)}$$

   Multiply by 0.85 for women

[a]Equation is available in hand-held calculators and in tabular form.
Source: Adapted from AS Levey et al: Am J Kidney Dis 39: S1, 2002, with permission.

often signifies a substantial reduction in GFR in most individuals.

Measurement of albuminuria is also helpful for monitoring nephron injury and the response to therapy in many forms of CKD, especially chronic glomerular diseases. While an accurate 24-h urine collection is the criterion standard for measurement of albuminuria, the measurement of protein-to-creatinine ratio in a spot first-morning urine sample is often more practical to obtain and correlates well, but not perfectly, with 24-h urine collections. Persistence in the urine of >17 mg of albumin per gram of creatinine in adult males and 25 mg albumin per gram of creatinine in adult females usually signifies chronic renal damage. *Microalbuminuria* refers to the excretion of amounts of albumin too small to detect by urinary dipstick or conventional measures of urine protein. It is a good screening test for early detection of renal disease, and may be a marker for the presence of micro-vascular disease in general. If a patient has a large amount of excreted albumin, there is no reason to test for microalbuminuria.

Stages 1 and 2 CKD are usually not associated with any symptoms arising from the decrement in GFR. However, there may be symptoms from the underlying renal disease itself, such as edema in patients with nephrotic syndrome or signs of hypertension secondary to the renal parenchymal disease in patients with polycystic kidney disease, some forms of glomerulonephritis, and many other parenchymal and vascular renal diseases, even with well-preserved GFR. If the decline in GFR progresses to stages 3 and 4, clinical and laboratory complications of CKD become more prominent. Virtually all organ systems are affected, but the most evident complications include anemia and associated easy fatigability; decreasing appetite with progressive malnutrition; abnormalities in calcium, phosphorus, and mineral-regulating hormones, such as $1,25(OH)_2D_3$ (calcitriol), parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF-23); and abnormalities in sodium, potassium, water, and acid-base homeostasis. Many patients, especially the elderly, will have eGFR values compatible with stage 2 or 3 CKD. However, the majority of these patients will show no further deterioration of renal function. The primary care physician is advised to recheck kidney function, and if it is stable and not associated with proteinuria, the patient can usually be managed in this setting. However, if there is evidence of decline of GFR and uncontrolled hypertension or proteinuria, referral to a nephrologist is appropriate. If the patient progresses to stage 5 CKD, toxins accumulate such that patients usually experience a marked disturbance in their activities of daily living, well-being, nutritional status, and water and electrolyte homeostasis, eventuating in the *uremic syndrome*. As noted, this state will culminate in death unless renal replacement therapy (dialysis or transplantation) is instituted.

ETIOLOGY AND EPIDEMIOLOGY

It has been estimated from population survey data that at least 6% of the adult population in the United States has CKD at stages 1 and 2. An unknown subset of this group will progress to more advanced stages of CKD. An additional 4.5% of the U.S. population is estimated to have stages 3 and 4 CKD. **Table 11-3** lists the five most frequent categories of causes of CKD, cumulatively accounting for greater than 90% of the CKD disease burden worldwide. The relative contribution of each category varies among different geographic regions. The most frequent cause of CKD in North America and Europe is diabetic nephropathy, most often secondary to type 2 diabetes mellitus. Patients with newly diagnosed CKD often also present with hypertension. When no overt evidence for a primary glomerular or tubulointerstitial kidney disease process is present, CKD is often attributed to hypertension. However, it is now appreciated that such individuals can be considered in two categories. The first includes patients with a silent primary glomerulopathy, such as focal segmental glomerulosclerosis,

TABLE 11-3

LEADING CATEGORIES OF ETIOLOGIES OF CKD[a]

Diabetic glomerular disease
Glomerulonephritis
Hypertensive nephropathy
- Primary glomerulopathy with hypertension
- Vascular and ischemic renal disease

Autosomal dominant polycystic kidney disease
Other cystic and tubulointerstitial nephropathy

[a]Relative contribution of each category varies with geographic region.

without the overt nephrotic or nephritic manifestations of glomerular disease (Chap. 15). The second includes patients in whom progressive nephrosclerosis and hypertension is the renal correlate of a systemic vascular disease, often also involving large- and small-vessel cardiac and cerebral pathology. This latter combination is especially common in the elderly, in whom chronic renal ischemia as a cause of CKD may be underdiagnosed. The increasing incidence of CKD in the elderly has been ascribed, in part, to decreased mortality rate from the cardiac and cerebral complications of atherosclerotic vascular disease, enabling a greater segment of the population to manifest the renal component of generalized vascular disease. Nevertheless, it should be appreciated that the vast majority of such patients with early stages of CKD will succumb to the cardiovascular and cerebrovascular consequences of the vascular disease before they can progress to the most advanced stages of CKD. Indeed, even a minor decrement in GFR or the presence of albuminuria is now recognized as a major risk factor for cardiovascular disease.

PATHOPHYSIOLOGY AND BIOCHEMISTRY OF UREMIA

Although serum urea and creatinine concentrations are used to measure the excretory capacity of the kidneys, accumulation of these two molecules themselves do not account for the many symptoms and signs that characterize the uremic syndrome in advanced renal failure. Hundreds of toxins that accumulate in renal failure have been implicated in the uremic syndrome. These include water-soluble, hydrophobic, protein-bound, charged, and uncharged compounds. Additional categories of nitrogenous excretory products include guanidino compounds, urates and hippurates, products of nucleic acid metabolism, polyamines, myoinositol, phenols, benzoates, and indoles. Compounds with a molecular mass between 500 and 1500 Da, the so-called middle molecules, are also retained and contribute to morbidity and mortality. It is thus evident that the serum concentrations of urea and creatinine should be viewed as being readily measured, but incomplete, surrogate markers for these compounds, and monitoring the levels of urea and creatinine in the patient with impaired kidney function represents a vast oversimplification of the uremic state.

The uremic syndrome and the disease state associated with advanced renal impairment involve more than renal excretory failure. A host of metabolic and endocrine functions normally performed by the kidneys is also impaired or suppressed, and this results in anemia, malnutrition, and abnormal metabolism of carbohydrates, fats, and proteins. Furthermore, plasma levels of many hormones, including PTH, FGF-23, insulin, glucagon, steroid hormones including vitamin D and sex hormones, and prolactin, change with renal failure as a result of urinary retention, decreased degradation, or abnormal regulation. Finally, progressive renal impairment is associated with worsening systemic inflammation. Elevated levels of C-reactive protein are detected along with other acute-phase reactants, while levels of so-called negative acute-phase reactants, such as albumin and fetuin, decline with progressive renal impairment, even in nonproteinuric kidney disease. Thus, the inflammation associated with renal impairment is important in the malnutrition-inflammation-atherosclerosis/calcification syndrome, which contributes in turn to the acceleration of vascular disease and comorbidity rate associated with advanced kidney disease.

In summary, the pathophysiology of the uremic syndrome can be divided into manifestations in three spheres of dysfunction: (1) those consequent to the accumulation of toxins that normally undergo renal excretion, including products of protein metabolism; (2) those consequent to the loss of other renal functions, such as fluid and electrolyte homeostasis and hormone regulation; and (3) progressive systemic inflammation and its vascular and nutritional consequences.

CLINICAL AND LABORATORY MANIFESTATIONS OF CHRONIC KIDNEY DISEASE AND UREMIA

Uremia leads to disturbances in the function of virtually every organ system. Chronic dialysis can reduce the incidence and severity of many of these disturbances, so that the overt and florid manifestations of uremia have largely disappeared in the modern health setting. However, as indicated in **Table 11-4**, even optimal dialysis therapy is not completely effective as renal replacement therapy, because some disturbances resulting from impaired renal function fail to respond to dialysis.

FLUID, ELECTROLYTE, AND ACID-BASE DISORDERS

Sodium and water homeostasis

In most patients with stable CKD, the total-body content of sodium and water is modestly increased, although this may not be apparent on clinical examination. Normal renal function guarantees that the tubular reabsorption of filtered sodium and water is adjusted so that urinary excretion matches intake. Many forms of renal disease (e.g., glomerulonephritis) disrupt this glomerulotubular balance such that dietary intake of sodium exceeds its urinary excretion, leading to sodium retention and attendant extracellular fluid volume (ECFV) expansion. This expansion may contribute to hypertension, which itself can accelerate the nephron injury.

TABLE 11-4

CLINICAL ABNORMALITIES IN UREMIA[a]

Fluid and electrolyte disturbances
Volume expansion (I)
Hyponatremia (I)
Hyperkalemia (I)
Hyperphosphatemia (I)

Endocrine-metabolic disturbances
Secondary hyperparathyroidism (I or P)
Adynamic bone (D)
Vitamin D–deficient osteomalacia (I)
Carbohydrate resistance (I)
Hyperuricemia (I or P)
Hypertriglyceridemia (I or P)
Increased Lp(a) level (P)
Decreased high-density lipoprotein level (P)
Protein-energy malnutrition (I or P)
Impaired growth and development (P)
Infertility and sexual dysfunction (P)
Amenorrhea (I/P)
β_2-Microglobulin–associated amyloidosis (P or D)

Neuromuscular disturbances
Fatigue (I)[b]
Sleep disorders (P)
Headache (P)
Impaired mentation (I)[b]
Lethargy (I)[b]
Asterixis (I)
Muscular irritability
Peripheral neuropathy (I or P)
Restless legs syndrome (I or P)
Myoclonus (I)
Seizures (I or P)
Coma (I)
Muscle cramps (P or D)
Dialysis disequilibrium syndrome (D)
Myopathy (P or D)

Cardiovascular and pulmonary disturbances
Arterial hypertension (I or P)
Congestive heart failure or pulmonary edema (I)
Pericarditis (I)
Hypertrophic or dilated cardiomyopathy (I, P, or D)
Uremic lung (I)
Accelerated atherosclerosis (P or D)
Hypotension and arrhythmias (D)
Vascular calcification (P or D)

Dermatologic disturbances
Pallor (I)[b]
Hyperpigmentation (I, P, or D)
Pruritus (P)
Ecchymoses (I)
Nephrogenic fibrosing dermopathy (D)
Uremic frost (I)

Gastrointestinal disturbances
Anorexia (I)
Nausea and vomiting (I)
Gastroenteritis (I)
Peptic ulcer (I or P)
Gastrointestinal bleeding (I, P, or D)
Idiopathic ascites (D)
Peritonitis (D)

Hematologic and immunologic disturbances
Anemia (I)[b]
Lymphocytopenia (P)
Bleeding diathesis (I or D)[b]
Increased susceptibility to infection (I or P)
Leukopenia (D)
Thrombocytopenia (D)

[a]Virtually all abnormalities in this table are completely reversed in time by successful renal transplantation. The response of these abnormalities to hemodialysis or peritoneal dialysis therapy is more variable. (I) denotes an abnormality that usually improves with an optimal program of dialysis and related therapy; (P) denotes an abnormality that tends to persist or even progress, despite an optimal program; (D) denotes an abnormality that develops only after initiation of dialysis therapy.
[b]Improves with dialysis and erythropoietin therapy.
Abbreviation: Lp(a), lipoprotein A.

As long as water intake does not exceed the capacity for water clearance, the ECFV expansion will be isotonic and the patient will have a normal plasma sodium concentration and effective osmolality (Chap. 2). Hyponatremia is not commonly seen in CKD patients but, when present, can respond to water restriction. If the patient has evidence of ECFV expansion (peripheral edema, sometimes hypertension poorly responsive to therapy), he or she should be counseled regarding salt restriction. Thiazide diuretics have limited utility in stages 3–5 CKD, such that administration of loop diuretics, including furosemide, bumetanide, or torsemide, may also be needed. Resistance to loop diuretics in renal failure often mandates use of higher doses than those used in patients with near-normal kidney function. The combination of loop diuretics with metolazone, which inhibits the sodium chloride co-transporter of the distal convoluted tubule, can help effect renal salt excretion. Ongoing diuretic resistance with intractable edema and hypertension in advanced CKD may serve as an indication to initiate dialysis.

In addition to problems with salt and water excretion, some patients with CKD may instead have impaired renal conservation of sodium and water. When an extrarenal cause for fluid loss, such as gastrointestinal (GI) loss, is present, these patients may be prone to ECFV depletion because of the inability of the failing kidney to reclaim filtered sodium adequately. Furthermore, depletion of ECFV, whether due to GI losses or overzealous diuretic therapy, can further compromise kidney function through underperfusion, or a "prerenal" basis, leading to acute-on-chronic kidney failure. In this setting, cautious volume repletion with normal saline may return the ECFV to normal and restore renal function to baseline without having to intervene with dialysis.

Potassium homeostasis

In CKD, the decline in GFR is not necessarily accompanied by a parallel decline in urinary potassium excretion, which is predominantly mediated

by aldosterone-dependent secretory events in distal nephron segments. Another defense against potassium retention in these patients is augmented potassium excretion in the GI tract. Notwithstanding these two homeostatic responses, hyperkalemia may be precipitated in certain settings. These include increased dietary potassium intake, protein catabolism, hemolysis, hemorrhage, transfusion of stored red blood cells, and metabolic acidosis. In addition, a host of medications can inhibit renal potassium excretion. The most important medications in this respect include the angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and spironolactone and other potassium-sparing diuretics such as amiloride, eplerenone, and triamterene.

Certain causes of CKD can be associated with earlier and more severe disruption of potassium-secretory mechanisms in the distal nephron, out of proportion to the decline in GFR. These include conditions associated with hyporeninemic hypoaldosteronism, such as diabetes, and renal diseases that preferentially affect the distal nephron, such as obstructive uropathy and sickle cell nephropathy.

Hypokalemia is not common in CKD and usually reflects markedly reduced dietary potassium intake, especially in association with excessive diuretic therapy or concurrent GI losses. Hypokalemia can also occur as a result of primary renal potassium wasting in association with other solute transport abnormalities, such as Fanconi's syndrome, renal tubular acidosis, or other forms of hereditary or acquired tubulointerstitial disease. However, even with these conditions, as the GFR declines, the tendency to hypokalemia diminishes and hyperkalemia may supervene. Therefore, the use of potassium supplements and potassium-sparing diuretics should be constantly reevaluated as GFR declines.

Metabolic acidosis

Metabolic acidosis is a common disturbance in advanced CKD. The majority of patients can still acidify the urine, but they produce less ammonia and therefore cannot excrete the normal quantity of protons in combination with this urinary buffer. Hyperkalemia, if present, further depresses ammonia production. The combination of hyperkalemia and hyperchloremic metabolic acidosis is often present, even at earlier stages of CKD (stages 1–3), in patients with diabetic nephropathy or in those with predominant tubulointerstitial disease or obstructive uropathy; this is a non-anion-gap metabolic acidosis. Treatment of hyperkalemia may increase renal ammonia production, improve renal generation of bicarbonate, and improve the metabolic acidosis.

With worsening renal function, the total urinary net daily acid excretion is usually limited to 30–40 mmol, and the anions of retained organic acids can then lead to an anion-gap metabolic acidosis. Thus, the non-anion-gap metabolic acidosis that can be seen in earlier stages of CKD may be complicated by the addition of an anion-gap metabolic acidosis as CKD progresses. In most patients, the metabolic acidosis is mild; the pH is rarely <7.35 and can usually be corrected with oral sodium bicarbonate supplementation. Animal and human studies have suggested that even modest degrees of metabolic acidosis may be associated with the development of protein catabolism. Alkali supplementation may attenuate the catabolic state and possibly slow CKD progression and accordingly is recommended when the serum bicarbonate concentration falls below 20–23 mmol/L. The concomitant sodium load mandates careful attention to volume status and the potential need for diuretic agents.

TREATMENT **Fluid, Electrolyte, and Acid-Base Disorders**

Adjustments in the dietary intake of salt and use of loop diuretics, occasionally in combination with metolazone, may be needed to maintain euvolemia. In contrast, overzealous salt restriction or diuretic use can lead to ECFV depletion and precipitate a further decline in GFR. The rare patient with salt-losing nephropathy may require a sodium-rich diet or salt supplementation. Water restriction is indicated only if there is a problem with hyponatremia. Otherwise, patients with CKD and an intact thirst mechanism may be instructed to drink fluids in a quantity that keeps them just ahead of their thirst. Intractable ECFV expansion, despite dietary salt restriction and diuretic therapy, may be an indication to start renal replacement therapy. Hyperkalemia often responds to dietary restriction of potassium, avoidance of potassium supplements (including occult sources, such as dietary salt substitutes) as well as potassium-retaining medications (especially ACE inhibitors or ARBs), or the use of kaliuretic diuretics. Kaliuretic diuretics promote urinary potassium excretion, while potassium-binding resins, such as calcium resonium or sodium polystyrene, can promote potassium loss through the GI tract and may reduce the incidence of hyperkalemia in CKD patients. Intractable hyperkalemia is an indication (although uncommon) to consider institution of dialysis in a CKD patient. The renal tubular acidosis and subsequent anion-gap metabolic acidosis in progressive CKD will respond to alkali supplementation, typically with sodium bicarbonate. Recent studies suggest that this replacement should be considered when the serum bicarbonate concentration falls below 20–23 mmol/L to avoid the protein catabolic state seen with even mild degrees of metabolic acidosis and to slow the progression of CKD.

DISORDERS OF CALCIUM AND PHOSPHATE METABOLISM

The principal complications of abnormalities of calcium and phosphate metabolism in CKD occur in the skeleton and the vascular bed, with occasional severe involvement of extraosseous soft tissues. It is likely that disorders of bone turnover and disorders of vascular and soft tissue calcification are related to each other (Fig. 11-2).

Bone manifestations of CKD

The major disorders of bone disease can be classified into those associated with high bone turnover with increased PTH levels (including osteitis fibrosa cystica, the classic lesion of secondary hyperparathyroidism) and low bone turnover with low or normal PTH levels (adynamic bone disease and osteomalacia).

The pathophysiology of secondary hyperparathyroidism and the consequent high-turnover bone disease is related to abnormal mineral metabolism through the following events: (1) declining GFR leads to reduced excretion of phosphate and, thus, phosphate retention; (2) the retained phosphate stimulates increased synthesis of PTH and growth of parathyroid gland mass; and (3) decreased levels of ionized calcium, resulting from diminished calcitriol production by the failing kidney as well as phosphate retention, also stimulate PTH production. Low calcitriol levels contribute to hyperparathyroidism, both by leading to hypocalcemia and also by a direct effect on PTH gene transcription. These changes start to occur when the GFR falls below 60 mL/min.

Fibroblast growth factor 23 (FGF-23) is part of a family of phosphatonins that promotes renal phosphate excretion. Recent studies have shown that levels of this hormone, secreted by osteocytes, increases early in the course of CKD. It may defend normal serum phosphorus in at least three ways: (1) increased renal phosphate excretion; (2) stimulation of PTH, which also increases renal phosphate excretion; and (3) suppression of the formation of $1,25(OH)_2D_3$, leading to diminished phosphorus absorption from the gastrointestinal tract. Interestingly, high levels of FGF-23 are also an independent risk factor for left ventricular hypertrophy and mortality in dialysis patients. Moreover, elevated levels of FGF-23 may indicate the need for therapeutic intervention (e.g., phosphate restriction), even when serum phosphate levels are within the normal range.

Hyperparathyroidism stimulates bone turnover and leads to *osteitis fibrosa cystica*. Bone histology shows abnormal osteoid, bone and bone marrow fibrosis, and in advanced stages, the formation of bone cysts, sometimes with hemorrhagic elements so that they appear brown in color, hence the term *brown tumor*. Clinical manifestations of severe hyperparathyroidism include bone pain and fragility, brown tumors, compression syndromes, tumors, and erythropoietin resistance in part related to the bone marrow fibrosis. Furthermore, PTH itself is considered a uremic toxin, and high levels are associated with muscle weakness, fibrosis of cardiac muscle, and nonspecific constitutional symptoms.

Low-turnover bone disease can be grouped into two categories—adynamic bone disease and osteomalacia. In the latter condition, there is accumulation of unmineralized bone matrix that may be caused by a number of processes, including vitamin D deficiency, metabolic acidosis, and in the past, aluminum deposition. Adynamic bone disease is increasing in prevalence, especially among diabetics and the elderly. It is characterized by reduced bone volume and mineralization and may result from excessive suppression of PTH production, chronic inflammation, or both. Suppression of PTH can result from the use of vitamin D preparations or from excessive calcium exposure in the form of calcium-containing phosphate binders or high-calcium dialysis solutions. Complications of adynamic bone disease include an increased incidence of fracture and bone pain and an association with increased vascular and cardiac calcification.

Calcium, phosphorus, and the cardiovascular system

Recent epidemiologic evidence has shown a strong association between hyperphosphatemia and increased cardiovascular mortality rate in patients with stage 5 CKD and even in patients with earlier stages of CKD. Hyperphosphatemia and hypercalcemia are associated with increased vascular calcification, but it is unclear whether the excessive mortality rate is mediated by this mechanism. Studies using CT and electron-beam CT scanning show that CKD patients have calcification of the media in coronary arteries and even heart valves that appear to be orders of magnitude greater than that in patients without renal disease. The magnitude of the calcification is proportional to age and hyperphosphatemia and is also associated with low PTH levels and low bone turnover. It is possible that in patients with advanced kidney disease, ingested calcium cannot be deposited in bones with low turnover and therefore is deposited at extraosseous sites, such as the vascular bed and soft tissues. It is interesting in this regard that there is also an association between osteoporosis and vascular calcification in the general population. Finally, there is recent evidence indicating that hyperphosphatemia can induce a change in gene expression in vascular cells to an osteoblast-like profile, leading to vascular calcification and even ossification.

Other complications of abnormal mineral metabolism

Calciphylaxis (calcific uremic arteriolopathy) is a devastating condition seen almost exclusively in patients with

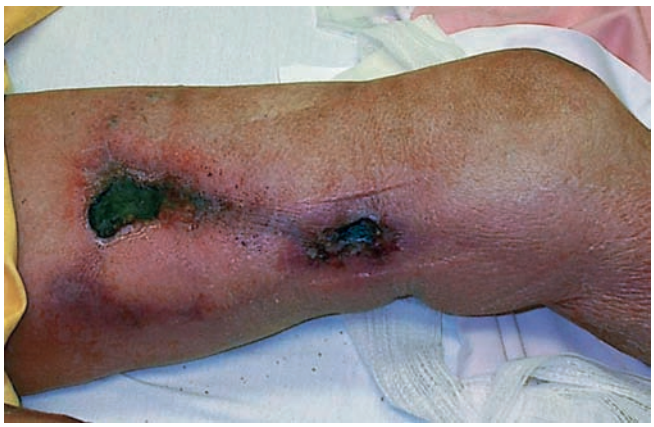

FIGURE 11-3
Calciphylaxis. This peritoneal dialysis patient was on chronic warfarin therapy for prophylactic anticoagulation for a mechanical heart valve. She slept with the dialysis catheter pressed between her legs. A small abrasion was followed by progressive skin necrosis along the catheter tract on her inner thighs. Despite treatment with hyperbaric oxygen, intravenous thiosulfate, and discontinuation of warfarin, she succumbed to systemic complications of the necrotic process.

advanced CKD. It is heralded by livedo reticularis and advances to patches of ischemic necrosis, especially on the legs, thighs, abdomen, and breasts **(Fig. 11-3)**. Pathologically, there is evidence of vascular occlusion in association with extensive vascular and soft tissue calcification. It appears that this condition is increasing in incidence. Originally it was ascribed to severe abnormalities in calcium and phosphorus control in dialysis patients, usually associated with advanced hyperparathyroidism. However, more recently, calciphylaxis has been seen with increasing frequency in the absence of severe hyperparathyroidism. Other etiologies have been suggested, including the increased use of oral calcium as a phosphate binder. Warfarin is commonly used in hemodialysis patients, and one of the effects of warfarin therapy is to decrease the vitamin K–dependent regeneration of matrix GLA protein. This latter protein is important in preventing vascular calcification. Thus, warfarin treatment is considered a risk factor for calciphylaxis, and if a patient develops this syndrome, this medication should be discontinued and replaced with alternative forms of anticoagulation.

TREATMENT **Disorders of Calcium and Phosphate Metabolism**

The optimal management of secondary hyperparathyroidism and osteitis fibrosa is prevention. Once the parathyroid gland mass is very large, it is difficult to control the disease. Careful attention should be paid to the plasma phosphate concentration in CKD patients, who should be counseled on a low-phosphate diet as well as the appropriate use of phosphate-binding agents. These are agents that are taken with meals and complex the dietary phosphate to limit its GI absorption. Examples of phosphate binders are calcium acetate and calcium carbonate. A major side effect of calcium-based phosphate binders is total-body calcium accumulation and hypercalcemia, especially in patients with low-turnover bone disease. Sevelamer and lanthanum are non-calcium-containing polymers that also function as phosphate binders; they do not predispose CKD patients to hypercalcemia and may attenuate calcium deposition in the vascular bed.

Calcitriol exerts a direct suppressive effect on PTH secretion and also indirectly suppresses PTH secretion by raising the concentration of ionized calcium. However, calcitriol therapy may result in hypercalcemia and/or hyperphosphatemia through increased GI absorption of these minerals. Certain analogues of calcitriol are available (e.g., paricalcitol) that suppress PTH secretion with less attendant hypercalcemia.

Recognition of the role of the extracellular calcium-sensing receptor has led to the development of calcimimetic agents that enhance the sensitivity of the parathyroid cell to the suppressive effect of calcium. This class of drug, which includes cinacalcet, produces a dose-dependent reduction in PTH and plasma calcium concentration in some patients.

Current KDOQI guidelines recommend a target PTH level between 150 and 300 pg/mL, recognizing that very low PTH levels are associated with adynamic bone disease and possible consequences of fracture and ectopic calcification.

CARDIOVASCULAR ABNORMALITIES

Cardiovascular disease is the leading cause of morbidity and mortality in patients at every stage of CKD. The incremental risk of cardiovascular disease in those with CKD compared to the age- and sex-matched general population ranges from 10- to 200-fold, depending on the stage of CKD. Between 30 and 45% of patients reaching stage 5 CKD already have advanced cardiovascular complications. As a result, most patients with CKD succumb to cardiovascular disease **(Fig. 11-4)** before ever reaching stage 5 CKD. Thus, the focus of patient care in earlier CKD stages should be directed to prevention of cardiovascular complications.

Ischemic vascular disease

The presence of any stage of CKD is a major risk factor for ischemic cardiovascular disease, including occlusive coronary, cerebrovascular, and peripheral vascular disease. The increased prevalence of vascular disease in CKD patients derives from both traditional (“classic”)

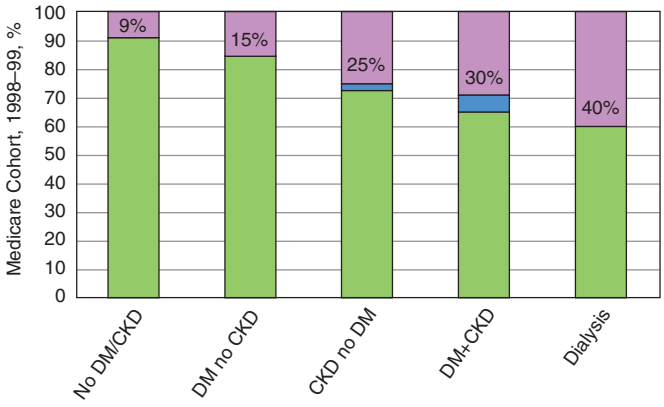

FIGURE 11-4

U.S. Renal Data System showing increased likelihood of dying rather than starting dialysis or reaching stage 5 chronic kidney disease (CKD). 1, Death; 2, ESRD/D; 3, event-free. DM; diabetes mellitus. (*Adapted from RN Foley et al: J Am Soc Nephrol 16:489-95, 2005.*)

and nontraditional (CKD-related) risk factors. Traditional risk factors include hypertension, hypervolemia, dyslipidemia, sympathetic overactivity, and hyperhomocysteinemia. The CKD-related risk factors comprise anemia, hyperphosphatemia, hyperparathyroidism, sleep apnea, and generalized inflammation. The inflammatory state associated with a reduction in kidney function is reflected in increased circulating acute-phase reactants, such as inflammatory cytokines and C-reactive protein, with a corresponding fall in the "negative acute-phase reactants," such as serum albumin and fetuin. The inflammatory state appears to accelerate vascular occlusive disease, and low levels of fetuin may permit more rapid vascular calcification, especially in the face of hyperphosphatemia. Other abnormalities seen in CKD may augment myocardial ischemia, including left ventricular hypertrophy and microvascular disease. Coronary reserve, defined as the increase in coronary blood flow in response to greater demand, is also attenuated. There is diminished availability of nitric oxide because of increased concentration of asymmetric dimethyl-l-arginine and increased scavenging by reactive oxygen species. In addition, hemodialysis, with its attendant episodes of hypotension and hypovolemia, may further aggravate coronary ischemia. Interestingly, however, the largest increment in cardiovascular mortality rate in dialysis patients is not necessarily directly associated with documented acute myocardial infarction but, instead, presents with congestive heart failure and all of its manifestations, including sudden death.

Cardiac troponin levels are frequently elevated in CKD without evidence of acute ischemia. The elevation complicates the diagnosis of acute myocardial infarction in this population. Serial measurements may be needed, and if the level is unchanged, it is possible that there is no acute myocardial ischemia. On the other hand, an increase upon subsequent testing suggests cardiac injury. Therefore, the trend in levels over the hours after presentation may be more informative than a single, elevated level. Interestingly, consistently elevated levels are an independent prognostic factor for adverse cardiovascular events in this population.

Heart failure

Abnormal cardiac function secondary to myocardial ischemia, left ventricular hypertrophy, and frank cardiomyopathy, in combination with the salt and water retention that can be seen with CKD, often results in heart failure or even episodes of pulmonary edema. Heart failure can be a consequence of diastolic or systolic dysfunction, or both. A form of "low-pressure" pulmonary edema can also occur in advanced CKD, manifesting as shortness of breath and a "bat wing" distribution of alveolar edema fluid on the chest x-ray. This finding can occur even in the absence of ECFV overload and is associated with normal or mildly elevated pulmonary capillary wedge pressure. This process has been ascribed to increased permeability of alveolar capillary membranes as a manifestation of the uremic state, and it responds to dialysis. Other CKD-related risk factors, including anemia and sleep apnea, may contribute to the risk of heart failure.

Hypertension and left ventricular hypertrophy

Hypertension is one of the most common complications of CKD. It usually develops early during the course of CKD and is associated with adverse outcomes, including the development of ventricular hypertrophy and a more rapid loss of renal function. Many studies have shown a relationship between the level of blood pressure and the rate of progression of diabetic and nondiabetic kidney disease. Left ventricular hypertrophy and dilated cardiomyopathy are among the strongest risk factors for cardiovascular morbidity and mortality in patients with CKD and are thought to be related primarily, but not exclusively, to prolonged hypertension and ECFV overload. In addition, anemia and the placement of an arteriovenous fistula for hemodialysis can generate a high cardiac output state and consequent heart failure.

The absence of hypertension may signify the presence of a salt-wasting form of renal disease, the effect of antihypertensive therapy, or volume depletion or may signify poor left ventricular function. Indeed, in epidemiologic studies of dialysis patients, low blood pressure actually carries a worse prognosis than does high blood pressure. This mechanism, in part, accounts for the "reverse causation" seen in dialysis patients, wherein the presence of traditional risk factors, such as hypertension, hyperlipidemia, and obesity, appear to portend a

better prognosis. Importantly, these observations derive from cross-sectional studies of late-stage CKD patients and should not be interpreted to discourage appropriate management of these risk factors in CKD patients, especially at early stages. In contrast to the general population, it is possible that in late-stage CKD, low blood pressure, reduced body mass index, and hypolipidemia indicate the presence of an advanced malnutrition-inflammation state, with poor prognosis.

The use of exogenous erythropoiesis-stimulating agents can increase blood pressure and the requirement for antihypertensive drugs. Chronic ECFV overload is also a contributor to hypertension, and improvement in blood pressure can often be seen with the use of dietary sodium restriction, diuretics, and fluid removal with dialysis. Nevertheless, because of activation of the renin-angiotensin-aldosterone axis and other disturbances in the balance of vasoconstrictors and vasodilators, some patients remain hypertensive despite careful attention to ECFV status.

TREATMENT Cardiovascular Abnormalities

MANAGEMENT OF HYPERTENSION There are two overall goals of therapy for hypertension in these patients: to slow the progression of the kidney disease itself, and to prevent the extrarenal complications of high blood pressure, such as cardiovascular disease and stroke. In all patients with CKD, blood pressure should be controlled to levels recommended by national guideline panels. In CKD patients with diabetes or proteinuria >1 g per 24 h, blood pressure should be reduced to 125/75, if achievable without prohibitive adverse effects. Salt restriction should be the first line of therapy. When volume management alone is not sufficient, the choice of antihypertensive agent is similar to that in the general population. The ACE inhibitors and ARBs slow the rate of decline of kidney function, but occasionally can precipitate an episode of acute kidney injury, especially when used in patients with ischemic renovascular disease. The use of ACE inhibitors and ARBs may also be complicated by the development of hyperkalemia. Often the concomitant use of a kaliuretic diuretic, such as metolazone, can improve potassium excretion in addition to improving blood pressure control. Potassium-sparing diuretics should be used with caution or avoided altogether in most patients. Indeed, increased usage of spironolactone for the management of heart failure has resulted in an increase in serious hyperkalemic events in patients with reduced kidney function.

MANAGEMENT OF CARDIOVASCULAR DISEASE There are many strategies available to treat the traditional and nontraditional risk factors in CKD patients. While these have been proved effective in the general population, there is little evidence for their benefit in patients with advanced CKD, especially those on dialysis. Certainly hypertension, elevated serum levels of homocysteine, and dyslipidemia promote atherosclerotic disease and are treatable complications of CKD. Renal disease complicated by nephrotic syndrome is associated with a very atherogenic lipid profile and hypercoagulability, which increases the risk of occlusive vascular disease. Since diabetes mellitus and hypertension are the two most frequent causes of advanced CKD, it is not surprising that cardiovascular disease is the most frequent cause of death in dialysis patients. The role of "inflammation" may be quantitatively more important in patients with kidney disease, and the treatment of more traditional risk factors may result in only modest success. However, modulation of traditional risk factors may be the only weapon in the therapeutic armamentarium for these patients until the nature of inflammation in CKD and its treatment are better understood.

Lifestyle changes, including regular exercise, should be advocated but are not often implemented. Hyperlipidemia in patients with CKD should be managed according to national guidelines. If dietary measures are not sufficient, preferred lipid-lowering medications, such as statins, should be used. Again, the use of these agents has not been of proven benefit for patients with advanced CKD.

Pericardial disease

Chest pain with respiratory accentuation, accompanied by a friction rub, is diagnostic of pericarditis. Classic electrocardiographic abnormalities include PR-interval depression and diffuse ST-segment elevation. Pericarditis can be accompanied by pericardial effusion that is seen on echocardiography and can rarely lead to tamponade. However, the pericardial effusion can be asymptomatic, and pericarditis can be seen without significant effusion.

Pericarditis is observed in advanced uremia, and with the advent of timely initiation of dialysis, is not as common as it once was. It is now more often observed in underdialyzed, nonadherent patients than in those starting dialysis.

TREATMENT Pericardial Disease

Uremic pericarditis is an absolute indication for the urgent initiation of dialysis or for intensification of the dialysis prescription in those already receiving dialysis. Because of the propensity to hemorrhage in pericardial

fluid, hemodialysis should be performed without heparin. A pericardial drainage procedure should be considered in patients with recurrent pericardial effusion, especially with echocardiographic signs of impending tamponade. Nonuremic causes of pericarditis and effusion include viral, malignant, tuberculous, and autoimmune etiologies. It may also be seen after myocardial infarction and as a complication of treatment with the antihypertensive drug minoxidil.

HEMATOLOGIC ABNORMALITIES

Anemia

A normocytic, normochromic anemia is observed as early as stage 3 CKD and is almost universal by stage 4. The primary cause in patients with CKD is insufficient production of erythropoietin (EPO) by the diseased kidneys. Additional factors include iron deficiency, acute and chronic inflammation with impaired iron utilization ("anemia of chronic disease"), severe hyperparathyroidism with consequent bone marrow fibrosis, and shortened red cell survival in the uremic environment. In addition, comorbid conditions such as hemoglobinopathy can worsen the anemia **(Table 11-5)**.

The anemia of CKD is associated with a number of adverse pathophysiologic consequences, including decreased tissue oxygen delivery and utilization, increased cardiac output, ventricular dilation, and ventricular hypertrophy. Clinical manifestations include fatigue and diminished exercise tolerance, angina, heart failure, decreased cognition and mental acuity, and impaired host defense against infection. In addition, anemia may play a role in growth retardation in children with CKD. While many studies in CKD patients have found that anemia and resistance to exogenous EPO are associated with a poor prognosis, the relative contribution to a poor outcome of the low hematocrit itself, versus inflammation as a cause of the anemia, remains unclear.

TABLE 11-5

CAUSES OF ANEMIA IN CKD
Relative deficiency of erythropoietin
Diminished red blood cell survival
Bleeding diathesis
Iron deficiency
Hyperparathyroidism/bone marrow fibrosis
"Chronic inflammation"
Folate or vitamin B_{12} deficiency
Hemoglobinopathy
Comorbid conditions: hypo/hyperthyroidism, pregnancy, HIV-associated disease, autoimmune disease, immunosuppressive drugs

TREATMENT Anemia

The availability of recombinant human EPO and modified EPO products, such as darbepoetin-alpha, has been one of the most significant advances in the care of renal patients since the introduction of dialysis and renal transplantation. The routine use of these products has obviated the need for regular blood transfusions in severely anemic CKD patients, thus dramatically reducing the incidence of transfusion-associated infections and iron overload. Frequent blood transfusions in dialysis patients also leads to the development of allo-antibodies that could sensitize the patient to donor kidney antigens and make renal transplantation more problematic.

Adequate bone marrow iron stores should be available before treatment with EPO is initiated. Iron supplementation is usually essential to ensure an optimal response to EPO in patients with CKD because the demand for iron by the marrow frequently exceeds the amount of iron that is immediately available for erythropoiesis (measured by percent transferrin saturation), as well as the amount in iron stores (measured by serum ferritin). For the CKD patient not yet on dialysis or the patient treated with peritoneal dialysis, oral iron supplementation should be attempted. If there is GI intolerance, the patient may have to undergo IV iron infusion. For patients on hemodialysis, IV iron can be administered during dialysis. In addition to iron, an adequate supply of other major substrates and cofactors for red cell production must be ensured, including vitamin B_{12} and folate. Anemia resistant to recommended doses of EPO in the face of adequate iron stores may be due to some combination of the following: acute or chronic inflammation, inadequate dialysis, severe hyperparathyroidism, chronic blood loss or hemolysis, chronic infection, or malignancy. Patients with a hemoglobinopathy, such as sickle cell disease or thalassemia, will usually not respond normally to exogenous EPO; however, an increase in hemoglobin concentration is still seen in many of these patients. Blood transfusions increase the risk of hepatitis, iron overload, and transplant sensitization; they should be avoided unless the anemia fails to respond to EPO and the patient is symptomatic.

At least three randomized, controlled trials of erythropoietin-stimulating agents in CKD have failed to show an improvement in cardiovascular outcomes with this therapy. Indeed, there has been an indication that the use of EPO in CKD may be associated with an increased risk of stroke in those with type 2 diabetes, an increase in thromboembolic events, and perhaps a faster progression to the need for dialysis. Therefore, any benefit in terms of improvement of anemic symptoms needs to be balanced against the potential cardiovascular risk of EPO therapy in CKD. While further studies are needed, it

is quite clear that complete normalization of the hemoglobin concentration has not been demonstrated to be of incremental benefit to CKD patients. Current practice is to target a hemoglobin concentration of 100–115 g/L.

Abnormal hemostasis

Patients with later stages of CKD may have a prolonged bleeding time, decreased activity of platelet factor III, abnormal platelet aggregation and adhesiveness, and impaired prothrombin consumption. Clinical manifestations include an increased tendency to bleeding and bruising, prolonged bleeding from surgical incisions, menorrhagia, and spontaneous GI bleeding. Interestingly, CKD patients also have a greater susceptibility to thromboembolism, especially if they have renal disease that includes nephrotic-range proteinuria. The latter condition results in hypoalbuminemia and renal loss of anticoagulant factors, which can lead to a thrombophilic state.

TREATMENT **Abnormal Hemostasis**

Abnormal bleeding time and coagulopathy in patients with renal failure may be reversed temporarily with desmopressin (DDAVP), cryoprecipitate, IV conjugated estrogens, blood transfusions, and EPO therapy. Optimal dialysis will usually correct a prolonged bleeding time.

Given the coexistence of bleeding disorders and a propensity to thrombosis that is unique in the CKD patient, decisions about anticoagulation that have a favorable risk-benefit profile in the general population may not be applicable to the patient with advanced CKD. One example is warfarin anticoagulation for atrial fibrillation: the decision to anticoagulate should be made on an individual basis in the CKD patient, as there appears to be a greater risk of bleeding complications.

Certain anticoagulants, such as fractionated low-molecular-weight heparin, may need to be avoided or dose adjusted in these patients, with monitoring of factor Xa activity where available. It is often more prudent to use conventional high-molecular-weight heparin, titrated to the measured partial thromboplastin time, in hospitalized patients requiring an alternative to warfarin anticoagulation.

NEUROMUSCULAR ABNORMALITIES

Central nervous system (CNS), peripheral, and autonomic neuropathy as well as abnormalities in muscle structure and function are all well-recognized complications of CKD. Retained nitrogenous metabolites and middle molecules, including PTH, contribute to the pathophysiology of neuromuscular abnormalities. Subtle clinical manifestations of uremic neuromuscular disease usually become evident at stage 3 CKD. Early manifestations of CNS complications include mild disturbances in memory and concentration and sleep disturbance. Neuromuscular irritability, including hiccups, ramps, and fasciculations or twitching of muscles, becomes evident at later stages. In advanced untreated kidney failure, asterixis, myoclonus, seizures, and coma can be seen.

Peripheral neuropathy usually becomes clinically evident after the patient reaches stage 4 CKD, although electrophysiologic and histologic evidence occurs earlier. Initially, sensory nerves are involved more than motor, lower extremities more than upper, and distal parts of the extremities more than proximal. The "restless legs syndrome" is characterized by ill-defined sensations of sometimes debilitating discomfort in the legs and feet relieved by frequent leg movement. If dialysis is not instituted soon after onset of sensory abnormalities, motor involvement follows, including muscle weakness. Evidence of peripheral neuropathy without another cause (e.g., diabetes mellitus) is a firm indication for starting renal replacement therapy. Many of the complications described above will resolve with dialysis, although subtle nonspecific abnormalities may persist. Successful renal transplantation may reverse residual neurologic changes.

GASTROINTESTINAL AND NUTRITIONAL ABNORMALITIES

Uremic fetor, a urine-like odor on the breath, derives from the breakdown of urea to ammonia in saliva and is often associated with an unpleasant metallic taste (dysgeusia). Gastritis, peptic disease, and mucosal ulcerations at any level of the GI tract occur in uremic patients and can lead to abdominal pain, nausea, vomiting, and GI bleeding. These patients are also prone to constipation, which can be worsened by the administration of calcium and iron supplements. The retention of uremic toxins also leads to anorexia, nausea, and vomiting.

Protein restriction may be useful to decrease nausea and vomiting; however, it may put the patient at risk for malnutrition and should be carried out, if possible, in consultation with a registered dietitian specializing in the management of CKD patients. Protein-energy malnutrition, a consequence of low protein and caloric intake, is common in advanced CKD and is often an indication for initiation of renal replacement therapy. In addition to diminished intake, these patients are resistant to the anabolic actions of insulin and other hormones and growth factors. Metabolic acidosis and the activation of inflammatory cytokines can promote protein catabolism. Assessment for protein-energy malnutrition should begin at stage 3 CKD. A number of indices are useful in this assessment and include dietary history, including food diary and subjective global assessment;

edema-free body weight; and measurement of urinary protein nitrogen appearance. Dual-energy x-ray absorptiometry is now widely used to estimate lean body mass versus ECFV. Adjunctive tools include clinical signs, such as skin-fold thickness, mid-arm muscle circumference, and additional laboratory tests such as serum prealbumin and cholesterol levels. Nutritional guidelines for patients with CKD are summarized in the "Treatment" section below.

ENDOCRINE-METABOLIC DISTURBANCES

Glucose metabolism is impaired in CKD, as evidenced by a slowing of the rate at which blood glucose levels decline after a glucose load. However, fasting blood glucose is usually normal or only slightly elevated, and the mild glucose intolerance does not require specific therapy. Because the kidney contributes to insulin removal from the circulation, plasma levels of insulin are slightly to moderately elevated in most uremic patients, both in the fasting and postprandial states. Because of this diminished renal degradation of insulin, patients on insulin therapy may need progressive reduction in dose as their renal function worsens. Many hypoglycemic agents require dose reduction in renal failure, and some, such as metformin, are contraindicated when the GFR is less than half of normal.

In women with CKD, estrogen levels are low, and menstrual abnormalities and inability to carry pregnancies to term are common. When the GFR has declined to ~40 mL/min, pregnancy is associated with a high rate of spontaneous abortion, with only ~20% of pregnancies leading to live births, and pregnancy may hasten the progression of the kidney disease itself. Women with CKD who are contemplating pregnancy should consult first with a nephrologist in conjunction with an obstetrician specializing in high-risk pregnancy. Men with CKD have reduced plasma testosterone levels, and sexual dysfunction and oligospermia may supervene. Sexual maturation may be delayed or impaired in adolescent children with CKD, even among those treated with dialysis. Many of these abnormalities improve or reverse with intensive dialysis or most importantly with successful renal transplantation.

DERMATOLOGIC ABNORMALITIES

Abnormalities of the skin are prevalent in progressive CKD. Pruritus is quite common and one of the most vexing manifestations of the uremic state. In advanced CKD, even on dialysis, patients may become more pigmented, and this is felt to reflect the deposition of retained pigmented metabolites, or *urochromes*. Although many of the cutaneous abnormalities improve with dialysis, pruritus is often tenacious. The first lines of management are to rule out unrelated skin disorders, such as scabies, and to treat hyperphosphatemia, which can cause itch. EPO therapy was initially reported to improve uremic pruritus, although that is not always the case. Local moisturizers, mild topical glucocorticoids, oral antihistamines, and ultraviolet radiation have been reported to be helpful.

A skin condition unique to CKD patients called *nephrogenic fibrosing dermopathy* consists of progressive subcutaneous induration, especially on the arms and legs. The condition is similar to scleromyxedema and is seen in patients with CKD who have been exposed to the magnetic resonance contrast agent gadolinium. Current recommendations are that patients with CKD stage 2 (GFR 30–59 mL/min) should minimize exposure to gadolinium, and those with CKD stages 3–5 (GFR <30 mL/min) should avoid the use of gadolinium agents unless it is medically necessary. Concomitant liver disease appears to be a risk factor. However, no patient should be denied an imaging investigation that is critical to clinical management, and under such circumstances, rapid removal of gadolinium by hemodialysis (even in patients not yet receiving renal replacement therapy) shortly after the imaging procedure may mitigate this sometimes devastating complication.

EVALUATION AND MANAGEMENT OF PATIENTS WITH CKD

INITIAL APPROACH

History and physical examination

Symptoms and overt signs of kidney disease are often subtle or absent until renal failure supervenes. Thus, the diagnosis of kidney disease often surprises patients and may be a cause of skepticism and denial. Particular aspects of the history that are germane to renal disease include a history of hypertension (which can cause CKD or more commonly be a consequence of CKD), diabetes mellitus, abnormal urinalyses, and problems with pregnancy such as preeclampsia or early pregnancy loss. A careful drug history should be elicited: patients may not volunteer use of analgesics, for example. Other drugs to consider include nonsteroidal anti-inflammatory agents, gold, penicillamine, antimicrobials, chemotherapeutic agents, antiretroviral agents, proton pump inhibitors, phosphate-containing bowel cathartics, and lithium, as well as prior exposure to medical imaging radiocontrast agents. In evaluating the uremic syndrome, questions about appetite, weight loss, nausea, hiccups, peripheral edema, muscle cramps, pruritus, and restless legs are especially helpful. A careful family history of kidney disease, together with assessment of manifestations in other organ systems such as auditory, visual, integumentary and others, may lead to the diagnosis of a heritable form of CKD (e.g., Alport or

Fabry syndrome, cystinuria, among others) or shared environmental exposure to nephrotoxic agents (e.g., heavy metals, aristolochic acid). It should be noted that clustering of CKD, sometimes of different etiologies, is often observed within families.

The physical examination should focus on blood pressure and target organ damage from hypertension. Thus, funduscopy and precordial examination (left ventricular heave, a fourth heart sound) should be carried out. Funduscopy is important in the diabetic patient, as it may show evidence of diabetic retinopathy, which is associated with nephropathy. Other physical examination manifestations of CKD include edema and sensory polyneuropathy. The finding of asterixis or a pericardial friction rub not attributable to other causes usually signifies the presence of the uremic syndrome.

Laboratory investigation

Laboratory studies should focus on a search for clues to an underlying causative or aggravating disease process and on the degree of renal damage and its consequences. Serum and urine protein electrophoresis, looking for multiple myeloma, should be obtained in all patients >35 years with unexplained CKD, especially if there is associated anemia and elevated, or even inappropriately normal, serum calcium concentration in the face of renal insufficiency. In the presence of glomerulonephritis, autoimmune diseases such as lupus and underlying infectious etiologies such as hepatitis B and C and HIV should be assessed. Serial measurements of renal function should be obtained to determine the pace of renal deterioration and ensure that the disease is truly chronic rather than acute or subacute and hence potentially reversible. Serum concentrations of calcium, phosphorus, vitamin D, and PTH should be measured to evaluate metabolic bone disease. Hemoglobin concentration, iron, B_{12}, and folate should also be evaluated. A 24-h urine collection may be helpful, as protein excretion >300 mg may be an indication for therapy with ACE inhibitors or ARBs.

Imaging studies

The most useful imaging study is a renal ultrasound, which can verify the presence of two kidneys, determine if they are symmetric, provide an estimate of kidney size, and rule out renal masses and evidence of obstruction. Since it takes time for kidneys to shrink as a result of chronic disease, the finding of bilaterally small kidneys supports the diagnosis of CKD of long-standing duration, with an irreversible component of scarring. If the kidney size is normal, it is possible that the renal disease is acute or subacute. The exceptions are diabetic nephropathy (where kidney size is increased at the onset of diabetic nephropathy before CKD with loss of GFR supervenes), amyloidosis, and HIV nephropathy, where kidney size may be normal in the face of CKD. Polycystic kidney disease that has reached some degree of renal failure will almost always present with enlarged kidneys with multiple cysts (Chap. 16). A discrepancy >1 cm in kidney length suggests either a unilateral developmental abnormality or disease process or renovascular disease with arterial insufficiency affecting one kidney more than the other. The diagnosis of renovascular disease can be undertaken with different techniques, including Doppler sonography, nuclear medicine studies, or CT or MRI studies. If there is a suspicion of reflux nephropathy (recurrent childhood urinary tract infection, asymmetric renal size with scars on the renal poles), a voiding cystogram may be indicated. However, in most cases by the time the patient has CKD, the reflux has resolved, and even if still present, repair does not improve renal function. Radiographic contrast imaging studies are not particularly helpful in the investigation of CKD. Intravenous or intraarterial dye should be avoided where possible in the CKD patient, especially with diabetic nephropathy, because of the risk of radiographic contrast dye–induced renal failure. When unavoidable, appropriate precautionary measures include avoidance of hypovolemia at the time of contrast exposure, minimization of the dye load, and choice of radiographic contrast preparations with the least nephrotoxic potential. Additional measures thought to attenuate contrast-induced worsening of renal function include judicious administration of sodium bicarbonate–containing solutions and *N*-acetyl-cysteine.

Renal biopsy

In the patient with bilaterally small kidneys, renal biopsy is not advised because (1) it is technically difficult and has a greater likelihood of causing bleeding and other adverse consequences, (2) there is usually so much scarring that the underlying disease may not be apparent, and (3) the window of opportunity to render disease-specific therapy has passed. Other contraindications to renal biopsy include uncontrolled hypertension, active urinary tract infection, bleeding diathesis (including ongoing anticoagulation), and severe obesity. Ultrasound-guided percutaneous biopsy is the favored approach, but a surgical or laparoscopic approach can be considered, especially in the patient with a single kidney where direct visualization and control of bleeding are crucial. In the CKD patient in whom a kidney biopsy is indicated (e.g., suspicion of a concomitant or superimposed active process such as interstitial nephritis or in the face of accelerated loss of GFR), the bleeding time should be measured, and, if increased, desmopressin should be administered immediately prior to the procedure.

A brief run of hemodialysis (without heparin) may also be considered prior to renal biopsy to normalize the bleeding time.

ESTABLISHING THE DIAGNOSIS AND ETIOLOGY OF CKD

The most important initial diagnostic step in the evaluation of a patient presenting with elevated serum creatinine is to distinguish newly diagnosed CKD from acute or subacute renal failure because the latter two conditions may respond to therapy specific to the disease. Previous measurements of serum creatinine concentration are particularly helpful in this regard. Normal values from recent months or even years suggest that the current extent of renal dysfunction could be more acute, and hence reversible, than might otherwise be appreciated. In contrast, elevated serum creatinine concentration in the past suggests that the renal disease represents the progression of a chronic process. Even if there is evidence of chronicity, there is the possibility of a superimposed acute process (e.g., ECFV depletion, urinary infection or obstruction, or nephrotoxin exposure) supervening on the chronic condition. If the history suggests multiple systemic manifestations of recent onset (e.g., fever, polyarthritis, and rash), it should be assumed that renal insufficiency is part of the acute process.

Some of the laboratory tests and imaging studies outlined above can be helpful. Evidence of metabolic bone disease with hyperphosphatemia, hypocalcemia, and elevated PTH and bone alkaline phosphatase levels suggests chronicity. Normochromic, normocytic anemia suggests that the process has been ongoing for some time. The finding of bilaterally reduced kidney size (<8.5 cm in all but the smallest adults) favors CKD.

While renal biopsy can usually be performed in early CKD (stages 1–3), it is not always indicated. For example, in a patient with a history of type 1 diabetes mellitus for 15–20 years with retinopathy, nephrotic-range proteinuria, and absence of hematuria, the diagnosis of diabetic nephropathy is very likely and biopsy is usually not necessary. However, if there were some other finding not typical of diabetic nephropathy, such as hematuria or white blood cell casts, or absence of diabetic retinopathy, some other disease may be present and a biopsy may be indicated. Ischemic nephropathy is usually diagnosed clinically by the presence of long-standing hypertension, evidence of ischemic disease elsewhere (e.g., cardiac or peripheral vascular disease), and the finding of nonnephrotic proteinuria in the absence of urinary blood or red cell casts. It is important to consider progressive ischemic nephropathy because a small subset of these patients may respond to revascularization procedures, although this remains controversial.

In the absence of a clinical diagnosis, renal biopsy may be the only recourse to establish an etiology in early-stage CKD. However, as noted above, once the CKD is advanced and the kidneys are small and scarred, there is little utility and significant risk in attempting to arrive at a specific diagnosis.

TREATMENT **Chronic Kidney Disease**

Treatments aimed at specific causes of CKD are discussed elsewhere. Among others, these include optimized glucose control in diabetes mellitus, immunomodulatory agents for glomerulonephritis, and emerging specific therapies to retard cytogenesis in polycystic kidney disease. The optimal timing of both specific and nonspecific therapy is usually well before there has been a measurable decline in GFR and certainly before CKD is established (Table 11-6). It is helpful to sequentially measure and plot the rate of decline of GFR in all patients. Any acceleration in the rate of decline should prompt a search for superimposed acute or subacute processes that may be reversible. These include ECFV depletion, uncontrolled hypertension, urinary tract infection, new obstructive uropathy, exposure to nephrotoxic agents [such as nonsteroidal anti-inflammatory drugs (NSAIDs) or radiographic dye], and reactivation or flare of the original disease, such as lupus or vasculitis.

TABLE 11-6
CLINICAL ACTION PLAN

STAGE	DESCRIPTION	GFR, mL/min PER 1.73 m^2	ACTION[a]
1	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment, treatment of comorbid conditions, slowing progression, CVD risk reduction
2	Kidney damage with mild ↓ GFR	60–89	Estimating progression
3	Moderate ↓ GFR	30–59	Evaluating and treating complications
4	Severe ↓ GFR	15–29	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	Kidney replacement (if uremia present)

[a]Includes actions from preceding stages.
Abbreviations: CVD, cardiovascular disease; GFR, glomerular filtration rate.
Source: National Kidney Foundation: Am J Kidney Dis 39:S1, 2002.

SLOWING THE PROGRESSION OF CKD There is variation in the rate of decline of GFR among patients with CKD. However, the following interventions should be considered in an effort to stabilize or slow the decline of renal function.

Reducing Intraglomerular Hypertension and Proteinuria Increased intraglomerular filtration pressures and glomerular hypertrophy develop as a response to loss of nephron number from different kidney diseases. This response is maladaptive, as it promotes the ongoing decline of kidney function even if the inciting process has been treated or spontaneously resolved. Control of systemic and glomerular hypertension is important in slowing the progression of CKD. Therefore, in addition to reduction of cardiovascular disease risk, antihypertensive therapy in patients with CKD also aims to slow the progression of nephron injury by reducing intraglomerular hypertension. Elevated blood pressure increases proteinuria by increasing its flux across the glomerular capillaries. Conversely, the renoprotective effect of antihypertensive medications is gauged through the consequent reduction of proteinuria. Thus, the more effective a given treatment is in lowering protein excretion, the greater the subsequent impact on protection from decline in GFR. This observation is the basis for the treatment guideline establishing 125/75 mmHg as the target blood pressure in proteinuric CKD patients.

ACE inhibitors and ARBs inhibit the angiotensin-induced vasoconstriction of the efferent arterioles of the glomerular microcirculation. This inhibition leads to a reduction in both intraglomerular filtration pressure and proteinuria. Several controlled studies have shown that these drugs are effective in slowing the progression of renal failure in patients with advanced stages of both diabetic and nondiabetic CKD. This slowing in progression of CKD is strongly associated with the proteinuria-lowering effect. In the absence of an anti-proteinuric response with either agent alone, combined treatment with both ACE inhibitors and ARBs has been considered. The combination is associated with a greater reduction in proteinuria compared to either agent alone. Insofar as reduction in proteinuria is a surrogate for improved renal outcome, the combination would appear to be advantageous. However, a recent randomized, controlled study found a greater incidence of acute renal failure and adverse cardiac events from such combination therapy. It is uncertain, therefore, whether the ACE plus ARB therapy can be advised routinely. Adverse effects from these agents include cough and angioedema with ACE inhibitors, anaphylaxis, and hyperkalemia with either class. A progressive increase in serum creatinine concentration with these agents may suggest the presence of renovascular disease within the large or small arteries. Development of these side effects may mandate the use of second-line antihypertensive agents instead of the ACE inhibitors or ARBs. Among the calcium channel blockers, diltiazem and verapamil may exhibit superior antiproteinuric and renoprotective effects compared to the dihydropyridines. At least two different categories of response can be considered: one in which progression is strongly associated with systemic and intraglomerular hypertension and proteinuria (e.g., diabetic nephropathy, glomerular diseases) and in which ACE inhibitors and ARBs are likely to be the first choice; and another in which proteinuria is mild or absent initially (e.g., adult polycystic kidney disease and other tubulointerstitial diseases), where the contribution of intraglomerular hypertension is less prominent, and other antihypertensive agents can be useful for control of systemic hypertension.

SLOWING PROGRESSION OF DIABETIC RENAL DISEASE Diabetic nephropathy is now the leading cause of CKD requiring renal replacement therapy in many parts of the world, and its prevalence is increasing disproportionately in the developing world. Furthermore, the prognosis of diabetic patients on dialysis is poor, with survival comparable to many forms of cancer. Accordingly, it is mandatory to develop strategies whose aim is to prevent or slow the progression of diabetic nephropathy in these patients.

Control of Blood Glucose Excellent glycemic control reduces the risk of kidney disease and its progression in both type 1 and type 2 diabetes mellitus. It is recommended that plasma values for preprandial glucose be kept in the 5.0–7.2 mmol/L (90–130 mg/dL) range and hemoglobin A_{1C} should be <7%. As the GFR decreases with progressive nephropathy, the use and dose of oral hypoglycemics needs to be reevaluated. For example, chlorpropamide may be associated with prolonged hypoglycemia in patients with decreased renal function; metformin can cause lactic acidosis in the patient with renal impairment and should be discontinued when the GFR is reduced; and the thiazolidinediones (e.g., rosiglitazone, pioglitazone, and others) may increase renal salt and water absorption and aggravate volume-overload states, and contribute to adverse cardiovascular events. Finally, as renal function declines, renal degradation of administered insulin will also decline, so that less insulin may be required for glycemic control.

Control of Blood Pressure and Proteinuria Hypertension is found in the majority of type 2 diabetic patients at diagnosis. This finding correlates with the presence of albuminuria and is a strong predictor of cardiovascular events and nephropathy. Microalbuminuria,

the finding of albumin in the urine not detectable by the urine dipstick, precedes the decline in GFR and heralds renal and cardiovascular complications. Testing for microalbumin is recommended in all diabetic patients, at least annually. If the patient already has established proteinuria, then testing for microalbumin is not necessary. Antihypertensive treatment reduces albuminuria and diminishes its progression even in normotensive diabetic patients. In addition to treatment of hypertension in general, the use of ACE inhibitors and ARBs in particular is associated with additional renoprotection. These salutary effects are mediated by reducing intraglomerular pressure and inhibition of angiotensin-driven sclerosing pathways, in part through inhibition of TGF-β–mediated pathways. Recent studies have highlighted the benefit of renin-angiotensin axis blockade on the development of retinopathy in diabetic patients, but do not necessarily show a clear-cut renal benefit of intervention at the very earliest stages, prior to onset of overt proteinuria. In any case, as noted above, the combination of ACE inhibitors with ARBs is not recommended.

Protein Restriction While protein restriction has been advocated to reduce symptoms associated with uremia, it may also slow the rate of renal decline at earlier stages of renal disease. This concept is based on clinical and experimental evidence that protein-mediated hyperfiltration contributes to ongoing decline in renal function in many different forms of renal disease. A number of studies have shown that protein restriction may be effective in slowing the progression of CKD, especially proteinuric and diabetic renal diseases. However, the Modification of Diet in Renal Disease study was unable to demonstrate a robust benefit in delaying progression to advanced stages of CKD with dietary restriction of protein intake. Nonetheless, restriction of dietary protein intake has been recommended for CKD patients. KDOQI clinical practice guidelines include a daily protein intake of between 0.60 and 0.75 g/kg per day, depending upon patient adherence, comorbid disease, presence of proteinuria, and nutritional status. It is further advised that at least 50% of the protein intake be of high biologic value. As patients approach stage 5 CKD, spontaneous protein intake tends to decrease, and patients may enter a state of protein-energy malnutrition. In these circumstances, a protein intake of up to 0.90 g/kg per day might be recommended, again with an emphasis on proteins of high biologic value.

Sufficient energy intake is important to prevent protein-calorie malnutrition, and 35 kcal/kg is recommended. Monitoring of parameters of nutritional status must accompany the dietary intervention, using the parameters outlined above in the section on GI and nutritional abnormalities.

MANAGING OTHER COMPLICATIONS OF CHRONIC KIDNEY DISEASE

Medication Dose Adjustment Although the loading dose of most drugs is not affected by CKD because no renal elimination is used in the calculation, the maintenance doses of many drugs will need to be adjusted. For those agents in which >70% excretion is by a nonrenal route, such as hepatic elimination, dose adjustment may not be needed. Some drugs that should be avoided include metformin, meperidine, and oral hypoglycemics that are eliminated by the kidney. NSAIDs should be avoided because of the risk of further worsening of kidney function. Many antibiotics, antihypertensives, and antiarrhythmics may require a reduction in dosage or change in the dose interval. Several online web-based databases for dose adjustment of medications according to stage of CKD or estimated GFR are available (e.g., *http://www.globalrph.com/renaldosing2.htm*). Nephrotoxic medical imaging radiocontrast agents and gadolinium should be avoided or used according to strict guidelines when medically necessary as described above.

Preparation for Renal Replacement Therapy (See also Chap. 13) Temporary relief of symptoms and signs of impending uremia, such as anorexia, nausea, vomiting, lassitude, and pruritus, may sometimes be achieved with protein restriction. However, this carries a significant risk of protein-energy malnutrition, and thus plans for more long-term management should be in place.

Maintenance dialysis and kidney transplantation has extended the lives of hundreds of thousands of patients with CKD worldwide. Clear indications for initiation of renal replacement therapy for patients with CKD include uremic pericarditis, encephalopathy, intractable muscle cramping, anorexia, and nausea not attributable to reversible causes such as peptic ulcer disease, evidence of malnutrition, and fluid and electrolyte abnormalities, principally hyperkalemia or ECF volume overload, that are refractory to other measures.

Recommendations for the optimal time for initiation of renal replacement therapy have been established by the National Kidney Foundation in their KDOQI Guidelines and are based on recent evidence demonstrating that delaying initiation of renal replacement therapy until patients are malnourished or have severe uremic complications leads to a worse prognosis on dialysis or with transplantation. Because of the interindividual variability in the severity of uremic symptoms and renal function, it is ill advised to assign an arbitrary urea nitrogen or creatinine level to the need to start dialysis. Moreover, patients may become accustomed to chronic uremia and deny symptoms, only to find that they feel better with dialysis and realize in retrospect how poorly they were feeling before its initiation.

Previous studies suggested that starting dialysis before the onset of severe symptoms and signs of uremia was associated with prolongation of survival. This led to the concept of "healthy" start and is congruent with the philosophy that it is better to keep patients feeling well all along rather than allowing them to become ill with uremia before trying to return them to better health with dialysis or transplantation. Although recent studies have not confirmed a clear association of early-start dialysis with improved patient survival, there is still merit in this approach. On a practical level, advanced preparation may help to avoid problems with the dialysis process itself (e.g., a poorly functioning fistula for hemodialysis or malfunctioning peritoneal dialysis catheter) and thus preempt the morbidity associated with resorting to the insertion of temporary hemodialysis access with its attendant risks of sepsis, bleeding, and thrombosis.

Patient Education Social, psychological, and physical preparation for the transition to renal replacement therapy and the choice of the optimal initial modality are best accomplished with a gradual approach involving a multidisciplinary team. Along with conservative measures discussed in the sections above, it is important to prepare patients with an intensive educational program, explaining the likelihood and timing of initiation of renal replacement therapy and the various forms of therapy available. The more knowledgeable that patients are about hemodialysis (both in center and home based), peritoneal dialysis, and kidney transplantation, the easier and more appropriate will be their decisions. Patients who are provided with educational programs are more likely to choose home-based dialysis therapy. This approach is of societal benefit because home-based therapy is less expensive and is associated with improved quality of life. The educational programs should be commenced no later than stage 4 CKD so that the patient has sufficient time and cognitive function to learn the important concepts, make informed choices, and implement preparatory measures for renal replacement therapy.

Exploration of social service support is also important. In those who may perform home dialysis or undergo preemptive renal transplantation, early education of family members for selection and preparation of a home dialysis helper, or a biologically or emotionally related potential living kidney donor, should occur long before the onset of symptomatic renal failure.

Kidney transplantation (Chap. 13) offers the best potential for complete rehabilitation, because dialysis replaces only a small fraction of the kidneys' filtration function and none of the other renal functions, including endocrine and anti-inflammatory effects. Generally, kidney transplantation follows a period of dialysis treatment, although preemptive kidney transplantation (usually from a living donor) can be carried out if it is certain that the renal failure is irreversible.

IMPLICATIONS FOR GLOBAL HEALTH

In distinction to the natural decline and successful eradication of many devastating infectious diseases, there is rapid growth in the prevalence of metabolic and vascular disease in developing countries. Diabetes mellitus is becoming increasingly prevalent in these countries, perhaps due in part to change in dietary habits, diminished physical activity, and weight gain. Therefore, it follows that there will be a proportionate increase in vascular and renal disease. Healthcare agencies must plan for improved screening for early detection, prevention, and treatment plans in these nations and must start considering options for improved availability of renal replacement therapies.

CHAPTER 12

DIALYSIS IN THE TREATMENT OF RENAL FAILURE

Kathleen D. Liu ■ Glenn M. Chertow

Dialysis may be required for the treatment of either acute or chronic kidney disease. The use of continuous renal replacement therapies (CRRTs) and slow low-efficiency dialysis (SLED) is specific to the management of acute renal failure and is discussed in Chap. 10. These modalities are performed continuously (CRRT) or over 6–12 hours per session (SLED), in contrast to the 3–4 hours of an intermittent hemodialysis session. Advantages and disadvantages of CRRT and SLED are discussed in Chap. 10.

Peritoneal dialysis is rarely used in developed countries for the treatment of acute renal failure because of the increased risk of infection and (as will be discussed in more detail below) less efficient clearance per unit of time. The focus of the majority of this chapter will be on the use of peritoneal dialysis and hemodialysis for end-stage renal disease (ESRD).

With the widespread availability of dialysis, the lives of hundreds of thousands of patients with ESRD have been prolonged. In the United States alone, there are now approximately 530,000 patients with ESRD, the vast majority of whom require dialysis. The incidence rate for ESRD is 350 cases per million population per year. The incidence of ESRD is disproportionately higher in African Americans (approximately 1000 per million population per year) as compared with white Americans (275 per million population per year). In the United States, the leading cause of ESRD is diabetes mellitus, currently accounting for nearly 55% of newly diagnosed cases of ESRD. Approximately one-third (33%) of patients have ESRD that has been attributed to hypertension, although it is unclear whether in these cases hypertension is the cause or a consequence of vascular disease or other unknown causes of kidney failure. Other prevalent causes of ESRD include glomerulonephritis, polycystic kidney disease, and obstructive uropathy.

Globally, mortality rates for patients with ESRD are lowest in Europe and Japan but are very high in the developing world because of the limited availability of dialysis. In the United States, the mortality rate of patients on dialysis is approximately 18–20% per year, with a 5-year survival rate of approximately 30–35%. Deaths are due mainly to cardiovascular diseases and infections (approximately 50 and 15% of deaths, respectively). Older age, male sex, nonblack race, diabetes mellitus, malnutrition, and underlying heart disease are important predictors of death.

TREATMENT OPTIONS FOR ESRD PATIENTS

Commonly accepted criteria for initiating patients on maintenance dialysis include the presence of uremic symptoms, the presence of hyperkalemia unresponsive to conservative measures, persistent extracellular volume expansion despite diuretic therapy, acidosis refractory to medical therapy, a bleeding diathesis, and a creatinine clearance or estimated glomerular filtration rate (GFR) below 10 mL/min per 1.73 m^2 (see Chap. 11 for estimating equations). Timely referral to a nephrologist for advanced planning and creation of a dialysis access, education about ESRD treatment options, and management of the complications of advanced chronic kidney disease (CKD), including hypertension, anemia, acidosis, and secondary hyperparathyroidism, is advisable. Recent data have suggested that a sizable fraction of ESRD cases result following episodes of acute renal failure, particularly among persons with underlying CKD.

In ESRD, treatment options include hemodialysis (in center or at home); peritoneal dialysis, as either continuous ambulatory peritoneal dialysis (CAPD) or continuous

cyclic peritoneal dialysis (CCPD); or transplantation (Chap. 13). Although there are significant geographic variations and differences in practice patterns, hemodialysis remains the most common therapeutic modality for ESRD (>90% of patients) in the United States. In contrast to hemodialysis, peritoneal dialysis is continuous but much less efficient, in terms of solute clearance. While no large-scale clinical trials have been completed comparing outcomes among patients randomized to either hemodialysis or peritoneal dialysis, outcomes associated with both therapies are similar in most reports, and the decision of which modality to select is often based on personal preferences and quality-of-life considerations.

HEMODIALYSIS

Hemodialysis relies on the principles of solute diffusion across a semipermeable membrane. Movement of metabolic waste products takes place down a concentration gradient from the circulation into the dialysate. The rate of diffusive transport increases in response to several factors, including the magnitude of the concentration gradient, the membrane surface area, and the mass transfer coefficient of the membrane. The latter is a function of the porosity and thickness of the membrane, the size of the solute molecule, and the conditions of flow on the two sides of the membrane. According to laws of diffusion, the larger the molecule, the slower its rate of transfer across the membrane. A small molecule, such as urea (60 Da), undergoes substantial clearance, whereas a larger molecule, such as creatinine (113 Da), is cleared less efficiently. In addition to diffusive clearance, movement of waste products from the circulation into the dialysate may occur as a result of ultrafiltration. Convective clearance occurs because of solvent drag, with solutes being swept along with water across the semipermeable dialysis membrane.

THE DIALYZER

There are three essential components to hemodialysis: the dialyzer, the composition and delivery of the dialysate, and the blood delivery system **(Fig. 12-1)**. The dialyzer is a plastic chamber with the ability to perfuse blood and dialysate compartments simultaneously at very high flow rates. The surface area of modern dialysis membranes in adult patients is usually in the range of 1.5–2.0 m^2. The hollow-fiber dialyzer is the most common in use in the United States. These dialyzers are composed of bundles of capillary tubes through which blood circulates while dialysate travels on the outside of the fiber bundle.

Recent advances have led to the development of many different types of membrane material. Broadly, there are four categories of dialysis membranes: cellulose, substituted cellulose, cellulosynthetic, and synthetic. Over the past three decades, there has been a gradual switch

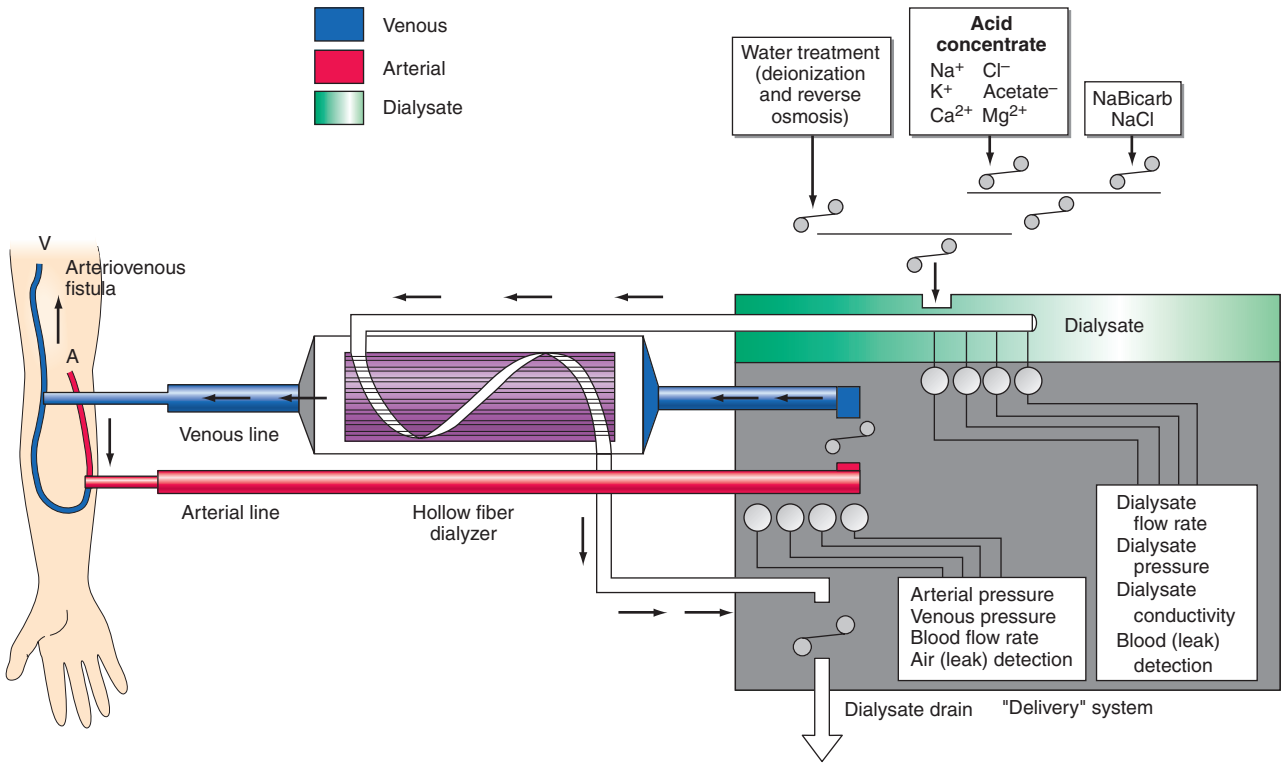

FIGURE 12-1
Schema for hemodialysis.

from cellulose-derived to synthetic membranes, because the latter are more "biocompatible." *Bioincompatibility* is generally defined as the ability of the membrane to activate the complement cascade. Cellulosic membranes are bioincompatible because of the presence of free hydroxyl groups on the membrane surface. In contrast, with the substituted cellulose membranes (e.g., cellulose acetate) or the cellulosynthetic membranes, the hydroxyl groups are chemically bound to either acetate or tertiary amino groups, resulting in limited complement activation. Synthetic membranes, such as polysulfone, polymethylmethacrylate, and polyacrylonitrile membranes, are even more biocompatible because of the absence of these hydroxyl groups. The majority of dialyzers now manufactured in the United States are derived from polysulfone or newer derivatives (polyarylethersulfone).

Reprocessing and reuse of hemodialyzers are often employed for patients on maintenance hemodialysis in the United States. However, as the manufacturing costs for disposable dialyzers have declined, more and more outpatient dialysis facilities are no longer reprocessing dialyzers. In most centers employing reuse, only the dialyzer unit is reprocessed and reused, whereas in the developing world blood lines are also frequently reused. The reprocessing procedure can be either manual or automated. It consists of the sequential rinsing of the blood and dialysate compartments with water, a chemical cleansing step with reverse ultrafiltration from the dialysate to the blood compartment, the testing of the patency of the dialyzer, and, finally, disinfection of the dialyzer. Formaldehyde, peracetic acid–hydrogen peroxide, glutaraldehyde, and bleach have all been used as reprocessing agents.

DIALYSATE

The potassium concentration of dialysate may be varied from 0 to 4 mmol/L depending on the predialysis serum potassium concentration. The usual dialysate calcium concentration in U.S. hemodialysis centers is 1.25 mmol/L (2.5 meq/L), although modification may be required in selected settings (e.g., higher dialysate calcium concentrations may be used in patients with hypocalcemia associated with secondary hyperparathyroidism or following parathyroidectomy). The usual dialysate sodium concentration is 140 mmol/L. Lower dialysate sodium concentrations are associated with a higher frequency of hypotension, cramping, nausea, vomiting, fatigue, and dizziness in some patients, although may attenuate thirst. In patients who frequently develop hypotension during their dialysis run, "sodium modeling" to counterbalance urea-related osmolar gradients is often employed. With sodium modeling, the dialysate sodium concentration is gradually lowered from the range of 145–155 mmol/L to isotonic concentrations (140 mmol/L) near the end of the dialysis treatment, typically declining either in steps or in a linear or exponential fashion. Higher dialysate sodium concentrations and sodium modeling may predispose patients to positive sodium balance; thus, these strategies to ameliorate intradialytic hypotension may be undesirable in hypertensive patients or in patients with large interdialytic weight gains. Because patients are exposed to approximately 120 L of water during each dialysis treatment, water used for the dialysate is subjected to filtration, softening, deionization, and, ultimately, reverse osmosis. During the reverse osmosis process, water is forced through a semipermeable membrane at very high pressure to remove microbiologic contaminants and >90% of dissolved ions.

BLOOD DELIVERY SYSTEM

The blood delivery system is composed of the extracorporeal circuit in the dialysis machine and the dialysis access. The dialysis machine consists of a blood pump, dialysis solution delivery system, and various safety monitors. The blood pump moves blood from the access site, through the dialyzer, and back to the patient. The blood flow rate may range from 250–500 mL/min, depending largely on the type and integrity of the vascular access. Negative hydrostatic pressure on the dialysate side can be manipulated to achieve desirable fluid removal or *ultrafiltration*. Dialysis membranes have different ultrafiltration coefficients (i.e., mL removed/min per mmHg) so that along with hydrostatic changes, fluid removal can be varied. The dialysis solution delivery system dilutes the concentrated dialysate with water and monitors the temperature, conductivity, and flow of dialysate.

DIALYSIS ACCESS

The fistula, graft, or catheter through which blood is obtained for hemodialysis is often referred to as a *dialysis access*. A native fistula created by the anastomosis of an artery to a vein (e.g., the Brescia-Cimino fistula, in which the cephalic vein is anastomosed end-to-side to the radial artery) results in arterialization of the vein. This facilitates its subsequent use in the placement of large needles (typically 15 gauge) to access the circulation. Although fistulas have the highest long-term patency rate of all dialysis access options, fistulas are created in a minority of patients in the United States. Many patients undergo placement of an arteriovenous graft (i.e., the interposition of prosthetic material, usually polytetrafluoroethylene, between an artery and a vein) or a tunneled dialysis catheter. In recent years, nephrologists, vascular surgeons, and health care policy makers in the United States have encouraged the creation of arteriovenous fistulas in a larger fraction of patients (the "fistula

first" initiative). Unfortunately, even when created, arteriovenous fistulas may not mature sufficiently to provide reliable access to the circulation, or they may thrombose early in their development. Novel surgical approaches (e.g., brachiobasilic fistula creation with transposition of the basilic vein fistula to the arm surface) have increased options for "native" vascular access.

Grafts and catheters tend to be used among persons with smaller-caliber veins or persons whose veins have been damaged by repeated venipuncture, or after prolonged hospitalization. The most important complication of arteriovenous grafts is thrombosis of the graft and graft failure, due principally to intimal hyperplasia at the anastomosis between the graft and recipient vein. When grafts (or fistulas) fail, catheter-guided angioplasty can be used to dilate stenoses; monitoring of venous pressures on dialysis and of access flow, although not routinely performed, may assist in the early recognition of impending vascular access failure. In addition to an increased rate of access failure, grafts and (in particular) catheters are associated with much higher rates of infection than fistulas.

Intravenous large-bore catheters are often used in patients with acute and chronic kidney disease. For persons on maintenance hemodialysis, tunneled catheters (either two separate catheters or a single catheter with two lumens) are often used when arteriovenous fistulas and grafts have failed or are not feasible due to anatomic considerations. These catheters are tunneled under the skin; the tunnel reduces bacterial translocation from the skin, resulting in a lower infection rate than with nontunneled temporary catheters. Most tunneled catheters are placed in the internal jugular veins; the external jugular, femoral, and subclavian veins may also be used.

Nephrologists, interventional radiologists, and vascular surgeons generally prefer to avoid placement of catheters into the subclavian veins; while flow rates are usually excellent, subclavian stenosis is a frequent complication and, if present, will likely prohibit permanent vascular access (i.e., a fistula or graft) in the ipsilateral extremity. Infection rates may be higher with femoral catheters. For patients with multiple vascular access complications and no other options for permanent vascular access, tunneled catheters may be the last "lifeline" for hemodialysis. Translumbar or transhepatic approaches into the inferior vena cava may be required if the superior vena cava or other central veins draining the upper extremities are stenosed or thrombosed.

GOALS OF DIALYSIS

The hemodialysis procedure is targeted at removing both low- and high-molecular-weight solutes. The procedure consists of pumping heparinized blood through the dialyzer at a flow rate of 300–500 mL/min, while dialysate flows in an opposite *counter-current* direction at 500–800 mL/min. The efficiency of dialysis is determined by blood and dialysate flow through the dialyzer as well as dialyzer characteristics (i.e., its efficiency in removing solute). The *dose* of dialysis, which is currently defined as a derivation of the fractional urea clearance during a single dialysis treatment, is further governed by patient size, residual kidney function, dietary protein intake, the degree of anabolism or catabolism, and the presence of comorbid conditions.

Since the landmark studies of Sargent and Gotch relating the measurement of the dose of dialysis using urea concentrations with morbidity in the National Cooperative Dialysis Study, the *delivered* dose of dialysis has been measured and considered as a quality assurance and improvement tool. While the fractional removal of urea nitrogen and derivations thereof are considered to be the standard methods by which "adequacy of dialysis" is measured, a large multicenter randomized clinical trial (the HEMO study) failed to show a difference in mortality associated with a large difference in urea clearance. Still, multiple observational studies and widespread expert opinion have suggested that higher dialysis dose is warranted; current targets include a urea reduction ratio (the fractional reduction in blood urea nitrogen per hemodialysis session) of >65–70% and a body water–indexed clearance × time product (KT/V) above 1.2 or 1.05, depending on whether urea concentrations are "equilibrated." For the majority of patients with ESRD, between 9 and 12 h of dialysis are required each week, usually divided into three equal sessions. Several studies have suggested that longer hemodialysis session lengths may be beneficial (independent of urea clearance), although these studies are confounded by a variety of patient characteristics, including body size and nutritional status. Hemodialysis "dose" should be individualized, and factors other than the urea nitrogen should be considered, including the adequacy of ultrafiltration or fluid removal and control of hyperkalemia, hyperphosphatemia, and metabolic acidosis. Several authors have highlighted improved intermediate outcomes associated with more frequent hemodialysis (i.e., more than three times a week), although these studies are also confounded by multiple factors. A randomized clinical trial is currently under way to test whether more frequent dialysis results in differences in a variety of physiologic and functional markers.

COMPLICATIONS DURING HEMODIALYSIS

Hypotension is the most common acute complication of hemodialysis, particularly among patients with diabetes mellitus. Numerous factors appear to increase the risk of hypotension, including excessive ultrafiltration with inadequate compensatory vascular filling, impaired vasoactive or autonomic responses, osmolar

shifts, overzealous use of antihypertensive agents, and reduced cardiac reserve. Patients with arteriovenous fistulas and grafts may develop high output cardiac failure due to shunting of blood through the dialysis access; on rare occasions, this may necessitate ligation of the fistula or graft. Because of the vasodilatory and cardiodepressive effects of acetate, its use as the buffer in dialysate was once a common cause of hypotension. Since the introduction of bicarbonate-containing dialysate, dialysis-associated hypotension has become less common. The management of hypotension during dialysis consists of discontinuing ultrafiltration, the administration of 100–250 mL of isotonic saline or 10 mL of 23% saturated hypertonic saline, or administration of salt-poor albumin. Hypotension during dialysis can frequently be prevented by careful evaluation of the dry weight and by ultrafiltration modeling, such that more fluid is removed at the beginning rather than the end of the dialysis procedure. Additional maneuvers include the performance of sequential ultrafiltration followed by dialysis, cooling of the dialysate during dialysis treatment, and avoiding heavy meals during dialysis. Midodrine, a selective α_1 adrenergic pressor agent, has been advocated by some practitioners, although there is insufficient evidence of its safety and efficacy to support its routine use.

Muscle cramps during dialysis are also a common complication of the procedure. The etiology of dialysis-associated cramps remains obscure. Changes in muscle perfusion because of excessively aggressive volume removal, particularly below the estimated dry weight, and the use of low-sodium–containing dialysate have been proposed as precipitants of dialysis-associated cramps. Strategies that may be used to prevent cramps include reducing volume removal during dialysis, ultrafiltration profiling, and the use of higher concentrations of sodium in the dialysate or sodium modeling (see earlier in the chapter).

Anaphylactoid reactions to the dialyzer, particularly on its first use, have been reported most frequently with the bioincompatible cellulosic-containing membranes. With the gradual phasing out of cuprophane membranes in the United States, dialyzer reactions have become uncommon. Dialyzer reactions can be divided into two types: A and B. Type A reactions are attributed to an IgE-mediated intermediate hypersensitivity reaction to ethylene oxide used in the sterilization of new dialyzers. This reaction typically occurs soon after the initiation of a treatment (within the first few minutes) and can progress to full-blown anaphylaxis if the therapy is not promptly discontinued. Treatment with steroids or epinephrine may be needed if symptoms are severe. The type B reaction consists of a symptom complex of nonspecific chest and back pain, which appears to result from complement activation and cytokine release. These symptoms typically occur several minutes into the dialysis run and typically resolve over time with continued dialysis.

Cardiovascular disease constitutes the major cause of death in patients with ESRD. Cardiovascular mortality and event rates are higher in dialysis patients than in patients posttransplantation, although rates are extraordinarily high in both populations. The underlying cause of cardiovascular disease is unclear but may be related to shared risk factors (e.g., diabetes mellitus, hypertension, atherosclerotic and arteriosclerotic vascular disease), chronic inflammation, massive changes in extracellular volume (especially with high interdialytic weight gains), inadequate treatment of hypertension, dyslipidemia, anemia, dystrophic vascular calcification, hyperhomocysteinemia, and, perhaps, alterations in cardiovascular dynamics during the dialysis treatment. Few studies have targeted cardiovascular risk reduction in ESRD patients; none have demonstrated consistent benefit. Two clinical trials of statin agents in ESRD demonstrated significant reductions in low-density lipoprotein (LDL) cholesterol concentrations but no significant reductions in death or cardiovascular events [Die Deutsche Diabetes Dialyse study (4D) and AURORA study]. Nevertheless, most experts recommend conventional cardioprotective strategies (e.g., lipid-lowering agents, aspirin, β-adrenergic antagonists) in dialysis patients based on the patients' cardiovascular risk profile, which appears to be increased by more than an order of magnitude relative to persons unaffected by kidney disease.

PERITONEAL DIALYSIS

In peritoneal dialysis, 1.5–3 L of a dextrose-containing solution is infused into the peritoneal cavity and allowed to dwell for a set period of time, usually 2–4 h. As with hemodialysis, toxic materials are removed through a combination of convective clearance generated through ultrafiltration and diffusive clearance down a concentration gradient. The clearance of solutes and water during a peritoneal dialysis exchange depends on the balance between the movement of solute and water into the peritoneal cavity versus absorption from the peritoneal cavity. The rate of diffusion diminishes with time and eventually stops when equilibration between plasma and dialysate is reached. Absorption of solutes and water from the peritoneal cavity occurs across the peritoneal membrane into the peritoneal capillary circulation and via peritoneal lymphatics into the lymphatic circulation. The rate of peritoneal solute transport varies from patient to patient and may be altered by the presence of infection (peritonitis), drugs, and physical factors such as position and exercise.

FORMS OF PERITONEAL DIALYSIS

Peritoneal dialysis may be carried out as CAPD, CCPD, or a combination of both. In CAPD, dialysis solution is

manually infused into the peritoneal cavity during the day and exchanged three to five times daily. A nighttime dwell is frequently instilled at bedtime and remains in the peritoneal cavity through the night. The drainage of spent dialysate is performed manually with the assistance of gravity to move fluid out of the abdomen. In CCPD, exchanges are performed in an automated fashion, usually at night; the patient is connected to an automated cycler that performs a series of exchange cycles while the patient sleeps. The number of exchange cycles required to optimize peritoneal solute clearance varies by the peritoneal membrane characteristics; as with hemodialysis, experts suggest careful tracking of solute clearances to ensure dialysis "adequacy."

Peritoneal dialysis solutions are available in volumes typically ranging from 1.5 to 3 L. Lactate is the preferred buffer in peritoneal dialysis solutions. The most common additives to peritoneal dialysis solutions are heparin, to prevent obstruction of the dialysis catheter lumen, with fibrin and antibiotics during an episode of acute peritonitis. Insulin may also be added in patients with diabetes mellitus.

ACCESS TO THE PERITONEAL CAVITY

Access to the peritoneal cavity is obtained through a peritoneal catheter. Catheters used for maintenance peritoneal dialysis are flexible, being made of silicone rubber with numerous side holes at the distal end. These catheters usually have two Dacron cuffs to promote fibroblast proliferation, granulation, and invasion of the cuff. The scarring that occurs around the cuffs anchors the catheter and seals it from bacteria tracking from the skin surface into the peritoneal cavity; it also prevents the external leakage of fluid from the peritoneal cavity. The cuffs are placed in the preperitoneal plane and ~2 cm from the skin surface.

The *peritoneal equilibrium test* is a formal evaluation of peritoneal membrane characteristics that measures the transfer rates of creatinine and glucose across the peritoneal membrane. Patients are classified as low, low–average, high–average, and high transporters. Patients with rapid equilibration (i.e., high transporters) tend to absorb more glucose and lose efficiency of ultrafiltration with long daytime dwells. High transporters also tend to lose larger quantities of albumin and other proteins across the peritoneal membrane. In general, patients with rapid transporting characteristics require more frequent, shorter dwell time exchanges, nearly always obligating use of a cycler for feasibility. Slower (low and low–average) transporters tend to do well with fewer exchanges. The efficiency of solute clearance also depends on the volume of dialysate infused. Larger volumes allow for greater solute clearance, particularly with CAPD in patients with low and low–average transport characteristics. Interestingly, solute clearance also increases with physical activity, presumably related to more efficient flow dynamics within the peritoneal cavity.

As with hemodialysis, the optimal dose of peritoneal dialysis is unknown. Several observational studies have suggested that higher rates of urea and creatinine clearance (the latter generally measured in L/week) are associated with lower mortality rates and fewer uremic complications. However, a randomized clinical trial [Adequacy of Peritoneal Dialysis in Mexico (ADEMEX)] failed to show a significant reduction in mortality or complications with a relatively large increment in urea clearance. In general, patients on peritoneal dialysis do well when they retain residual kidney function. The rates of technique failure increase with years on dialysis and have been correlated with loss of residual function to a greater extent than loss of peritoneal membrane capacity. Recently, a nonabsorbable carbohydrate (icodextrin) has been introduced as an alternative osmotic agent. Studies have demonstrated more efficient ultrafiltration with icodextrin than with dextrose-containing solutions. Icodextrin is typically used as the "last fill" for patients on CCPD or for the longest dwell in patients on CAPD. For some patients in whom CCPD does not provide sufficient solute clearance, a hybrid approach can be adopted where one or more daytime exchanges are added to the CCPD regimen. While this approach can enhance solute clearance and prolong a patient's capacity to remain on peritoneal dialysis, the burden of the hybrid approach can be overwhelming to some.

COMPLICATIONS DURING PERITONEAL DIALYSIS

The major complications of peritoneal dialysis are peritonitis, catheter-associated nonperitonitis infections, weight gain and other metabolic disturbances, and residual uremia (especially among patients with no residual kidney function).

Peritonitis typically develops when there has been a break in sterile technique during one or more of the exchange procedures. Peritonitis is usually defined by an elevated peritoneal fluid leukocyte count (100/mm^3, of which at least 50% are polymorphonuclear neutrophils); these cutoffs are lower than those in spontaneous bacterial peritonitis because of the presence of dextrose in peritoneal dialysis solutions and rapid bacterial proliferation in this environment without antibiotic therapy. The clinical presentation typically consists of pain and cloudy dialysate, often with fever and other constitutional symptoms. The most common culprit organisms are gram-positive cocci, including *Staphylococcus,* reflecting the origin from the skin. Gram-negative rod infections are less common; fungal and mycobacterial infections can be seen in selected patients, particularly

after antibacterial therapy. Most cases of peritonitis can be managed either with intraperitoneal or oral antibiotics, depending on the organism; many patients with peritonitis do not require hospitalization. In cases where peritonitis is due to hydrophilic gram-negative rods (e.g., *Pseudomonas* sp.) or yeast, antimicrobial therapy is usually not sufficient, and catheter removal is required to ensure complete eradication of infection. Nonperitonitis catheter-associated infections (often termed *tunnel infections*) vary widely in severity. Some cases can be managed with local antibiotic or silver nitrate administration, while others are severe enough to require parenteral antibiotic therapy and catheter removal.

Peritoneal dialysis is associated with a variety of metabolic complications. As noted above, albumin and other proteins can be lost across the peritoneal membrane in concert with the loss of metabolic wastes. The hypoproteinemia induced by peritoneal dialysis obligates a higher dietary protein intake in order to maintain nitrogen balance. Hyperglycemia and weight gain are also common complications of peritoneal dialysis. Several hundred calories in the form of dextrose are absorbed each day, depending on the concentration employed. Peritoneal dialysis patients, particularly those with type II diabetes mellitus, are then prone to other complications of insulin resistance, including hypertriglyceridemia. On the positive side, the continuous nature of peritoneal dialysis usually allows for a more liberal diet, due to continuous removal of potassium and phosphorus—two major dietary components whose accumulation can be hazardous in ESRD.

GLOBAL PERSPECTIVE

The incidence of ESRD is increasing worldwide with longer life expectancies and improved care of infectious and cardiovascular diseases. The management of ESRD varies widely by country and within country by region, and it is influenced by economic and other major factors. In general, peritoneal dialysis is more commonly performed in poorer countries owing to its lower expense and the high cost of establishing in-center hemodialysis units.

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CHAPTER 13

TRANSPLANTATION IN THE TREATMENT OF RENAL FAILURE

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Transplantation of the human kidney is the treatment of choice for advanced chronic renal failure. Worldwide, tens of thousands of these procedures have been performed. When azathioprine and prednisone initially were used as immunosuppressive drugs in the 1960s, the results with properly matched familial donors were superior to those with organs from deceased donors: 75–90% compared with 50–60% graft survival rates at 1 year. During the 1970s and 1980s, the success rate at the 1-year mark for deceased-donor transplants rose progressively. Currently, deceased-donor grafts have an 89% 1-year survival and living-donor grafts have a 95% 1-year survival. Although there has been improvement in long-term survival, it has not been as impressive as the short-term survival, and currently the "average" ($t_{1/2}$) life expectancy of a living-donor graft is around 20 years and that of a deceased-donor graft is close to 14 years.

Mortality rates after transplantation are highest in the first year and are age related: 2% for ages 18–34 years, 3% for ages 35–49 years, and 6.8% for ages ≥50–60 years. These rates compare favorably with those in the chronic dialysis population even after risk adjustments for age, diabetes, and cardiovascular status. Occasionally, acute irreversible rejection may occur after many months of good function, especially if the patient neglects to take the prescribed immunosuppressive drugs. Most grafts, however, succumb at varying rates to a chronic process consisting of interstitial fibrosis, tubular atrophy, vasculopathy, and glomerulopathy, the pathogenesis of which is incompletely understood. Overall, transplantation returns most patients to an improved lifestyle and an improved life expectancy compared with patients on dialysis. There are at least 100,000 patients with functioning kidney transplants in the United States, and when one adds in the numbers of kidney transplants in centers around the world, the total activity is doubled.

RECENT ACTIVITY AND RESULTS

In 2008 there were more than 10,500 deceased-donor kidney transplants and 6000 living-donor transplants in the United States, with the ratio of deceased to living donors being stable over the last few years. The backlog of patients with end-stage renal disease (ESRD) has been increasing every year, and it always lags behind the number of available donors. As the number of patients with end-stage kidney disease increases, the demand for kidney transplants continues to increase. In 2008, 33,051 new registrants were added to the waiting list and fewer than 17,000 patients were transplanted. This imbalance is set to worsen over the coming years with the predicted increased rates of obesity and diabetes worldwide. In an attempt to increase utilization of deceased-donor kidneys and reduce discard rates of organs, criteria for the use of so-called expanded criteria donor (ECD) kidneys and kidneys from donors after cardiac death (DCD) have been developed **(Table 13-1)**. ECD kidneys are usually used for older patients who are expected to fare less well on dialysis.

The overall results of transplantation are presented in **Table 13-2** as the survival of grafts and of patients. At the 1-year mark, graft survival is higher for living-donor recipients, most likely because those grafts are not subject to as much ischemic injury. The more powerful drugs now in use for immunosuppression have almost equalized the risk of graft rejection in all patients for the first year. At 5 and 10 years, however, there has been a steeper decline in survival of those with deceased-donor kidneys.

TABLE 13-1

DEFINITION OF AN EXPANDED CRITERIA DONOR (ECD) AND A NON-HEART-BEATING DONOR [DONATION AFTER CARDIAC DEATH (DCD)]

Expanded Criteria Donor (ECD)
Deceased donor >60 years
Deceased donor >50 years and hypertension and creatinine >1.5 mg/dL
Deceased donor >50 years and hypertension and death caused by cerebrovascular accident (CVA)
Deceased donor >50 years and death caused by CVA and creatinine >1.5 mg/dL
Donation after Cardiac Death[a] (DCD)
I Brought in dead
II Unsuccessful resuscitation
III Awaiting cardiac arrest
IV Cardiac arrest after brainstem death
V Cardiac arrest in a hospital patient

[a]Kidneys can be used for transplantation from categories II–V but are commonly only used from categories III and IV. The survival of these kidneys has not been shown to be inferior to that of deceased-donor kidneys.

Note: Kidneys can be bought ECD and DCD. ECD kidneys have been shown to have a poorer survival, and there is a separate, shorter waiting list for ECD kidneys. They are generally utilized for patients for whom the benefits of being transplanted earlier outweigh the associated risks of using an ECD kidney.

RECIPIENT SELECTION

There are few absolute contraindications to renal transplantation. The transplant procedure is relatively noninvasive, as the organ is placed in the inguinal fossa without entering the peritoneal cavity. Recipients without perioperative complications often can be discharged from the hospital in excellent condition within 5 days of the operation.

Virtually all patients with ESRD who receive a transplant have a greater life expectancy than do risk-matched patients who remain on dialysis. Even though diabetic patients and older candidates have a higher mortality rate than other transplant recipients, their survival is improved with transplantation compared with remaining on dialysis. This global benefit of transplantation as a treatment modality poses substantial ethical issues for policy makers, as the number of deceased kidneys available is far from sufficient to meet the current needs of the candidates. The current standard of care is that the candidate should have a life expectancy of >5 years to be put on a deceased organ wait list. Even for living donation, the candidate should have >5 years of life expectancy. This standard has been established because the benefits of kidney transplantation over dialysis are realized only after a perioperative period in which the mortality rate is higher in transplanted patients than in dialysis patients with comparable risk profiles.

All candidates must have a thorough risk-versus-benefit evaluation before being approved for transplantation. In particular, an aggressive approach to diagnosis of correctable coronary artery disease, presence of latent or indolent infection (HIV, hepatitis B or C, tuberculosis), and neoplasm should be a routine part of the candidate workup. Most transplant centers consider overt AIDS and active hepatitis absolute contraindications to transplantation because of the high risk of opportunistic infection. Some centers are now transplanting individuals with hepatitis and even HIV infection under strict protocols to determine whether the risks and benefits favor transplantation over dialysis.

Among the few absolute "immunologic" contraindications to transplantation is the presence of a potentially harmful antibody against the donor kidney at the time of the anticipated transplant. Harmful antibodies that can cause very early graft loss include natural antibodies against the ABO blood group antigens and antibodies against human leukocyte antigen (HLA) class I (A, B, C) or class II (DR) antigens. These antibodies are routinely excluded by proper screening of the candidate's ABO compatibility, HLA typing of donor and recipient, and direct cross-matching of candidate serum with lymphocytes of the donor.

TABLE 13-2

MEAN RATES OF GRAFT AND PATIENT SURVIVAL FOR KIDNEYS TRANSPLANTED IN THE UNITED STATES FROM 1992 TO 2002[a]

	1-YEAR FOLLOW-UP		5-YEAR FOLLOW-UP		10-YEAR FOLLOW-UP	
	GRAFTS, %	PATIENTS, %	GRAFTS, %	PATIENTS, %	GRAFTS, %	PATIENTS, %
Deceased donor	89	95	67	81	41	61
Living donor	95	98	80	90	56	76

[a]All patients transplanted are included, and the follow-up unadjusted survival data from the 1-, 5-, and 10-year periods are presented to show the attrition rates over time within the two types of organ donors.

Source: Data from Summary Tables, 2004 and 2005 Annual Reports, Scientific Registry of Transplant Recipients.

DONOR SELECTION

Donors can be deceased or volunteer living donors. The latter are usually family members selected to have at least partial compatibility for HLA antigens. Living volunteer donors should be normal on physical examination and of the same major ABO blood group, because crossing major blood group barriers prejudices survival of the allograft. It is possible, however, to transplant a kidney of a type O donor into an A, B, or AB recipient. Selective renal arteriography should be performed on donors to rule out the presence of multiple or abnormal renal arteries because the surgical procedure is difficult and the ischemic time of the transplanted kidney is long when there are vascular abnormalities. Transplant surgeons are now using a laparoscopic method to isolate and remove the living donor's kidney. This operation has the advantage of less evident surgical scars, and, because there is less tissue trauma, the laparoscopic donors have a substantially shorter hospital stay and less discomfort than those who have the traditional surgery. Deceased donors should be free of malignant neoplastic disease, hepatitis, and HIV because of possible transmission to the recipient. Increased risk of graft failure exists when the donor is elderly or has renal failure and when the kidney has a prolonged period of ischemia and storage.

In the United States, there is a coordinated national system of regulations, allocation support, and outcomes analysis for kidney transplantation called the Organ Procurement Transplant Network. It is now possible to remove deceased-donor kidneys and maintain them for up to 48 h on cold pulsatile perfusion or simple flushing and cooling. This approach permits adequate time for typing, cross-matching, transportation, and selection problems to be solved.

TISSUE TYPING AND CLINICAL IMMUNOGENETICS

Matching for antigens of the HLA major histocompatibility gene complex is an important criterion for selection of donors for renal allografts. Each mammalian species has a single chromosomal region that encodes the strong, or major, transplantation antigens, and this region on the human sixth chromosome is called *HLA*. HLA antigens have been classically defined by serologic techniques, but methods to define specific nucleotide sequences in genomic DNA are increasingly being used. Other "minor" antigens may play crucial roles, in addition to the ABH(O) blood groups and endothelial antigens that are not shared with lymphocytes. The Rh system is not expressed on graft tissue. Evidence for designation of HLA as the genetic region that encodes major transplantation antigens comes from the success rate in living related donor renal and bone marrow transplantation, with superior results in HLA-identical sibling pairs. Nevertheless, 5% of HLA-identical renal allografts are rejected, often within the first weeks after transplantation. These failures represent states of prior sensitization to non-HLA antigens. Non-HLA minor antigens are relatively weak when initially encountered and are therefore suppressible by conventional immunosuppressive therapy. Once priming has occurred, however, secondary responses are much more refractory to treatment.

LIVING DONORS

When first-degree relatives are donors, graft survival rates at 1 year are 5–7% greater than those for deceased-donor grafts. The 5-year survival rates still favor a partially matched (3/6 HLA mismatched) family donor over a randomly selected cadaver donor **(Table 13-3)**. In addition, living donors provide the advantage of immediate availability. For both living and deceased donors, the 5-year outcomes are poor if there is a complete (6/6) HLA mismatch.

The survival rate of living unrelated renal allografts is as high as that of perfectly HLA-matched cadaver renal transplants and comparable to that of kidneys from living relatives. This outcome is probably a consequence of both short cold ischemia time and the extra care taken to document that the condition and renal function of the donor are optimal before proceeding with a living unrelated donation. It is illegal in the United States to purchase organs for transplantation.

Concern has been expressed about the potential risk to a volunteer kidney donor of premature renal failure

TABLE 13-3

EFFECT OF HLA-A, -B, -DR MISMATCHING ON KIDNEY GRAFT SURVIVAL

DEGREE OF DONOR MISMATCH	1-YEAR SURVIVAL, %	5-YEAR SURVIVAL, %
Cadaver donor (all)	89.2	61.3
0/6-HLA mismatch	91.3	68.2
3/6-HLA mismatch	90.1	60.8
6/6-HLA mismatch	85.2	55.3
Living related donor (all)	94.7	76.0
0/6-HLA mismatch	96.7	87.0
3/6-HLA mismatch	94.3	73.2
6/6-HLA mismatch	92.7	57.7

Note: 0-mismatched related donor transplants are virtually all from HLA-identical siblings, whereas 3/6-mismatched transplants can be one haplotype mismatched (1-A, 1-B, and 1-DR antigen) from a parent, child, or sibling; 6/6-HLA-mismatched living related kidneys are derived from siblings or relatives outside the nuclear family.

after several years of increased blood flow and hyperfiltration per nephron in the remaining kidney. There are a few reports of the development of hypertension, proteinuria, and even lesions of focal segmental sclerosis in donors over long-term follow-up. Difficulties in donors followed for ≥20 years are unusual, however, and it may be that having a single kidney becomes significant only when another condition, such as hypertension, is superimposed. It is also desirable to consider the risk of development of type 1 diabetes mellitus in a family member who is a potential donor to a diabetic renal failure patient. Anti-insulin and anti-islet cell antibodies should be measured, and glucose tolerance tests should be performed in such donors to exclude a prediabetic state.

PRESENSITIZATION

A positive cytotoxic cross-match of recipient serum with donor T lymphocytes representing anti-HLA class I is usually predictive of an acute vasculitic event termed *hyperacute rejection*. Patients with anti-HLA antibodies can be transplanted safely if careful cross-matching of donor blood lymphocytes with recipient serum is performed. The known sources of such sensitization are blood transfusion, a prior transplant, and pregnancy. Patients sustained by dialysis often show fluctuating antibody titers and specificity patterns. At the time of assignment of a cadaveric kidney, cross-matches are performed with at least a current serum. Previously analyzed antibody specificities and additional cross-matches are performed accordingly. The minimal purpose for the cross-match is avoidance of hyperacute rejection mediated by recipient antibodies to donor HLA class I antigens. More sensitive tests, such as flow cytometry, can be useful for avoidance of accelerated, and often untreatable, early graft rejection in patients receiving second or third transplants. Donor T lymphocytes, which express only class I antigens, are used as targets for detection of anti–class I (HLA-A and -B) antibodies.

Preformed anti–class II (HLA-DR) antibodies against the donor carry a higher risk of graft loss as well, particularly in recipients who have suffered early loss of a prior kidney transplant. B lymphocytes expressing both class I and class II antigens are used in these assays. Non-HLA antigens restricted in expression to endothelium and sometimes monocytes have been described, but clinical relevance is not well established. A series of minor histocompatibility antigens do not elicit antibodies, and sensitization to these antigens is detectable only by cytotoxic T cells, an assay too cumbersome for routine use. Desensitization before transplantation by reducing the level of antidonor antibodies via plasmapheresis of blood and administration of pooled immunoglobulin or both has been useful in reducing the hazard of hyperacute rejection.

IMMUNOLOGY OF REJECTION

Both cellular and humoral (antibody-mediated) effector mechanisms can play roles in kidney transplant rejection. Antibodies can also initiate a form of antibody-dependent but cell-mediated cytotoxicity by recipient cells that bear receptors for the Fc portion of immunoglobulin.

Cellular rejection is mediated by lymphocytes that respond to HLA antigens expressed within the organ. The CD4+ lymphocyte responds to class II (HLA-DR) incompatibility by proliferating and releasing proinflammatory cytokines that augment the proliferative response of both CD4+ and CD8+ cells. CD8+ cytotoxic lymphocyte precursors respond primarily to class I (HLA-A, -B) antigens and mature into cytotoxic effector cells. The cytotoxic effector ("killer") T cells cause organ damage through direct contact and lysis of donor target cells. The natural role of HLA antigen molecules is to present processed peptide fragments of antigen to T lymphocytes, the fragments residing in a "groove" of the HLA molecule distal to the cell surface. T cells can be directly stimulated by intact nonself HLA molecules expressed on donor parenchymal cells and residual donor leukocytes residing in the kidney interstitium. In addition, donor HLA molecules can be processed by a variety of donor or recipient cells capable of antigen presentation of peptides and then presented to T cells in the same manner as most other antigens. The former mode of stimulation is sometimes called *direct presentation*, and the latter mode *indirect presentation* **(Fig. 13-1)**. There is evidence that non-HLA antigens can also play a role in renal transplant rejection episodes. Recipients who receive a kidney from an HLA-identical sibling can have rejection episodes and require maintenance immunosuppression, whereas identical twin transplants require no immunosuppression. There are documented non-HLA antigens, such as an endothelial-specific antigen system with limited polymorphism and a tubular antigen, that can be targets of humoral or cellular rejection responses, respectively.

IMMUNOSUPPRESSIVE TREATMENT

Immunosuppressive therapy, as currently available, generally suppresses all immune responses, including those to bacteria, fungi, and even malignant tumors. In the 1950s, when clinical renal transplantation began, sublethal total-body irradiation was employed. We have now reached the point where sophisticated pharmacologic immunosuppression is available, but it still has the hazard of promoting infection and malignancy. In general, all clinically useful drugs are more selective to primary than to memory immune responses. Agents to suppress the immune response are discussed in the

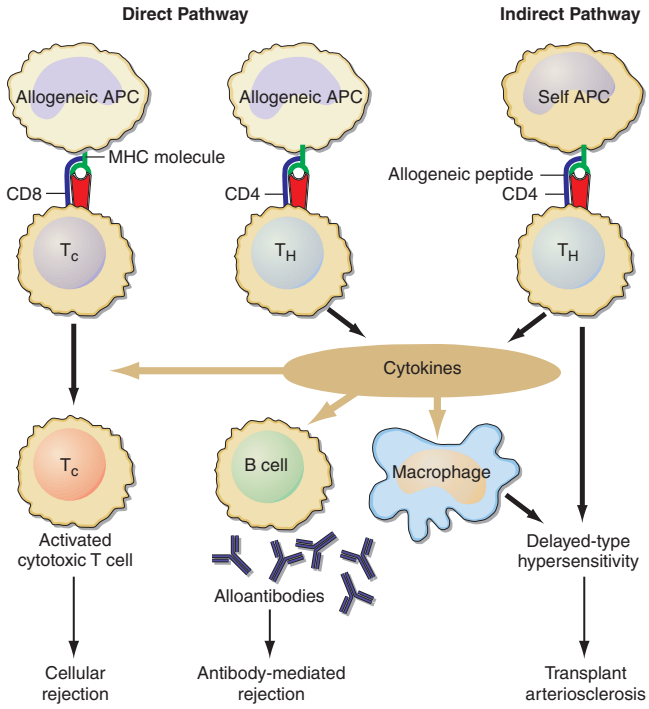


FIGURE 13-1

Recognition pathways for major histocompatibility complex (MHC) antigens. Graft rejection is initiated by CD4 helper T lymphocytes (T_H) having antigen receptors that bind to specific complexes of peptides and MHC class II molecules on antigen-presenting cells (APCs). In transplantation, in contrast to other immunologic responses, there are two sets of T-cell clones involved in rejection. In the direct pathway the class II MHC of donor allogeneic APCs is recognized by CD4 T_H cells that bind to the intact MHC molecules, and class I MHC allogeneic cells are recognized by CD8 T cells. The latter generally proliferate into cytotoxic cells (T_C). In the indirect pathway, the incompatible MHC molecules are processed into peptides that are presented by the self-APCs of the recipient. The indirect, but not the direct, pathway is the normal physiologic process in T-cell recognition of foreign antigens. Once T_H cells are activated, they proliferate and, by secretion of cytokines and direct contact, exert strong helper effects on macrophages, T_C, and B cells. (*From MH Sayegh, LH Turka: N Engl J Med, 338:1813, 1998. Copyright 1998, Massachusetts Medical Society. All rights reserved.*)

following paragraphs, and those currently in clinical use are listed in **Table 13-4**.

DRUGS

Azathioprine, an analogue of mercaptopurine, was for two decades the keystone to immunosuppressive therapy in humans but has given way to more effective agents. This agent can inhibit synthesis of DNA, RNA, or both. Therapy with azathioprine in doses of 1.5–2 mg/kg per d is generally added to cyclosporine as a means of decreasing the requirements for the latter. Reduction in the dose is required because of leukopenia and occasionally thrombocytopenia. Excessive amounts of azathioprine may also cause jaundice, anemia, and alopecia. If it is essential to administer allopurinol concurrently, the azathioprine dose must be reduced. As inhibition of xanthine oxidase delays degradation, this combination is best avoided.

Mycophenolate mofetil or mycophenolate sodium, both of which are metabolized to mycophenolic acid, is now used in place of azathioprine in most centers. It has a similar mode of action and a mild degree of gastrointestinal toxicity but produces minimal bone marrow suppression. Its advantage is its increased potency in preventing or reversing rejection. Patients with hyperuricemia can be given allopurinol without adjustment of the mycophenolic acid dose. The usual dose is 2–3 g/d in divided doses.

Glucocorticoids are important adjuncts to immunosuppressive therapy. Among all the agents employed, prednisone has effects that are easiest to assess, and in large doses it is usually effective for the reversal of rejection. In general, 200–300 mg prednisone is given immediately before or at the time of transplantation, and the dose is reduced to 30 mg within a week. The side effects of the glucocorticoids, particularly impairment of wound healing and predisposition to infection, make it desirable to taper the dose as rapidly as possible in the immediate postoperative period. Many centers now have protocols for early discontinuance or avoidance of steroids because of long-term adverse effects on bone, skin, and glucose metabolism. For treatment of acute rejection, methylprednisolone, 0.5–1 g IV, is administered immediately upon diagnosis of beginning rejection and continued once daily for 3 days. When the drug is effective, the results are usually apparent within 96 h. Such "pulse" doses are not effective in chronic rejection. Most patients whose renal function is stable after 6 months or a year do not require large doses of prednisone; maintenance doses of 10–15 mg/d are the rule. Many patients tolerate an alternate-day course of steroids without an increased risk of rejection. A major effect of steroids is on the monocyte-macrophage system, preventing the release of interleukin (IL)-6 and IL-1.

Cyclosporine is a fungal peptide with potent immunosuppressive activity. It acts on the calcineurin pathway to block transcription of mRNA for IL-2 and other proinflammatory cytokines, thereby inhibiting T-cell proliferation. Although it works alone, cyclosporine is more effective in conjunction with glucocorticoids and mycophenolate. Clinical results with tens of thousands of renal transplants have been impressive. Among its toxic effects (nephrotoxicity, hepatotoxicity, hirsutism, tremor, gingival hyperplasia, diabetes), only nephrotoxicity presents a serious management problem and is further discussed below.

TABLE 13-4

MAINTENANCE IMMUNOSUPPRESSIVE DRUGS

AGENT	PHARMACOLOGY	MECHANISMS	SIDE EFFECTS
Glucocorticoids	Increased bioavailability with hypoalbuminemia and liver disease; prednisone/prednisolone generally used	Binds cytosolic receptors and heat shock proteins. Blocks transcription of IL-1, -2, -3, -6; TNF-α; and IFN-γ	Hypertension, glucose intolerance, dyslipidemia, osteoporosis
Cyclosporine (CsA)	Lipid-soluble polypeptide, variable absorption, microemulsion more predictable	Trimolecular complex with cyclophilin and calcineurin → block in cytokine (e.g., IL-2) production; however, stimulates TGF-β production	Nephrotoxicity, hypertension, dyslipidemia, glucose intolerance, hirsutism/hyperplasia of gums
Tacrolimus (FK506)	Macrolide, well absorbed	Trimolecular complex with FKBP-12 and calcineurin → block in cytokine (e.g., IL-2) production; may stimulate TGF-β production	Similar to CsA, but hirsutism/hyperplasia of gums unusual, and diabetes more likely
Azathioprine	Mercaptopurine analogue	Hepatic metabolites inhibit purine synthesis	Marrow suppression (WBC > RBC > platelets)
Mycophenolate mofetil (MMF)	Metabolized to mycophenolic acid	Inhibits purine synthesis via inosine monophosphate dehydrogenase	Diarrhea/cramps; dose-related liver and marrow suppression is uncommon
Sirolimus	Macrolide, poor oral bioavailability	Complexes with FKBP-12 and then blocks p70 S6 kinase in the IL-2 receptor pathway for proliferation	Hyperlipidemia, thrombocytopenia

Abbreviations: FKBP-12, FK506-binding protein 12; IFN, interferon; IL, interleukin; RBC, red blood cell; TGF, transforming growth factor; TNF, tumor necrosis factor; WBC, white blood cell.

Tacrolimus (previously called FK506) is a fungal macrolide that has the same mode of action as cyclosporine as well as a similar side-effect profile; it does not, however, produce hirsutism or gingival hyperplasia. De novo diabetes mellitus is more common with tacrolimus. The drug was first used in liver transplantation and may substitute for cyclosporine entirely or be tried as an alternative in renal patients whose rejections are poorly controlled by cyclosporine.

Sirolimus (previously called rapamycin) is another fungal macrolide but has a different mode of action, i.e., it inhibits T-cell growth factor signaling pathways, preventing the response to IL-2 and other cytokines. Sirolimus can be used in conjunction with cyclosporine or tacrolimus, or with mycophenolic acid, to avoid calcineurin inhibitors. Its use with tacrolimus alone shows promise as a steroid-sparing regimen, especially in patients who would benefit from pancreatic islet cell transplantation, where steroids have an adverse effect on islet survival.

ANTIBODIES TO LYMPHOCYTES

When serum from animals made immune to host lymphocytes is injected into the recipient, a marked suppression of cellular immunity to the tissue graft results. The action on cell-mediated immunity is greater than the action on humoral immunity. A globulin fraction of serum [antilymphocyte globulin (ALG)] is the agent generally employed. For use in humans, peripheral human lymphocytes, thymocytes, or lymphocytes from spleens or thoracic duct fistulas have been injected into horses, rabbits, or goats to produce antilymphocyte serum, from which the globulin fraction is then separated. A rabbit antithymocyte globulin (thymoglobulin) is the agent most commonly in use currently. Monoclonal antibodies against defined lymphocyte subsets offer a more precise and standardized form of therapy. OKT3 is directed to the CD3 molecules that form a portion of the T-cell antigen-receptor complex and is thus expressed on all mature T cells.

Another approach to more selective therapy is to target the 55-kDa alpha chain of the IL-2 receptor, which is expressed only on T cells that have been recently activated. Two such antibodies to the IL-2 receptor, in which either a chimeric protein has been made between mouse Fab with human Fc (basiliximab) or the antibody has been "humanized" by splicing the combining sites of the mouse into a molecule that is 90% human IgG (daclizumab), are in use for prophylaxis of acute rejection in the immediate posttransplant period. They are effective at decreasing the acute rejection rate and have few adverse side effects.

More recently, two new strategies have involved administration of engineered biologic agents: a depleting T-cell antibody (alemtuzumab) as induction therapy to minimize maintenance immunosuppression and a

fusion protein (Belatacept) to block B7 T-cell costimulatory signals. The latter has shown promise in phase 2 trials and is currently being tested in phase 3 trials in kidney transplantation. Both of these new biologics as well as antilymphocyte globulin are increasingly being used as "induction" therapy at the time of transplantation to minimize or eliminate the use of either steroids or calcineurin inhibitors because of their perceived toxicities. The next step in the evolution of this therapeutic strategy, which has already been achieved in the short term in small numbers of immunologically well-matched patients, is the elimination of all maintenance immunosuppression therapy altogether.

CLINICAL COURSE AND MANAGEMENT OF THE RECIPIENT

Adequate hemodialysis should be performed within 48 h of surgery, and care should be taken that the serum potassium level is not markedly elevated so that intraoperative cardiac arrhythmias can be averted. The diuresis that commonly occurs postoperatively must be carefully monitored. In some instances, it may be massive, reflecting the inability of ischemic tubules to regulate sodium and water excretion; with large diureses, massive potassium losses may occur. Most chronically uremic patients have some excess of extracellular fluid, and it is useful to maintain an expanded fluid volume in the immediate postoperative period. Acute tubular necrosis (ATN) may cause immediate oliguria or may follow an initial short period of graft function. ATN is most likely when cadaveric donors have been underperfused or if the interval between cessation of blood flow and organ harvest (warm ischemic time) is more than a few minutes. Recovery usually occurs within 3 weeks, although periods as long as 6 weeks have been reported. Superimposition of rejection on ATN is common, and the differential diagnosis may be difficult without a graft biopsy. Cyclosporine therapy prolongs ATN, and some patients do not diurese until the dose is reduced drastically. Many centers avoid starting cyclosporine for the first several days, using ALG or a monoclonal antibody along with mycophenolic acid and prednisone until renal function is established. **Figure 13-2** illustrates an algorithm followed by many transplant centers for early posttransplant management of recipients at high or low risk of early renal dysfunction.

THE REJECTION EPISODE

Early diagnosis of rejection allows prompt institution of therapy to preserve renal function and prevent irreversible damage. Clinical evidence of rejection is rarely characterized by fever, swelling, and tenderness over the allograft. Rejection may present only with a rise in serum creatinine, with or without a reduction in urine volume. The focus should be on ruling out other causes of functional deterioration.

Doppler ultrasonography or magnetic resonance angiography may be useful in ascertaining changes in the renal vasculature and in renal blood flow, even in the absence of changes in urinary flow. Thrombosis of the renal vein occurs rarely; it may be reversible if it is caused by technical factors and intervention is prompt. Diagnostic ultrasound is the procedure of choice to rule out urinary obstruction or to confirm the presence of perirenal collections of urine, blood, or lymph. When renal function has been good initially, a rise in the serum creatinine level is the most sensitive and reliable indicator of possible rejection and may be the only sign.

Calcineurin inhibitors (cyclosporine and tacrolimus) may cause deterioration in renal function in a manner similar to a rejection episode. In fact, rejection processes tend to be more indolent with these inhibitors, and the only way to make a diagnosis may be by renal biopsy. Calcineurin inhibitors have an afferent arteriolar constrictor effect on the kidney and may produce permanent vascular and interstitial injury after sustained high-dose therapy. The addition of angiotensin-converting enzyme (ACE) inhibitors or nonsteroidal anti-inflammatory drugs is likely to raise serum creatinine levels. The former are generally safe to use after the early months, whereas the latter are best avoided in all renal transplant patients. There is no universally accepted lesion that makes a diagnosis of calcineurin inhibitor toxicity, although interstitial fibrosis, isometric tubular vacuolization, and thickening of arteriolar walls have been noted by some. Basically, if the biopsy does not reveal moderate and active cellular rejection activity, the serum creatinine most likely will respond to a reduction in dose. Blood levels of drug can be useful if they are very high or very low but do not correlate precisely with renal function, although serial changes in a patient can be useful. If rejection activity is present in the biopsy, appropriate therapy is indicated. The first rejection episode is usually treated with IV administration of methylprednisolone, 500–1000 mg daily for 3 days. Failure to respond is an indication for antibody therapy, usually with OKT3 or antithymocyte globulin.

Biopsy may be necessary to confirm the presence of rejection; when evidence of antibody-mediated injury is present with endothelial injury and deposition of complement component C4d is detected by fluorescence labeling, one can usually detect the antibody in recipient blood. The prognosis is poor, and aggressive use of plasmapheresis, immunoglobulin infusions, or anti-CD20 monoclonal antibody (rituximab) that targets B lymphocytes is indicated.

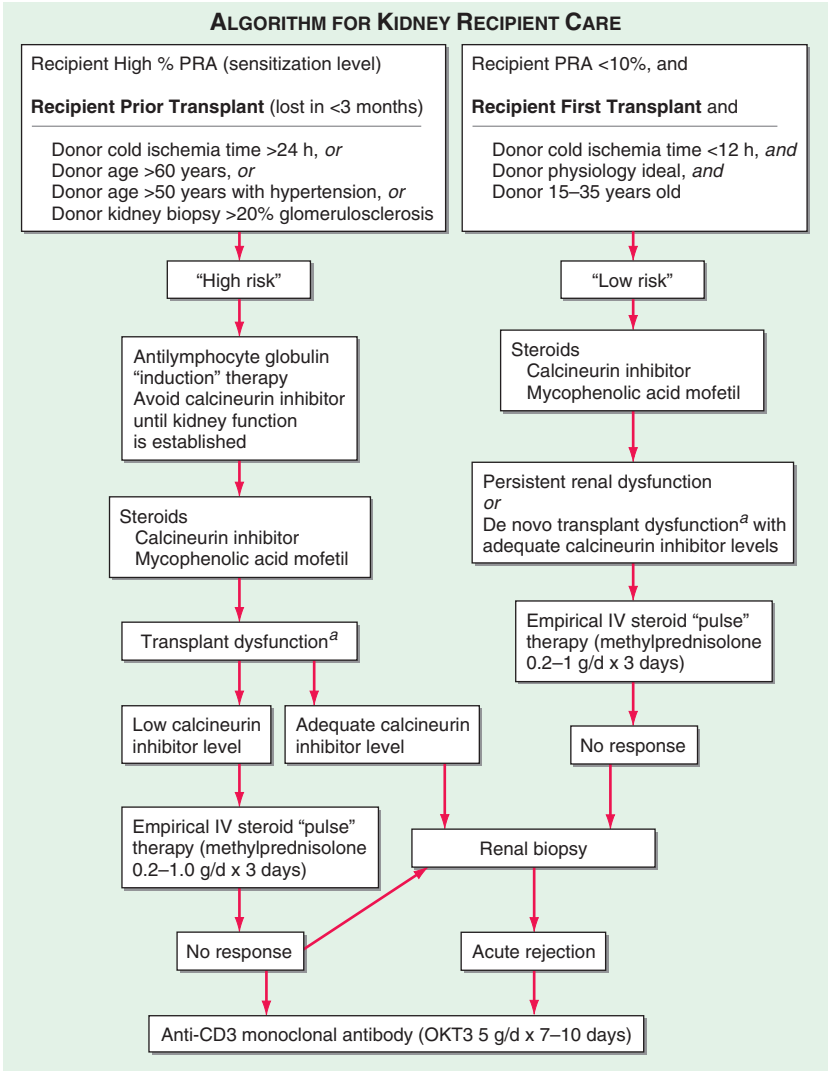


FIGURE 13-2

A typical algorithm for early posttransplant care of a kidney recipient. If any of the recipient or donor "high-risk" factors exist, more aggressive management is called for. Low-risk patients can be treated with a standard immunosuppressive regimen. Patients at higher risk of rejection or early ischemic and nephrotoxic transplant dysfunction are often induced with an antilymphocyte globulin to provide more potent early immunosuppression or to spare calcineurin nephrotoxicity. [a]When there is early transplant dysfunction, prerenal, obstructive, and vascular causes must be ruled out by ultrasonographic examination. The panel reactive antibody (PRA) is a quantitation of how much antibody is present in a candidate against a panel of cells representing the distribution of antigens in the donor pool. APC, antigen-presenting cell; MHC, major histocompatibility complex.

MANAGEMENT PROBLEMS

The usual clinical manifestations of infection in the posttransplant period are blunted by immunosuppressive therapy. The major toxic effect of azathioprine is bone marrow suppression, which is less likely with mycophenolic acid, whereas calcineurin inhibitors have no marrow effects. All drugs predispose to unusual opportunistic infections, however. The typical times after transplantation when the most common opportunistic infections occur are shown in Table 13-5. The signs and symptoms of infection may be masked or distorted. Fever without obvious cause is common, and only after days or weeks may it become apparent that it has a viral or fungal origin. Bacterial infections are most common during the first month after transplantation. The importance of blood cultures in such patients cannot be overemphasized because systemic infection without obvious foci is common, although wound infections with or without urinary fistulas are the most common. Particularly ominous are rapidly occurring pulmonary lesions, which may result in death within 5 days of onset. When these lesions become apparent, immunosuppressive agents should be discontinued, except for maintenance doses of prednisone.

Aggressive diagnostic procedures, including transbronchial and open-lung biopsy, are frequently indicated.

TABLE 13-5

THE MOST COMMON OPPORTUNISTIC INFECTIONS IN RENAL TRANSPLANT RECIPIENTS

Peritransplant (<1 month)	Late (>6 months)
Wound infections	*Aspergillus*
Herpesvirus	*Nocardia*
Oral candidiasis	BK virus (polyoma)
Urinary tract infection	Herpes zoster
Early (1–6 months)	Hepatitis B
Pneumocystis carinii	Hepatitis C
Cytomegalovirus	
Legionella	
Listeria	
Hepatitis B	
Hepatitis C	

In the case of *Pneumocystis carinii* infection, trimethoprim-sulfamethoxazole (TMP-SMX) is the treatment of choice; amphotericin B has been used effectively in systemic fungal infections. Prophylaxis against *P. carinii* with daily or alternate-day low-dose TMP-SMX is very effective. Involvement of the oropharynx with *Candida* may be treated with local nystatin. Tissue-invasive fungal infections require treatment with systemic agents such as fluconazole. Small doses (a total of 300 mg) of amphotericin given over a period of 2 weeks may be effective in fungal infections refractory to fluconazole. Macrolide antibiotics, especially ketoconazole and erythromycin, and some calcium channel blockers (diltiazem, verapamil) compete with calcineurin inhibitors for P450 catabolism and cause elevated levels of these immunosuppressive drugs. Analeptics, such as phenytoin and carbamazepine, will increase catabolism to result in low levels. *Aspergillus*, *Nocardia*, and especially cytomegalovirus (CMV) infections also occur.

CMV is a common and dangerous DNA virus in transplant recipients. It does not generally appear until the end of the first posttransplant month. Active CMV infection is sometimes associated, or occasionally confused, with rejection episodes. Patients at highest risk for severe CMV disease are those without anti-CMV antibodies who receive a graft from a CMV antibody–positive donor (15% mortality). Valganciclovir is a cost-effective and bioavailable oral form of ganciclovir that has been proved effective in both prophylaxis and treatment of CMV disease. Early diagnosis in a febrile patient with clinical suspicion of CMV disease can be made by determining CMV viral load in the blood. A rise in IgM antibodies to CMV is also diagnostic. Culture of CMV from blood may be less sensitive. Tissue invasion of CMV is common in the gastrointestinal tract and lungs. CMV retinopathy occurs late in the course, if untreated. Treatment of active CMV disease with valganciclovir is always indicated. In many patients immune to CMV, viral activation can occur with major immunosuppressive regimens.

The polyoma group (BK, JC, SV40) is another class of DNA viruses that can become dormant in kidneys and can be activated by immunosuppression. When reactivation occurs with BK, there is a 50% chance of progressive fibrosis and loss of the graft within 1 year by the activated virus. Risk of infection is associated with the overall degree of immunosuppression rather than the individual immunosuppressive drugs used. Renal biopsy is necessary for the diagnosis. There have been promising results with leflunomide, cidofovir, and quinolone anitibiotics (which are effective against polyoma helicase), but it is most important to reduce the immunosuppressive load.

The complications of glucocorticoid therapy are well known and include gastrointestinal bleeding, impairment of wound healing, osteoporosis, diabetes mellitus, cataract formation, and hemorrhagic pancreatitis. The treatment of unexplained jaundice in transplant patients should include cessation or reduction of immunosuppressive drugs if hepatitis or drug toxicity is suspected. Therapy in such circumstances often does not result in rejection of a graft, at least for several weeks. Acyclovir is effective in therapy for herpes simplex virus infections.

CHRONIC LESIONS OF THE TRANSPLANTED KIDNEY

Although 1-year transplant survival is excellent, most recipients experience progressive decline in kidney function over time thereafter. Chronic renal transplant dysfunction can be caused by recurrent disease, hypertension, cyclosporine or tacrolimus nephrotoxicity, chronic immunologic rejection, secondary focal glomerulosclerosis, or a combination of these pathophysiologies. Chronic vascular changes with intimal proliferation and medial hypertrophy are commonly found. Control of systemic and intrarenal hypertension with ACE inhibitors is thought to have a beneficial influence on the rate of progression of chronic renal transplant dysfunction. Renal biopsy can distinguish subacute cellular rejection from recurrent disease or secondary focal sclerosis.

MALIGNANCY

The incidence of tumors in patients on immunosuppressive therapy is 5–6%, or approximately 100 times greater than that in the general population in the same age range. The most common lesions are cancer of the skin and lips and carcinoma in situ of the cervix, as well as lymphomas such as non-Hodgkin's lymphoma. The risks are increased in proportion to the total immunosuppressive load administered and the time elapsed since transplantation. Surveillance for skin and cervical cancers is necessary.

OTHER COMPLICATIONS

Hypercalcemia after transplantation may indicate failure of hyperplastic parathyroid glands to regress. Aseptic necrosis of the head of the femur is probably due to preexisting hyperparathyroidism, with aggravation by glucocorticoid treatment. With improved management of calcium and phosphorus metabolism during chronic dialysis, the incidence of parathyroid-related complications has fallen dramatically. Persistent hyperparathyroid activity may require subtotal parathyroidectomy.

Hypertension may be caused by (1) native kidney disease, (2) rejection activity in the transplant, (3) renal artery stenosis if an end-to-end anastomosis was constructed with an iliac artery branch, and (4) renal calcineurin inhibitor toxicity. This toxicity may improve with reduction in dose. Whereas ACE inhibitors may be useful, calcium channel blockers are more frequently used initially. Amelioration of hypertension to the range of 120–130/70–80 mmHg should be the goal in all patients.

Although most transplant patients have robust production of erythropoietin and normalization of hemoglobin, *anemia* is commonly seen in the posttransplant period. Often the anemia is attributable to bone marrow–suppressant immunosuppressive medications such as azathioprine, mycophenolic acid, and sirolimus. Gastrointestinal bleeding is a common side effect of high-dose and long-term steroid administration. Many transplant patients have creatinine clearances of 30–50 mL/min and can be considered in the same way as other patients with chronic renal insufficiency for anemia management, including supplemental erythropoietin.

Chronic hepatitis, particularly when due to hepatitis B virus, can be a progressive, fatal disease over a decade or so. Patients who are persistently hepatitis B surface antigen–positive are at higher risk, according to some studies, but the presence of hepatitis C virus is also a concern when one embarks on a course of immunosuppression in a transplant recipient.

Both chronic dialysis and renal transplant patients have a higher incidence of death from myocardial infarction and stroke than does the population at large, and this is particularly true in diabetic patients. Contributing factors are the use of glucocorticoids and sirolimus, as well as hypertension. Recipients of renal transplants have a high prevalence of coronary artery and peripheral vascular diseases. The percentage of deaths from these causes has been slowly rising as the numbers of transplanted diabetic patients and the average age of all recipients increase. More than 50% of renal recipient mortality is attributable to cardiovascular disease. In addition to strict control of blood pressure and blood lipid levels, close monitoring of patients for indications of further medical or surgical intervention is an important part of management.

CHAPTER 14

INFECTIONS IN KIDNEY TRANSPLANT RECIPIENTS

Robert Finberg ■ Joyce Fingeroth

KIDNEY TRANSPLANTATION

(See **Table 14-1**.)

EARLY INFECTIONS

Bacteria often cause infections that develop in the period immediately after kidney transplantation. There is a role for perioperative antibiotic prophylaxis, and many centers give cephalosporins to decrease the risk of postoperative complications. Urinary tract infections developing soon after transplantation are usually related to anatomic alterations resulting from surgery. Such early infections may require prolonged treatment (e.g., 6 weeks of antibiotic administration for pyelonephritis). Urinary tract infections that occur >6 months after transplantation may be treated for shorter periods because they do not seem to be associated with the high rate of pyelonephritis or relapse seen with infections that occur in the first 3 months.

Daily prophylaxis with one double-strength tablet of TMP-SMX (800 mg of sulfamethoxazole; 160 mg of trimethoprim) for the first 4–6 months after transplantation decreases the incidence of early and middle-period infections (see Table 14-1, and **Table 14-2**).

MIDDLE-PERIOD INFECTIONS

Because of continuing immunosuppression, kidney transplant recipients are predisposed to lung infections characteristic of those in patients with T-cell deficiency (i.e., infections with intracellular bacteria, mycobacteria, nocardiae, fungi, viruses, and parasites). A high mortality rate associated with *Legionella pneumophila* infection led to the closing of renal transplant units in hospitals with endemic legionellosis.

About 50% of all renal transplant recipients presenting with fever 1–4 months after transplantation have evidence of cytomegalovirus (CMV) disease; CMV itself accounts for the fever in more than two-thirds of cases and thus is the predominant pathogen during this period. CMV infection may also present as arthralgias, myalgias, or organ-specific symptoms. During this period, this infection may represent primary disease (in the case of a seronegative recipient of a kidney from a seropositive donor) or may represent reactivation disease or superinfection. Patients may have atypical lymphocytosis. Unlike immunocompetent patients, however, they rarely have lymphadenopathy or splenomegaly. Therefore, clinical suspicion and laboratory confirmation are necessary for diagnosis. The clinical syndrome may be accompanied by bone marrow suppression (particularly leukopenia).

TABLE 14-1

COMMON INFECTIONS AFTER KIDNEY TRANSPLANTATION

PERIOD AFTER TRANSPLANTATION		
Early (<1 Month)	**Middle (1–4 Months)**	**Late (>6 Months)**
Bacterial and fungal (*Candida*) infections (cystitis, pyelonephritis) associated with urinary tract catheters (highest risk in kidney transplantation)	Renal transplantation: BK virus infection (associated with nephropathy); JC virus infection	Renal transplantation: bacteria (late urinary tract infections, usually not associated with bacteremia); BK virus (nephropathy, graft failure, generalized vasculopathy)

TABLE 14-2

PROPHYLACTIC REGIMENS COMMONLY USED TO DECREASE RISK OF INFECTION IN TRANSPLANT RECIPIENTS

RISK FACTOR	ORGANISM	PROPHYLACTIC DRUG	EXAMINATION(S)[a]
Travel to or residence in area with known risk of endemic fungal infection	*Histoplasma*, *Blastomyces*, *Coccidioides*	Consider imidazoles based on clinical and laboratory assessment	Chest radiography, antigen testing, serology
Latent herpesviruses	HSV, VZV, CMV, EBV	Acyclovir after HSC transplantation to prevent HSV and VZV infection; ganciclovir for CMV (?EBV/?KSHV) in some settings	Serologic tests for HSV, VZV, CMV, HHV-6, EBV, KSHV; PCR
Latent fungi and parasites	*Pneumocystis jiroveci*, *Toxoplasma gondii*	Trimethoprim-sulfamethoxazole (dapsone or atovaquone)	Serologic test for *Toxoplasma*
History of exposure to active or latent tuberculosis	*Mycobacterium tuberculosis*	Isoniazid if recent conversion or positive chest imaging and/or no previous treatment	Chest imaging; TST and/or cell-based assay

[a]Serologic examination, TST (tuberculin skin test), and interferon assays may be less reliable after transplantation.
Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV-6, human herpesvirus type 6; HSC, hematopoietic stem cell; HSV, herpes simplex virus; KSHV, Kaposi's sarcoma–associated herpesvirus; PCR, polymerase chain reaction; VZV, varicella-zoster virus.

CMV also causes glomerulopathy and is associated with an increased incidence of other opportunistic infections. Because of the frequency and severity of disease, a considerable effort has been made to prevent and treat CMV infection in renal transplant recipients. An immune globulin preparation enriched with antibodies to CMV was used by many centers in the past in an effort to protect the group at highest risk for severe infection (seronegative recipients of seropositive kidneys). However, with the development of effective oral antiviral agents, CMV immune globulin is no longer used. Ganciclovir (valganciclovir) is beneficial when prophylaxis is indicated and for the treatment of serious CMV disease. The availability of valganciclovir has allowed most centers to move to oral prophylaxis for transplant recipients. Infection with the other herpesviruses may become evident within 6 months after transplantation or later. Early after transplantation, herpes simplex virus (HSV) may cause either oral or anogenital lesions that are usually responsive to acyclovir. Large ulcerating lesions in the anogenital area may lead to bladder and rectal dysfunction as well as predisposing to bacterial infection. Varicella-zoster virus (VZV) may cause fatal disseminated infection in nonimmune kidney transplant recipients, but in immune patients reactivation zoster usually does not disseminate outside the dermatome; thus disseminated VZV infection is a less fearsome complication in kidney transplantation than in hematopoeitic stem cell (HSC) transplantation. Human herpesvirus type 6 (HHV-6) reactivation may take place and (although usually asymptomatic) may be associated with fever, rash, marrow suppression, or rarely encephalitis.

Epstein-Barr virus (EBV) disease is more serious; it may present as an extranodal proliferation of B cells that invade the CNS, nasopharynx, liver, small bowel, heart, and other organs, including the transplanted kidney. The disease is diagnosed by the finding of a mass of proliferating EBV-positive B cells. The incidence of Epstein-Barr virus-associated lymphoproliferative disorder (EBV-LPD) is higher among patients who acquire EBV infection from the donor and among patients given high doses of cyclosporine, tacrolimus, glucocorticoids, and anti–T-cell antibodies. Disease may regress once immunocompetence is restored. Kaposi's sarcoma-associated herpesvirus (KSHV) infection can be transmitted with the donor kidney and result in development of Kaposi's sarcoma, although it more often represents reactivation of latent infection of the recipient. Kaposi's sarcoma often appears within 1 year after transplantation, although the range of onset is wide (1 month to ~20 years). Avoidance of immunosuppressive agents that inhibit calcineurin has been associated with less Kaposi's sarcoma, less EBV disease, and even less CMV replication. The use of rapamycin (sirolimus) has independently led to regression of Kaposi's sarcoma.

The papovaviruses BK virus and JC virus (polyomavirus hominis types 1 and 2) have been cultured from the urine of kidney transplant recipients (as they have from that of HSC transplant recipients) in the setting of profound immunosuppression. High levels of BK virus replication detected by polymerase chain reaction (PCR) in urine and blood are predictive of pathology, especially in the setting of renal transplantation. JC virus may rarely cause similar disease in kidney transplantation. Urinary excretion of BK virus and BK viremia are associated with the development of ureteral strictures, polyomavirus-associated nephropathy (1–10% of renal transplant recipients), and (less commonly) generalized vasculopathy. Timely detection and early reduction of immunosuppression are critical and can reduce rates of graft loss related to polyomavirus-associated nephropathy from 90% to 10–30%. Therapeutic responses

to IVIg, quinolones, leflunomide, and cidofovir have been reported, but the efficacy of these agents has not been substantiated through adequate clinical study. Most centers approach the problem by reducing immunosuppression in an effort to enhance host immunity and decrease viral titers. JC virus is associated with rare cases of progressive multifocal leukoencephalopathy. Adenoviruses may persist and cause hemorrhagic nephritis/cystitis with continued immunosuppression in these patients, but disseminated disease as seen in HSC transplant recipients is much less common.

Kidney transplant recipients are also subject to infections with other intracellular organisms. These patients may develop pulmonary infections with *Mycobacterium*, *Aspergillus*, and *Mucor* species as well as infections with other pathogens in which the T-cell/macrophage axis plays an important role. *Listeria monocytogenes* is a common cause of bacteremia ≥1 month after renal transplantation and should be seriously considered in renal transplant recipients presenting with fever and headache. Kidney transplant recipients may develop *Salmonella* bacteremia, which can lead to endovascular infections and require prolonged therapy. Pulmonary infections with *Pneumocystis* are common unless the patient is maintained on TMP-SMX prophylaxis. *Nocardia* infection may present in the skin, bones, and lungs or in the CNS, where it usually takes the form of single or multiple brain abscesses. Nocardiosis generally occurs ≥1 month after transplantation and may follow immunosuppressive treatment for an episode of rejection. Pulmonary manifestations most commonly consist of localized disease with or without cavities, but the disease may be disseminated. The diagnosis is made by culture of the organism from sputum or from the involved nodule. As with *Pneumocystis*, prophylaxis with TMP-SMX is often efficacious in the prevention of disease.

Toxoplasmosis can occur in seropositive patients but is less common than in other transplant settings, usually developing in the first few months after kidney transplantation. Again, TMP-SMX is helpful in prevention. In endemic areas, histoplasmosis, coccidioidomycosis, and blastomycosis may cause pulmonary infiltrates or disseminated disease.

LATE INFECTIONS

Late infections (>6 months after kidney transplantation) may involve the CNS and include CMV retinitis as well as other CNS manifestations of CMV disease. Patients (particularly those whose immunosuppression has been increased) are at risk for subacute meningitis due to *Cryptococcus neoformans*. Cryptococcal disease may present in an insidious manner (sometimes as a skin infection before the development of clear CNS findings). *Listeria* meningitis may have an acute presentation and requires prompt therapy to avoid a fatal outcome. TMP-SMX prophylaxis may reduce the frequency of *Listeria* infections.

Patients who continue to take glucocorticoids are predisposed to ongoing infection. "Transplant elbow," a recurrent bacterial infection in and around the elbow that is thought to result from a combination of poor tensile strength of the skin of steroid-treated patients and steroid-induced proximal myopathy, requires patients to push themselves up with their elbows to get out of chairs. Bouts of cellulitis (usually caused by *Staphylococcus aureus*) recur until patients are provided with elbow protection.

Kidney transplant recipients are susceptible to invasive fungal infections, including those due to *Aspergillus* and *Rhizopus*, which may present as superficial lesions before dissemination. Mycobacterial infection (particularly that with *Mycobacterium marinum*) can be diagnosed by skin examination. Infection with *Prototheca wickerhamii* (an achlorophyllic alga) has been diagnosed by skin biopsy. Warts caused by human papillomaviruses (HPVs) are a late consequence of persistent immunosuppression; imiquimod or other forms of local therapy are usually satisfactory. Merkel cell carcinoma, a rare and aggressive neuroendocrine skin tumor, the frequency of which is increased fivefold in elderly solid-organ transplantation (SOT) (especially kidney) recipients, has been linked to a novel polyoma virus (Merkel cell polyomavirus).

Notably, although BK virus replication and virus-associated disease can be detected far earlier, the median time to clinical diagnosis of polyomavirus-associated nephropathy is ~300 days, qualifying it as a late-onset disease. With establishment of better screening procedures (e.g., blood PCR), it is likely that this disease will be detected earlier (see "Middle-Period Infections" discussed earlier).

SECTION IV

GLOMERULAR AND TUBULAR DISORDERS

CHAPTER 15

GLOMERULAR DISEASES

Julia B. Lewis ■ Eric G. Neilson

Two human kidneys harbor nearly 1.8 million glomerular capillary tufts. Each glomerular tuft resides within Bowman's space. The capsule circumscribing this space is lined by parietal epithelial cells that transition into tubular epithelia forming the proximal nephron or migrate into the tuft to replenish podocytes. The glomerular capillary tuft derives from an afferent arteriole that forms a branching capillary bed embedded in mesangial matrix **(Fig. 15-1)**. This capillary network funnels into an efferent arteriole, which passes filtered blood into cortical peritubular capillaries or medullary vasa recta that supply and exchange with a folded tubular architecture. Hence the glomerular capillary tuft, fed and drained by arterioles, represents an arteriolar portal system. Fenestrated endothelial cells resting on a glomerular basement membrane (GBM) line glomerular capillaries. Delicate foot processes extending from epithelial podocytes shroud the outer surface of these capillaries, and podocytes interconnect to each other by slit-pore membranes forming a selective filtration barrier.

The glomerular capillaries filter 120–180 L/d of plasma water containing various solutes for reclamation or discharge by downstream tubules. Most large proteins and all cells are excluded from filtration by a physicochemical barrier governed by pore size and negative electrostatic charge. The mechanics of filtration and reclamation are quite complicated for many solutes. For example, in the case of serum albumin, the glomerulus is an imperfect barrier. Although albumin has a negative charge, which would tend to repel the negatively charged GBM, it only has a physical radius of 3.6 nm, while pores in the GBM and slit-pore membranes have a radius of 4 nm. Consequently, variable amounts of albumin inevitably cross the filtration barrier to be reclaimed by megalin and cubilin receptors along the proximal tubule. Remarkably, humans with normal nephrons do not excrete more than 8–10 mg of albumin in daily voided urine, approximately 20–60% of total excreted protein. This amount of albumin, and other proteins, can rise to gram quantities following glomerular injury.

The breadth of diseases affecting the glomerulus is expansive because the glomerular capillaries can be injured in a variety of ways, producing many different lesions and several unique changes to urinalysis. Some order to this vast subject is brought by grouping all of these diseases into a smaller number of clinical syndromes.

PATHOGENESIS OF GLOMERULAR DISEASE

There are many forms of glomerular disease with pathogenesis variably linked to the presence of genetic mutations, infection, toxin exposure, autoimmunity, atherosclerosis, hypertension, emboli, thrombosis, or diabetes mellitus. Even after careful study, however, the cause often remains unknown, and the lesion is called *idiopathic*. Specific or unique features of pathogenesis are mentioned with the description of each of the glomerular diseases later in this chapter.

Some glomerular diseases result from genetic mutations producing familial disease or a founder effect: congenital nephrotic syndrome from mutations in *NPHS1* (nephrin) and *NPHS2* (podocin) affect the slit-pore membrane at birth, and *TRPC6* cation channel mutations produce *focal segmental glomerulosclerosis (FSGS)* in adulthood; polymorphisms in the gene encoding apolipoprotein L1 (APOL1) are a major risk for nearly 70% of African Americans with nondiabetic end-stage renal disease (ESRD), particularly FSGS; mutations in complement factor H associated with *membranoproliferative glomerulonephritis (MPGN)* or *atypical hemolytic uremic syndrome (aHUS)*, type II partial lipodystrophy from mutations in genes encoding lamin A/C, or PPARγ cause a metabolic syndrome associated with MPGN, which is sometimes accompanied by dense deposits and C3 nephritic factor; Alport's syndrome, from mutations

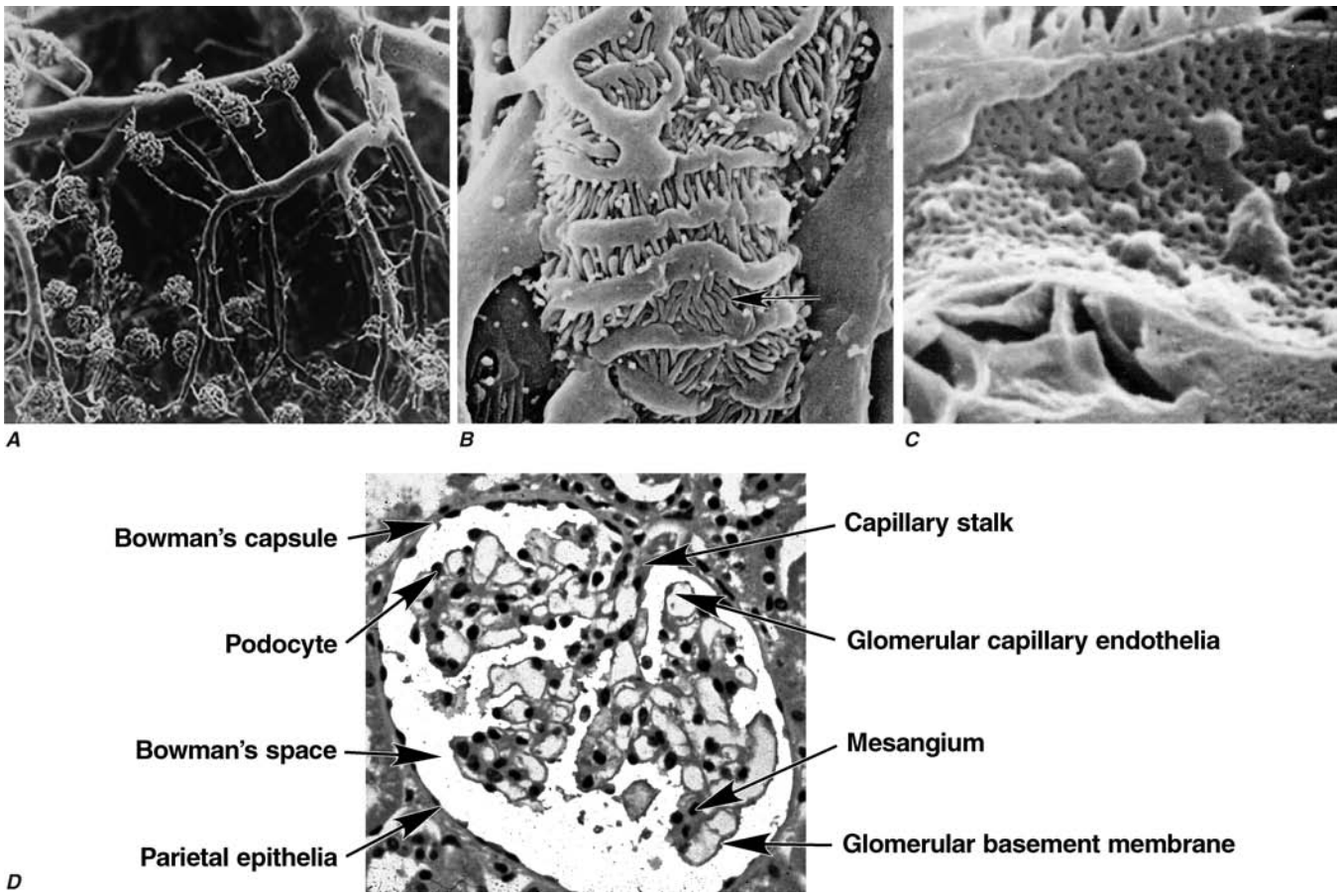


FIGURE 15-1

Glomerular architecture. ***A.*** The glomerular capillaries form from a branching network of renal arteries (arterioles) leading to an afferent arteriole, glomerular capillary bed (tuft), and a draining efferent arteriole. (*From VH Gattone II et al: Hypertension 5:8, 1983.*) ***B.*** Scanning electron micrograph of podocytes that line the outer surface of the glomerular capillaries *(arrow shows foot process)*. ***C.*** Scanning electron micrograph of the fenestrated endothelia lining the glomerular capillary. ***D.*** The various normal regions of the glomerulus on light microscopy. (***A–C****, courtesy of Dr. Vincent Gattone, Indiana University; with permission*.)

in the genes encoding for the α3, α4, or α5 chains of type IV collagen, produces *split-basement membranes* with *glomerulosclerosis*; and lysosomal storage diseases, such as α-galactosidase A deficiency causing Fabry's disease and *N*-acetylneuraminic acid hydrolase deficiency causing nephrosialidosis, produce FSGS.

Systemic hypertension and atherosclerosis can produce pressure stress, ischemia, or lipid oxidants that lead to *chronic glomerulosclerosis*. *Malignant hypertension* can quickly complicate glomerulosclerosis with fibrinoid necrosis of arterioles and glomeruli, thrombotic microangiopathy, and acute renal failure. *Diabetic nephropathy* is an acquired sclerotic injury associated with thickening of the GBM secondary to the long-standing effects of hyperglycemia, advanced glycosylation end products, and reactive oxygen species.

Inflammation of the glomerular capillaries is called *glomerulonephritis*. Most glomerular or mesangial antigens involved in *immune-mediated glomerulonephritis* are unknown **(Fig. 15-2)**. Glomerular epithelial or mesangial cells may shed or express epitopes that mimic other immunogenic proteins made elsewhere in the body. Bacteria, fungi, and viruses can directly infect the kidney producing their own antigens. Autoimmune diseases like idiopathic *membranous glomerulonephritis (MGN)* or MPGN are confined to the kidney, while systemic inflammatory diseases like *lupus nephritis* or *granulomatosis with polyangiitis (Wegener's)* spread to the kidney, causing secondary glomerular injury. *Antiglomerular basement membrane disease* producing Goodpasture's syndrome primarily injures both the lung and kidney because of the narrow distribution of the α3 NC1 domain of type IV collagen that is the target antigen.

Local activation of toll-like receptors on glomerular cells, deposition of immune complexes, or complement injury to glomerular structures induces mononuclear cell infiltration, which subsequently leads to an adaptive immune response attracted to the kidney by local release

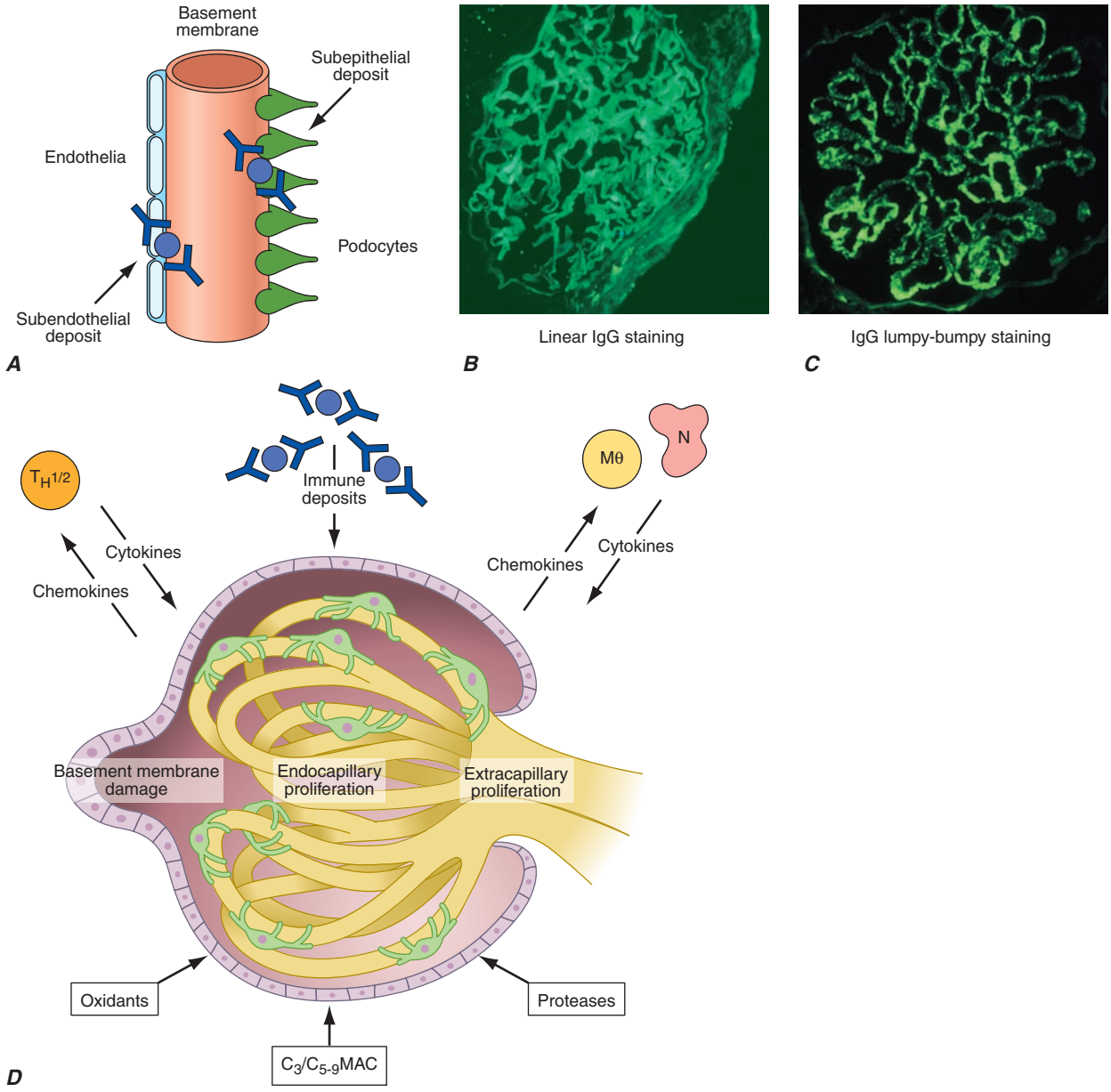


FIGURE 15-2

The glomerulus is injured by a variety of mechanisms. ***A.*** Preformed immune deposits can precipitate from the circulation and collect along the glomerular basement membrane (GBM) in the subendothelial space or can form in situ along the subepithelial space. ***B.*** Immunofluorescent staining of glomeruli with labeled anti-IgG demonstrating linear staining from a patient with anti-GBM disease or immune deposits from a patient with membranous glomerulonephritis. ***C.*** The mechanisms of glomerular injury have a complicated pathogenesis. Immune deposits and complement deposition classically draw macrophages and neutrophils into the glomerulus. T lymphocytes may follow to participate in the injury pattern as well. ***D.*** Amplification mediators as locally derived oxidants and proteases expand this inflammation, and, depending on the location of the target antigen and the genetic polymorphisms of the host, basement membranes are damaged with either endocapillary or extracapillary proliferation.

of chemokines. Neutrophils, macrophages, and T cells are drawn by chemokines into the glomerular tuft, where they react with antigens and epitopes on or near somatic cells or their structures, producing more cytokines and proteases that damage the mesangium, capillaries, and/or the GBM. While the adaptive immune response is similar to that of other tissues, early T-cell activation plays an important role in the mechanism of glomerulonephritis. Antigens presented by class II major histocompatibility complex (MHC) molecules on macrophages and dendritic cells in conjunction with associative recognition molecules engage the CD4/8 T-cell repertoire.

Mononuclear cells by themselves can injure the kidney, but autoimmune events that damage glomeruli

classically produce a humoral immune response. *Poststreptococcal glomerulonephritis*, *lupus nephritis*, and idiopathic *membranous nephritis* typically are associated with immune deposits along the GBM, while anti-GBM antibodies produce the linear binding of anti-GBM disease. Preformed circulating immune complexes can precipitate along the subendothelial side of the GBM, while other immune deposits form in situ on the subepithelial side. These latter deposits accumulate when circulating autoantibodies find their antigen trapped along the subepithelial edge of the GBM. Immune deposits in the glomerular mesangium may result from the deposition of preformed circulating complexes or in situ antigen-antibody interactions. Immune deposits stimulate the release of local proteases and activate the complement cascade, producing C_{5-9} attack complexes. In addition, local oxidants damage glomerular structures, producing proteinuria and effacement of the podocytes. Overlapping etiologies or pathophysiologic mechanisms can produce similar glomerular lesions, suggesting that downstream molecular and cellular responses often converge toward common patterns of injury.

PROGRESSION OF GLOMERULAR DISEASE

Persistent glomerulonephritis that worsens renal function is always accompanied by interstitial nephritis, renal fibrosis, and tubular atrophy (Fig. 4-27). What is not so obvious, however, is that renal failure in glomerulonephritis best correlates histologically with the appearance of tubulointerstitial nephritis rather than with the type of inciting glomerular injury.

Loss of renal function due to interstitial damage is explained hypothetically by several mechanisms. The simplest explanation is that urine flow is impeded by tubular obstruction as a result of interstitial inflammation and fibrosis. Thus, obstruction of the tubules with debris or by extrinsic compression results in aglomerular nephrons. A second mechanism suggests that interstitial changes, including interstitial edema or fibrosis, alter tubular and vascular architecture and thereby compromise the normal tubular transport of solutes and water from tubular lumen to vascular space. This failure increases the solute and water content of the tubule fluid, resulting in isosthenuria and polyuria. Adaptive mechanisms related to tubuloglomerular feedback also fail, resulting in a reduction of renin output from the juxtaglomerular apparatus trapped by interstitial inflammation. Consequently, the local vasoconstrictive influence of angiotensin II on the glomerular arterioles decreases, and filtration drops owing to a generalized decrease in arteriolar tone. A third mechanism involves changes in vascular resistance due to damage of peritubular capillaries. The cross-sectional volume of these capillaries is decreased by interstitial inflammation, edema, or fibrosis. These structural alterations in vascular resistance affect renal function through two mechanisms. First, tubular cells are very metabolically active, and, as a result, decreased perfusion leads to ischemic injury. Second, impairment of glomerular arteriolar outflow leads to increased intraglomerular hypertension in less-involved glomeruli; this selective intraglomerular hypertension aggravates and extends *mesangial sclerosis* and *glomerulosclerosis* to less-involved glomeruli. Regardless of the exact mechanism, early *acute tubulointerstitial nephritis* (Fig. 4-27) suggests potentially recoverable renal function, while the development of *chronic interstitial fibrosis* prognosticates permanent loss (Fig. 4-30).

Persistent damage to glomerular capillaries spreads to the tubulointerstitium in association with proteinuria. There is an untested hypothesis that efferent arterioles leading from inflamed glomeruli carry forward inflammatory mediators, which induces downstream interstitial nephritis, resulting in fibrosis. Glomerular filtrate from injured glomerular capillaries adherent to Bowman's capsule may also be misdirected to the periglomerular interstitium. Most nephrologists believe, however, that proteinuric glomerular filtrate forming tubular fluid is the primary route to downstream tubulointerstitial injury, although none of these hypotheses are mutually exclusive.

The simplest explanation for the effect of proteinuria on the development of interstitial nephritis is that increasingly severe proteinuria, carrying activated cytokines and lipoproteins producing reactive oxygen species, triggers a downstream inflammatory cascade in and around epithelial cells lining the tubular nephron. These effects induce T-lymphocyte and macrophage infiltrates in the interstitial spaces along with fibrosis and tubular atrophy.

Tubules disaggregate following direct damage to their basement membranes, leading to epithelial-mesenchymal transitions forming more interstitial fibroblasts at the site of injury. Transforming growth factor β (TGF-β), fibroblast growth factor 2 (FGF-2), hypoxemia-inducible factor 1α (HIF-1α), and platelet-derived growth factor (PDGF) are particularly active in this transition. With persistent nephritis, fibroblasts multiply and lay down tenascin and a fibronectin scaffold for the polymerization of new interstitial collagen types I/III. These events form scar tissue through a process called fibrogenesis. In experimental studies, bone morphogenetic protein 7 and hepatocyte growth factor can reverse early fibrogenesis and preserve tubular architecture. When fibroblasts outdistance their survival factors, apoptosis occurs, and the permanent renal scar becomes acellular, leading to irreversible renal failure.

APPROACH TO THE PATIENT

Glomerular Disease

HEMATURIA, PROTEINURIA, AND PYURIA

Patients with glomerular disease usually have some hematuria with varying degrees of proteinuria. Hematuria is typically asymptomatic. As few as three to five red blood cells in the spun sediment from first-voided morning urine is suspicious. The diagnosis of glomerular injury can be delayed because patients will not realize they have *microscopic hematuria*, and only rarely with the exception of IgA nephropathy and sickle cell disease is *gross hematuria* present. When working up microscopic hematuria, perhaps accompanied by minimal proteinuria (<500 mg/24 h), it is important to exclude anatomic lesions, such as malignancy of the urinary tract, particularly in older men. Microscopic hematuria may also appear with the onset of benign prostatic hypertrophy, interstitial nephritis, papillary necrosis, hypercalciuria, renal stones, cystic kidney diseases, or renal vascular injury. However, when red blood cell casts (Fig. 4-34) or dysmorphic red blood cells are found in the sediment, glomerulonephritis is likely.

Sustained proteinuria >1–2 g/24 h is also commonly associated with glomerular disease. Patients often will not know they have proteinuria unless they become edematous or notice foaming urine on voiding. *Sustained proteinuria* has to be distinguished from lesser amounts of so-called *benign proteinuria* in the normal population (Table 15-1). This latter class of proteinuria is nonsustained, generally <1 g/24 h, and is sometimes called *functional* or *transient proteinuria*. Fever, exercise, obesity, sleep apnea, emotional stress, and congestive heart failure can explain transient proteinuria. Proteinuria only seen with upright posture is called *orthostatic proteinuria* and has a benign prognosis. Isolated proteinuria sustained over multiple clinic visits is found in diabetic nephropathy, *nil lesion*, *mesangioproliferative glomerulonephritis*, and FSGS. Proteinuria in most adults with glomerular disease is *nonselective,* containing albumin and a mixture of other serum proteins, while in children with nil lesion from *minimal change disease,* the proteinuria is *selective* and composed largely of albumin.

Some patients with inflammatory glomerular disease, such as acute poststreptococcal glomerulonephritis or MPGN, have *pyuria* characterized by the presence of considerable numbers of leukocytes. This latter finding has to be distinguished from urine infected with bacteria.

CLINICAL SYNDROMES

Various forms of glomerular injury can also be parsed into several distinct syndromes on clinical grounds (Table 15-2). These syndromes, however, are not always mutually exclusive. There is an *acute nephritic syndrome* producing 1–2 g/24 h of proteinuria, hematuria with red blood cell casts, pyuria, hypertension, fluid retention, and a rise in serum creatinine associated with a reduction in glomerular filtration. If glomerular inflammation develops slowly, the serum creatinine will rise gradually over many weeks, but if the serum creatinine rises quickly, particularly over a few days, acute nephritis is sometimes called *rapidly progressive glomerulonephritis* (RPGN); the histopathologic term *crescentic glomerulonephritis* is the pathologic equivalent of the clinical presentation of RPGN. When patients with RPGN present with lung hemorrhage from Goodpasture's syndrome, antineutrophil cytoplasmic antibodies (ANCA)-associated small-vessel vasculitis, lupus erythematosus, or cryoglobulinemia, they are often diagnosed as having a *pulmonary-renal syndrome. Nephrotic syndrome* describes the onset of heavy proteinuria (>3.0 g/24 h), hypertension, hypercholesterolemia, hypoalbuminemia, edema/anasarca, and microscopic hematuria; if only large amounts of proteinuria are present without clinical manifestations, the condition is sometimes called *nephrotic-range proteinuria.* The glomerular filtration rate (GFR) in these patients may initially be normal or, rarely, higher than normal, but with persistent hyperfiltration and continued nephron loss, it typically declines over months to years. Patients with a *basement membrane syndrome* either have genetically abnormal basement membranes (Alport's syndrome) or an autoimmune response to basement membrane collagen IV (Goodpasture's syndrome) associated with microscopic hematuria, mild to heavy proteinuria, and hypertension with variable elevations in serum creatinine. *Glomerular-vascular syndrome* describes patients with

TABLE 15-1

URINE ASSAYS FOR ALBUMINURIA/PROTEINURIA

	24-h ALBUMIN[a] (mg/24 h)	ALBUMIN[a]/CREATININE RATIO (mg/g)	DIPSTICK PROTEINURIA	24-h URINE PROTEIN[b] (mg/24 h)
Normal	8–10	<30	–	<150
Microalbuminuria	30–300	30–300	–/Trace/1+	–
Proteinuria	>300	>300	Trace–3+	>150

[a]Albumin detected by radioimmunoassay.
[b]Albumin represents 30–70% of the total protein excreted in the urine.

TABLE 15-2

PATTERNS OF CLINICAL GLOMERULONEPHRITIS

GLOMERULAR SYNDROMES	PROTEINURIA	HEMATURIA	VASCULAR INJURY
Acute Nephritic Syndromes			
Poststreptococcal glomerulonephritis[a]	+/++	++/+++	–
Subacute bacterial endocarditis[a]	+/++	++	–
Lupus nephritis[a]	+/++	++/+++	–
Antiglomerular basement membrane disease[a]	++	++/+++	–
IgA nephropathy[a]	+/++	++/+++[c]	–
ANCA small-vessel vasculitis[a]			
Granulomatosis with polyangiitis (Wegener's)	+/++	++/+++	++++
Microscopic polyangiitis	+/++	++/+++	++++
Churg-Strauss syndrome	+/++	++/+++	++++
Henoch-Schönlein purpura[a]	+/++	++/+++	++++
Cryoglobulinemia[a]	+/++	++/+++	++++
Membranoproliferative glomerulonephritis[a]	++	++/+++	–
Mesangioproliferative glomerulonephritis	+	+/++	–
Pulmonary-Renal Syndromes			
Goodpasture's syndrome[a]	++	++/+++	–
ANCA small-vessel vasculitis[a]			
Granulomatosis with polyangiitis (Wegener's)	+/++	++/+++	++++
Microscopic polyangiitis	+/++	++/+++	++++
Churg-Strauss syndrome	+/++	++/+++	++++
Henoch-Schönlein purpura[a]	+/++	++/+++	++++
Cryoglobulinemia[a]	+/++	++/+++	++++
Nephrotic Syndromes			
Minimal change disease	++++	–	–
Focal segmental glomerulosclerosis	+++/++++	+	–
Membranous glomerulonephritis	++++	+	–
Diabetic nephropathy	++/++++	–/+	–
AL and AA amyloidosis	+++/++++	+	+/++
Light-chain deposition disease	+++	+	–
Fibrillary-immunotactoid disease	+++/++++	+	+
Fabry's disease	+	+	–
Basement Membrane Syndromes			
Anti-GBM disease[a]	++	++/+++	–
Alport's syndrome	++	++	–
Thin basement membrane disease	+	++	–
Nail-patella syndrome	++/+++	++	–
Glomerular Vascular Syndromes			
Atherosclerotic nephropathy	+	+	+++
Hypertensive nephropathy[b]	+/++	+/++	++
Cholesterol emboli	+/++	++	+++
Sickle cell disease	+/++	++[c]	+++

(*continued*)

TABLE 15-2

PATTERNS OF CLINICAL GLOMERULONEPHRITIS (*CONTINUED*)

GLOMERULAR SYNDROMES	PROTEINURIA	HEMATURIA	VASCULAR INJURY
Thrombotic microangiopathies	++	++	+++
Antiphospholipid syndrome	++	++	+++
ANCA small-vessel vasculitis[a]			
Granulomatosis with polyangiitis (Wegener's)	+/++	++/+++	++++
Microscopic polyangiitis	+/++	++/+++	++++
Churg-Strauss syndrome	+++	++/+++	++++
Henoch-Schönlein purpura[a]	+/++	++/+++	++++
Cryoglobulinemia[a]	+/++	++/+++	++++
AL and AA amyloidosis	+++/++++	+	+/++
Infectious Disease–Associated Syndromes			
Poststreptococcal glomerulonephritis[a]	+/++	++/+++	–
Subacute bacterial endocarditis[a]	+/++	++	–
HIV	+++	+/++	–
Hepatitis B and C	+++	+/++	–
Syphilis	+++	+	–
Leprosy	+++	+	–
Malaria	+++	+/++	–
Schistosomiasis	+++	+/++	–

[a]Can present as rapidly progressive glomerulonephritis (RPGN); sometimes called crescentic glomerulonephritis.
[b]Can present as a malignant hypertensive crisis producing an aggressive fibrinoid necrosis in arterioles and small arteries with microangiopathic hemolytic anemia.
[c]Can present with gross hematuria.
Abbreviations: AA, amyloid A; AL, amyloid L; ANCA, antineutrophil cytoplasmic antibodies; GBM, glomerular basement membrane.

vascular injury producing hematuria and moderate proteinuria. Affected individuals can have vasculitis, thrombotic microangiopathy, antiphospholipid syndrome, or, more commonly, a systemic disease such as atherosclerosis, cholesterol emboli, hypertension, sickle cell anemia, and autoimmunity. *Infectious disease–associated syndrome* is most important if one has an international perspective. Save for subacute bacterial endocarditis in the Western Hemisphere, malaria and schistosomiasis may be the most common causes of glomerulonephritis throughout the world, closely followed by HIV and chronic hepatitis B and C. These infectious diseases produce a variety of inflammatory reactions in glomerular capillaries, ranging from nephrotic syndrome to acute nephritic injury, and urinalyses that demonstrate a combination of hematuria and proteinuria.

These six general categories of syndromes are usually determined at the bedside with the help of a history and physical examination, blood chemistries, renal ultrasound, and urinalysis. These initial studies help frame further diagnostic workup that typically involves some testing of the serum for the presence of various proteins (HIV and hepatitis B and C antigens), antibodies [anti-GBM, antiphospholipid, antistreptolysin O (ASO), anti-DNAse, antihyaluronidase, ANCA, anti-DNA, cryoglobulins, anti-HIV, and anti-hepatitis B and C antibodies] or depletion of complement components (C_3 and C_4). The bedside history and physical examination can also help determine whether the glomerulonephritis is isolated to the kidney (*primary glomerulonephritis*) or is part of a systemic disease (*secondary glomerulonephritis*).

When confronted with an abnormal urinalysis and elevated serum creatinine, with or without edema or congestive heart failure, one must consider whether the glomerulonephritis is *acute* or *chronic*. This assessment is best made by careful history (last known urinalysis or serum creatinine during pregnancy or insurance physical, evidence of infection, or use of medication or recreational drugs); the size of the kidneys on renal ultrasound examination; and how the patient feels at presentation. Chronic glomerular disease often presents with decreased kidney size. Patients who quickly develop renal failure are fatigued and weak; feel miserable; often have uremic symptoms associated with nausea, vomiting, fluid retention, and somnolence. Primary glomerulonephritis presenting

with renal failure that has progressed slowly, however, can be remarkably asymptomatic, as are patients with acute glomerulonephritis without much loss in renal function. Once this initial information is collected, selected patients who are clinically stable, have adequate blood clotting parameters, and are willing and able to receive treatment are encouraged to have a renal biopsy. Biopsies can be done safely with an ultrasound-guided biopsy gun.

RENAL PATHOLOGY

A renal biopsy in the setting of glomerulonephritis quickly identifies the type of glomerular injury and often suggests a course of treatment. The biopsy is processed for light microscopy using stains for *hematoxylin and eosin (H&E)* to assess cellularity and architecture, *periodic acid–Schiff (PAS)* to stain carbohydrate moieties in the membranes of the glomerular tuft and tubules, *Jones-methenamine silver* to enhance basement membrane structure, *Congo red* for amyloid deposits, and *Masson's trichrome* to identify collagen deposition and assess the degree of glomerulosclerosis and interstitial fibrosis. Biopsies are also processed for direct immunofluorescence using conjugated antibodies against IgG, IgM, and IgA to detect the presence of "lumpy-bumpy" immune deposits or "linear" IgG or IgA antibodies bound to GBM, antibodies against trapped complement proteins (C_3 and C_4), or specific antibodies against a relevant antigen. High-resolution electron microscopy can clarify the principal location of immune deposits and the status of the basement membrane.

Each region of a renal biopsy is assessed separately. By light microscopy, glomeruli (at least 10 and ideally 20) are reviewed individually for discrete lesions; <50% involvement is considered *focal*, and >50% is *diffuse*. Injury in each glomerular tuft can be *segmental*, involving a portion of the tuft, or *global*, involving most of the glomerulus. Glomeruli having *proliferative* characteristics show increased cellularity. When cells in the capillary tuft proliferate, it is called *endocapillary*, and when cellular proliferation extends into Bowman's space, it is called *extracapillary*. *Synechiae* are formed when epithelial podocytes attach to Bowman's capsule in the setting of glomerular injury; *crescents*, which in some cases may be the extension of synechiae, develop when fibrocellular/fibrin collections fill all or part of Bowman's space; and *sclerotic* glomeruli show acellular, amorphous accumulations of proteinaceous material throughout the tuft with loss of functional capillaries and normal mesangium. Since *age-related glomerulosclerosis* is common in adults, one can estimate the background percentage of sclerosis by dividing the patient's age in half and subtracting 10. Immunofluorescent and electron microscopy can detect the presence and location of *subepithelial*, *subendothelial*, or *mesangial* immune deposits, or *reduplication* or *splitting* of the basement membrane. In the other regions of the biopsy, the vasculature surrounding glomeruli and tubules can show *angiopathy*, *vasculitis*, the presence of *fibrils*, or *thrombi*. The tubules can be assessed for adjacency to one another; separation can be the result of edema, tubular dropout, or collagen deposition resulting from interstitial fibrosis. Interstitial fibrosis is an ominous sign of irreversibility and progression to renal failure.

ACUTE NEPHRITIC SYNDROMES

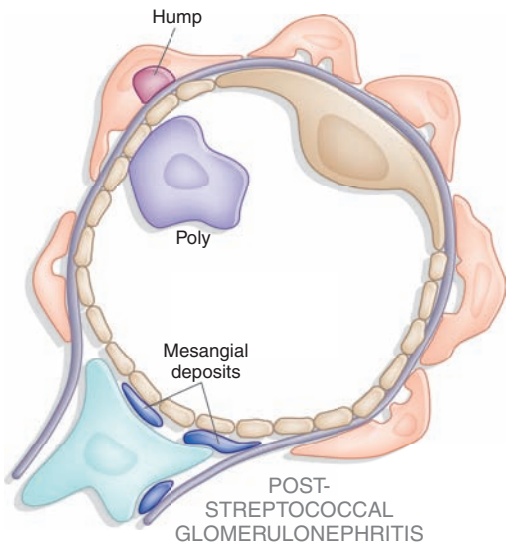
Acute nephritic syndromes classically present with hypertension, hematuria, red blood cell casts, pyuria, and mild to moderate proteinuria. Extensive inflammatory damage to glomeruli causes a fall in GFR and eventually produces uremic symptoms with salt and water retention, leading to edema and hypertension.

POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

Poststreptococcal glomerulonephritis is prototypical for *acute endocapillary proliferative glomerulonephritis*. The incidence of poststreptococcal glomerulonephritis has dramatically decreased in developed countries and in these locations is typically sporadic; epidemics are less common. Acute poststreptococcal glomerulonephritis in underdeveloped countries usually affects children between the ages of 2 and 14 years, but in developed countries is more typical in the elderly, especially in association with debilitating conditions. It is more common in males, and the familial or cohabitant incidence is as high as 40%. Skin and throat infections with particular M types of streptococci (nephritogenic strains) antedate glomerular disease; M types 47, 49, 55, 2, 60, and 57 are seen following impetigo and M types 1, 2, 4, 3, 25, 49, and 12 with pharyngitis. Poststreptococcal glomerulonephritis due to impetigo develops 2–6 weeks after skin infection and 1–3 weeks after streptococcal pharyngitis.

The renal biopsy in poststreptococcal glomerulonephritis demonstrates hypercellularity of mesangial and endothelial cells, glomerular infiltrates of polymorphonuclear leukocytes, granular subendothelial immune deposits of IgG, IgM, C_3, C_4, and $C_{5\text{-}9}$, and subepithelial deposits (which appear as "humps") (Fig. 4-6). (See Glomerular Schematic 1.) Poststreptococcal glomerulonephritis is an immune-mediated disease involving putative streptococcal antigens, circulating immune complexes, and activation of complement in association with cell-mediated injury. Many candidate antigens have been proposed over the years; candidates from nephritogenic streptococci of interest at the moment are a cationic cysteine proteinase known as streptococcal pyrogenic exotoxin B (SPEB) that is generated

Glomerular Schematic 1



by proteolysis of a zymogen precursor (zSPEB), and NAPlr, the nephritis-associated plasmin receptor. These two antigens have biochemical affinity for plasmin and bind as complexes facilitated by this relationship, and both activate the alternate complement pathway. The nephritogenic antigen, SPEB, has been demonstrated inside the subepithelial "humps" on biopsy.

The classic presentation is an acute nephritic picture with hematuria, pyuria, red blood cell casts, edema, hypertension, and oliguric renal failure, which may be severe enough to appear as RPGN. Systemic symptoms of headache, malaise, anorexia, and flank pain (due to swelling of the renal capsule) are reported in as many as 50% of cases. Five percent of children and 20% of adults have proteinuria in the nephrotic range. In the first week of symptoms, 90% of patients will have a depressed CH_{50} and decreased levels of C_3 with normal levels of C_4. Positive rheumatoid factor (30–40%), cryoglobulins and circulating immune complexes (60–70%), and ANCA against myeloperoxidase (10%) are also reported. Positive cultures for streptococcal infection are inconsistently present (10–70%), but increased titers of ASO (30%), anti-DNAse (70%), or antihyaluronidase antibodies (40%) can help confirm the diagnosis. Consequently, the diagnosis of poststreptococcal glomerulonephritis rarely requires a renal biopsy. A subclinical disease is reported in some series to be four to five times as common as clinical nephritis, and these latter cases are characterized by asymptomatic microscopic hematuria with low serum C_3 complement levels.

Treatment is supportive, with control of hypertension, edema, and dialysis as needed. Antibiotic treatment for streptococcal infection should be given to all patients and their cohabitants. There is no role for immunosuppressive therapy, even in the setting of crescents. Recurrent poststreptococcal glomerulonephritis is rare despite repeated streptococcal infections. Early death is rare in children but does occur in the elderly. Overall, the prognosis is good, with permanent renal failure being very uncommon, less than 1% in children. Complete resolution of the hematuria and proteinuria in the majority of children occurs within 3–6 weeks of the onset of nephritis but 3–10% of children may have persistent microscopic hematuria, non-nephrotic proteinuria, or hypertension. The prognosis in elderly patients is worse with a high incidence of azotemia (up to 60%), nephrotic-range proteinuria, and end-stage renal disease.

SUBACUTE BACTERIAL ENDOCARDITIS

Endocarditis-associated glomerulonephritis is typically a complication of subacute bacterial endocarditis, particularly in patients who remain untreated for a long time, have negative blood cultures, or have right-sided endocarditis. Glomerulonephritis is unusual in acute bacterial endocarditis because it takes 10–14 days to develop immune complex–mediated injury, by which time the patient has been treated, often with emergent surgery. Grossly, the kidneys in subacute bacterial endocarditis have subcapsular hemorrhages with a "flea-bitten" appearance, and microscopy on renal biopsy reveals focal proliferation around foci of necrosis associated with abundant mesangial, subendothelial, and subepithelial immune deposits of IgG, IgM, and C_3. Patients who present with a clinical picture of RPGN have crescents. Embolic infarcts or septic abscesses may also be present. The pathogenesis hinges on the renal deposition of circulating immune complexes in the kidney with complement activation. Patients present with gross or microscopic hematuria, pyuria, and mild proteinuria or, less commonly, RPGN with rapid loss of renal function. A normocytic anemia, elevated erythrocyte sedimentation rate, hypocomplementemia, high titers of rheumatoid factor, type III cryoglobulins, and circulating immune complexes are often present. Levels of serum creatinine may be elevated at diagnosis, but with modern therapy there is little progression to chronic renal failure. Primary treatment is eradication of the infection with 4–6 weeks of antibiotics, and if accomplished expeditiously, the prognosis for renal recovery is good. ANCA-associated vasculitis sometimes accompanies or is confused with subacute bacterial endocarditis (SBE) and should be ruled out, as the treatment is different.

As variants of persistent bacterial infection in blood, glomerulonephritis can occur in patients with ventriculoatrial and ventriculoperitoneal shunts; pulmonary, intraabdominal, pelvic, or cutaneous infections; and infected vascular prostheses. The clinical presentation of these conditions is variable and includes proteinuria, microscopic hematuria, and acute renal failure. Blood cultures are usually positive and serum complement levels low, and there may be elevated levels of C-reactive

proteins, rheumatoid factor, antinuclear antibodies, and cryoglobulins. Renal lesions include membranoproliferative glomerulonephritis (MPGN), diffuse proliferative glomerulonephritis (DPGN), or mesangioproliferative glomerulonephritis, sometimes leading to RPGN. Treatment focuses on eradicating the infection, with most patients treated as if they have endocarditis.

LUPUS NEPHRITIS

Lupus nephritis is a common and serious complication of systemic lupus erythematosus (SLE) and most severe in African-American female adolescents. Thirty to fifty percent of patients will have clinical manifestations of renal disease at the time of diagnosis, and 60% of adults and 80% of children develop renal abnormalities at some point in the course of their disease. Lupus nephritis results from the deposition of circulating immune complexes, which activate the complement cascade leading to complement-mediated damage, leukocyte infiltration, activation of procoagulant factors, and release of various cytokines. In situ immune complex formation following glomerular binding of nuclear antigens, particularly necrotic nucleosomes, also plays a role in renal injury. The presence of antiphospholipid antibodies may also trigger a thrombotic microangiopathy in a minority of patients.

The clinical manifestations, course of disease, and treatment of lupus nephritis are closely linked to renal pathology. The most common clinical sign of renal disease is proteinuria, but hematuria, hypertension, varying degrees of renal failure, and active urine sediment with red blood cell casts can all be present. Although significant renal pathology can be found on biopsy even in the absence of major abnormalities in the urinalysis, most nephrologists do not biopsy patients until the urinalysis is convincingly abnormal. The extrarenal manifestations of lupus are important in establishing a firm diagnosis of systemic lupus because, while serologic abnormalities are common in lupus nephritis, they are not diagnostic. Anti-dsDNA antibodies that fix complement correlate best with the presence of renal disease. Hypocomplementemia is common in patients with acute lupus nephritis (70–90%) and declining complement levels may herald a flare. Although urinary biomarkers of lupus nephritis are being identified to assist in predicting renal flares, renal biopsy is the only reliable method of identifying the morphologic variants of lupus nephritis.

The World Health Organization (WHO) workshop in 1974 first outlined several distinct patterns of lupus-related glomerular injury; these were modified in 1982. In 2004 the International Society of Nephrology in conjunction with the Renal Pathology Society again updated the classification. This latest version of lesions seen on biopsy **(Table 15-3)** best defines clinicopathologic correlations, provides valuable prognostic information, and forms the basis for modern treatment recommendations. Class I nephritis describes normal glomerular histology by any technique or normal light microscopy with minimal mesangial deposits on immunofluorescent or electron microscopy. Class II designates mesangial immune complexes with *mesangial proliferation*. Both class I and II lesions are typically associated with minimal renal manifestation and normal renal function; nephrotic syndrome is rare. Patients with lesions limited to the renal mesangium have an excellent prognosis and generally do not need therapy for their lupus nephritis.

TABLE 15-3

CLASSIFICATION FOR LUPUS NEPHRITIS		
Class I	Minimal mesangial	Normal histology with mesangial deposits
Class II	Mesangial proliferation	Mesangial hypercellularity with expansion of the mesangial matrix
Class III	Focal nephritis	Focal endocapillary ± extracapillary proliferation with focal subendothelial immune deposits and mild mesangial expansion
Class IV	Diffuse nephritis	Diffuse endocapillary ± extracapillary proliferation with diffuse subendothelial immune deposits and mesangial alterations
Class V	Membranous nephritis	Thickened basement membranes with diffuse subepithelial immune deposits; may occur with class III or IV lesions and is sometimes called mixed membranous and proliferative nephritis
Class VI	Sclerotic nephritis	Global sclerosis of nearly all glomerular capillaries

Note: Revised in 2004 by the International Society of Nephrology-Renal Pathology Society Study Group.

The subject of lupus nephritis is presented under acute nephritic syndromes because of the aggressive and important proliferative lesions seen in class III–V renal disease. Class III describes *focal lesions with proliferation or scarring*, often involving only a segment of the glomerulus (Fig. 4-12). Class III lesions have the most varied course. Hypertension, an active urinary sediment, and proteinuria are common with nephrotic-range proteinuria in 25–33% of patients. Elevated serum creatinine is present in 25% of patients. Patients with mild proliferation

involving a small percentage of glomeruli respond well to therapy with steroids alone, and fewer than 5% progress to renal failure over 5 years. Patients with more severe proliferation involving a greater percentage of glomeruli have a far worse prognosis and lower remission rates. Treatment of those patients is the same as that for class IV lesions. Most nephrologists believe that class III lesions are simply an early presentation of class IV disease. Others believe severe class III disease is a discrete lesion also requiring aggressive therapy. Class IV describes *global, diffuse proliferative lesions* involving the vast majority of glomeruli. Patients with class IV lesions commonly have high anti-DNA antibody titers, low serum complement, hematuria, red blood cell casts, proteinuria, hypertension, and decreased renal function; 50% of patients have nephrotic-range proteinuria. Patients with crescents on biopsy often have a rapidly progressive decline in renal function (Fig. 4-12). Without treatment, this aggressive lesion has the worst renal prognosis. However, if a remission—defined as a return to near-normal renal function and proteinuria ≤330 mg/dL per day—is achieved with treatment, renal outcomes are excellent. Current evidence suggests that inducing a remission with administration of high-dose steroids and either cyclophosphamide or mycophenolate mofetil for 2–6 months, followed by maintenance therapy with lower doses of steroids and mycophenolate mofetil, best balances the likelihood of successful remission with the side effects of therapy. There is no consensus on the use of high-dose intravenous methylprednisolone versus oral prednisone, monthly intravenous cyclophosphamide versus daily oral cyclophosphamide, or other immunosuppressants such as cyclosporine, tacrolimus, rituximab, or azathioprine. Nephrologists tend to avoid prolonged use of cyclophosphamide in patients of childbearing age without first banking eggs or sperm.

The class V lesion describes subepithelial immune deposits producing a *membranous pattern*; a subcategory of class V lesions is associated with proliferative lesions and is sometimes called *mixed membranous and proliferative disease* (Fig. 4-11)—this category of injury is treated like class IV glomerulonephritis. Sixty percent of patients present with nephrotic syndrome or lesser amounts of proteinuria. Patients with lupus nephritis class V, like patients with *idiopathic membranous nephropathy*, are predisposed to renal-vein thrombosis and other thrombotic complications. A minority of patients with class V will present with hypertension and renal dysfunction. There are conflicting data on the clinical course, prognosis, and appropriate therapy for patients with class V disease, which may reflect the heterogeneity of this group of patients. Patients with severe nephrotic syndrome, elevated serum creatinine, and a progressive course will probably benefit from therapy with steroids in combination with other immunosuppressive agents. Therapy with inhibitors of the renin-angiotensin system also may attenuate the proteinuria. Antiphospholipid antibodies present in lupus may result in glomerular microthromboses and complicate the course in up to 20% of lupus nephritis patients. The renal prognosis is worse even with anticoagulant therapy.

Patients with any of the above lesions also can transform to another lesion; hence patients often require reevaluation, including repeat renal biopsy. Lupus patients with class VI lesions have greater than 90% *sclerotic glomeruli* and end-stage renal disease with interstitial fibrosis. As a group, approximately 20% of patients with lupus nephritis will reach end-stage disease, requiring dialysis or transplantation. Systemic lupus tends to become quiescent once there is renal failure, perhaps due to the immunosuppressant effects of uremia. Renal transplantation in renal failure from lupus, usually performed after approximately 6 months of inactive disease, results in allograft survival rates comparable to patients transplanted for other reasons.

ANTIGLOMERULAR BASEMENT MEMBRANE DISEASE

Patients who develop autoantibodies directed against glomerular basement antigens frequently develop a glomerulonephritis termed *antiglomerular basement membrane (anti-GBM) disease*. When they present with lung hemorrhage and glomerulonephritis, they have a pulmonary-renal syndrome called *Goodpasture's syndrome*. The target epitopes for this autoimmune disease lie in the quaternary structure of α3 NC1 domain of collagen IV. MHC-restricted T cells initiate the autoantibody response because humans are not tolerant to the epitopes created by this quaternary structure. The epitopes are normally sequestered in the collagen IV hexamer and can be exposed by infection, smoking, oxidants, or solvents. Goodpasture's syndrome appears in two age groups: in young men in their late 20s and in men and women in their 60–70s. Disease in the younger age group is usually explosive, with hemoptysis, a sudden fall in hemoglobin, fever, dyspnea, and hematuria. Hemoptysis is largely confined to smokers, and those who present with lung hemorrhage as a group do better than older populations who have prolonged, asymptomatic renal injury; presentation with oliguria is often associated with a particularly bad outcome. The performance of an urgent kidney biopsy is important in suspected cases of Goodpasture's syndrome to confirm the diagnosis and assess prognosis. Renal biopsies typically show *focal or segmental necrosis* that later, with aggressive destruction of the capillaries by cellular proliferation, leads to crescent formation in Bowman's space (Fig. 4-14). As these

lesions progress, there is concomitant interstitial nephritis with fibrosis and tubular atrophy.

The presence of anti-GBM antibodies and complement is recognized on biopsy by linear immunofluorescent staining for IgG (rarely IgA). In testing serum for anti-GBM antibodies, it is particularly important that the α3 NC1 domain of collagen IV alone be used as the target. This is because nonnephritic antibodies against the α1 NC1 domain are seen in paraneoplastic syndromes and cannot be discerned from assays that use whole basement membrane fragments as the binding target. Between 10 and 15% of sera from patients with Goodpasture's syndrome also contain ANCA antibodies against myeloperoxidase. This subset of patients has a vasculitis-associated variant, which has a surprisingly good prognosis with treatment. Prognosis at presentation is worse if there are >50% crescents on renal biopsy with advanced fibrosis, if serum creatinine is >5–6 mg/dL, if oliguria is present, or if there is a need for acute dialysis. Although frequently attempted, most of these latter patients will not respond to plasmapheresis and steroids. Patients with advanced renal failure who present with hemoptysis should still be treated for their lung hemorrhage, as it responds to plasmapheresis and can be lifesaving. Treated patients with less severe disease typically respond to 8–10 treatments of plasmapheresis accompanied by oral prednisone and cyclophosphamide in the first 2 weeks. Kidney transplantation is possible, but because there is risk of recurrence, experience suggests that patients should wait for 6 months and until serum antibodies are undetectable.

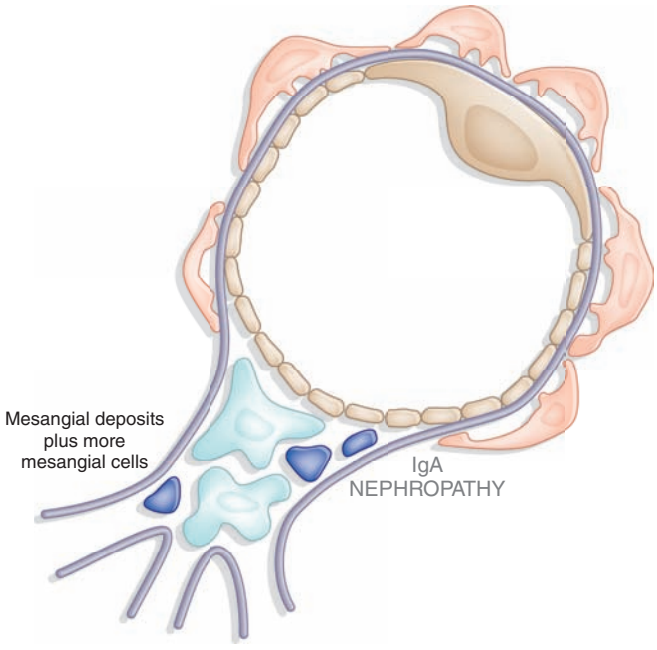
IgA NEPHROPATHY

Berger first described the glomerulonephritis now termed *IgA nephropathy*. It is classically characterized by episodic hematuria associated with the deposition of IgA in the mesangium. IgA nephropathy is one of the most common forms of glomerulonephritis worldwide. There is a male preponderance, a peak incidence in the second and third decades of life, and rare familial clustering. There are geographic differences in the prevalence of IgA nephropathy, with 30% prevalence along the Asian and Pacific Rim and 20% in southern Europe, compared to a much lower prevalence in northern Europe and North America. It was initially hypothesized that variation in detection, in part, accounted for regional differences. With clinical care in nephrology becoming more uniform, this variation in prevalence more likely reflects true differences among racial and ethnic groups.

IgA nephropathy is predominantly a sporadic disease but susceptibility to it has been shown uncommonly to have a genetic component depending on geography and the existence of "founder effects." Familial forms of IgA nephropathy are more common in northern Italy and eastern Kentucky. No single causal gene has been identified. Clinical and laboratory evidence suggests close similarities between Henoch-Schönlein purpura and IgA nephropathy. Henoch-Schönlein purpura is distinguished clinically from IgA nephropathy by prominent systemic symptoms, a younger age (<20 years old), preceding infection, and abdominal complaints. Deposits of IgA are also found in the glomerular mesangium in a variety of systemic diseases, including chronic liver disease, Crohn's disease, gastrointestinal adenocarcinoma, chronic bronchiectasis, idiopathic interstitial pneumonia, dermatitis herpetiformis, mycosis fungoides, leprosy, ankylosing spondylitis, relapsing polychondritis, and Sjögren's syndrome. IgA deposition in these entities is not usually associated with clinically significant glomerular inflammation or renal dysfunction and thus is not called IgA nephropathy.

IgA nephropathy is an immune complex–mediated glomerulonephritis defined by the presence of diffuse mesangial IgA deposits often associated with mesangial hypercellularity. (See Glomerular Schematic 2.) IgM, IgG, C_3, or immunoglobulin light chains may be codistributed with IgA. IgA deposited in the mesangium is typically polymeric and of the IgA1 subclass, the pathogenic significance of which is not clear. Abnormalities have been described in IgA production by plasma cells, particularly secretory IgA; in IgA clearance, predominantly by the liver; in mesangial IgA clearance and receptors for IgA; and in growth factor and cytokine-mediated events. Currently, however, abnormalities in the *O*-glycosylation of the hinge region of IgA seem

Glomerular Schematic 2



to best account for the pathogenesis of sporadic IgA nephropathy. Despite the presence of elevated serum IgA levels in 20–50% of patients, IgA deposition in skin biopsies in 15–55% of patients, or elevated levels of secretory IgA and IgA-fibronectin complexes, a renal biopsy is necessary to confirm the diagnosis. Although the immunofluorescent pattern of IgA on renal biopsy defines IgA nephropathy in the proper clinical context, a variety of histologic lesions may be seen on light microscopy (Fig. 4-8), including DPGN, *segmental sclerosis*, and, rarely, *segmental necrosis with cellular crescent formation*, which typically presents as RPGN.

The two most common presentations of IgA nephropathy are recurrent episodes of macroscopic hematuria during or immediately following an upper respiratory infection often accompanied by proteinuria or persistent asymptomatic microscopic hematuria. Nephrotic syndrome, however, is uncommon. Proteinuria can also first appear late in the course of the disease. Rarely patients present with acute renal failure and a rapidly progressive clinical picture. IgA nephropathy is a benign disease for the majority of patients, and 5–30% of patients may go into a complete remission, with others having hematuria but well preserved renal function. In the minority of patients who have progressive disease, progression is slow, with renal failure seen in only 25–30% of patients with IgA nephropathy over 20–25 years. This risk varies considerably among populations. Cumulatively, risk factors for the loss of renal function identified thus far account for less than 50% of the variation in observed outcome but include the presence of hypertension or proteinuria, the absence of episodes of macroscopic hematuria, male age, older age of onset, and extensive glomerulosclerosis or interstitial fibrosis on renal biopsy. Several analyses in large populations of patients found persistent proteinuria for 6 months or longer to have the greatest predictive power for adverse renal outcomes.

There is no agreement on optimal treatment. Both large studies that include patients with multiple glomerular diseases and small studies of patients with IgA nephropathy support the use of angiotensin-converting enzyme (ACE) inhibitors in patients with proteinuria or declining renal function. Tonsillectomy, steroid therapy, and fish oil have all been suggested in small studies to benefit select patients with IgA nephropathy. When presenting as RPGN, patients typically receive steroids, cytotoxic agents, and plasmapheresis.

ANCA SMALL-VESSEL VASCULITIS

A group of patients with small-vessel vasculitis (arterioles, capillaries, and venules; rarely small arteries) and glomerulonephritis have serum ANCA; the antibodies are of two types, anti-proteinase 3 (PR3) or anti-myeloperoxidase (MPO); Lamp-2 antibodies have also been reported experimentally as potentially pathogenic. ANCA are produced with the help of T cells and activate leukocytes and monocytes, which together damage the walls of small vessels. Endothelial injury also attracts more leukocytes and extends the inflammation. Granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis, and Churg-Strauss syndrome belong to this group because they are ANCA positive and have a *pauci-immune glomerulonephritis* with few immune complexes in small vessels and glomerular capillaries. Patients with any of these three diseases can have any combination of the above serum antibodies, but anti-PR3 antibodies are more common in granulomatosis with polyangiitis (Wegener's), and anti-MPO antibodies are more common in microscopic polyangiitis or Churg-Strauss. While each of these diseases have some unique clinical features, most features do not predict relapse or progression, and as a group they are generally treated in the same way. Since mortality is high without treatment, virtually all patients receive urgent treatment. Induction therapy usually includes some combination of plasmapheresis, methylprednisolone, and cyclophosphamide. The benefit of plasmapheresis in this setting is uncertain. Monthly "pulse" IV cyclophosphamide to induce remission of ANCA-associated vasculitis is as effective as daily oral cyclophosphamide and results in reduced cumulative adverse events but may be associated with increased relapses. Steroids are tapered soon after acute inflammation subsides, and patients are maintained on cyclophosphamide or azathioprine for up to a year to minimize the risk of relapse.

Granulomatosis with polyangiitis (Wegener's)

Patients with this disease classically present with fever, purulent rhinorrhea, nasal ulcers, sinus pain, polyarthralgias/arthritis, cough, hemoptysis, shortness of breath, microscopic hematuria, and 0.5–1 g/24 h of proteinuria; occasionally there may be cutaneous purpura and mononeuritis multiplex. Presentation without renal involvement is termed *limited granulomatosis with polyangiitis (Wegener's)*, although some of these patients will show signs of renal injury later. Chest x-ray often reveals nodules and persistent infiltrates, sometimes with cavities. Biopsy of involved tissue will show a small-vessel vasculitis and adjacent noncaseating granulomas. Renal biopsies during active disease demonstrate *segmental necrotizing glomerulonephritis* without immune deposits (Fig. 4-13). The cause of granulomatosis with polyangiitis (Wegener's) is unknown. In case-controlled studies there is greater risk associated with exposure to silica dust. The disease is also more common in patients with α_1-antitrypsin deficiency, which is an inhibitor of PR3. Relapse after achieving remission is more common in patients with granulomatosis with polyangiitis (Wegener's) than the other ANCA-associated vasculitis, necessitating diligent follow-up care.

Microscopic polyangiitis

Clinically, these patients look somewhat similar to those with granulomatosis with polyangiitis (Wegener's), except they rarely have significant lung disease or destructive sinusitis. The distinction is made on biopsy, where the vasculitis in microscopic polyangiitis is without granulomas. Some patients will also have injury limited to the capillaries and venules.

Churg-Strauss syndrome

When small-vessel vasculitis is associated with peripheral eosinophilia, cutaneous purpura, mononeuritis, asthma, and allergic rhinitis, a diagnosis of Churg-Strauss syndrome is considered. Hypergammaglobulinemia, elevated levels of serum IgE, or the presence of rheumatoid factor sometimes accompanies the allergic state. Lung inflammation, including fleeting cough and pulmonary infiltrates, often precedes the systemic manifestations of disease by years; lung manifestations are rarely absent. A third of patients may have exudative pleural effusions associated with eosinophils. Small-vessel vasculitis and *focal segmental necrotizing glomerulonephritis* can be seen on renal biopsy, usually absent eosinophils or granulomas. The cause of Churg-Strauss syndrome is autoimmune, but the inciting factors are unknown. Interestingly, some asthma patients treated with leukotriene receptor antagonists will develop this vasculitis.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

MPGN is sometimes called *mesangiocapillary glomerulonephritis* or *lobar glomerulonephritis*. It is an immune-mediated glomerulonephritis characterized by thickening of the GBM with mesangioproliferative changes; 70% of patients have hypocomplementemia. MPGN is rare in African Americans, and idiopathic disease usually presents in childhood or young adulthood. MPGN is subdivided pathologically into type I, type II, and type III disease. *Type I MPGN* is commonly associated with persistent hepatitis C infections, autoimmune diseases like lupus or cryoglobulinemia, or neoplastic diseases **(Table 15-4)**. *Types II and III MPGN* are usually idiopathic, except in patients with complement factor H deficiency, in the presence of C_3 nephritic factor and/or in partial lipodystrophy producing type II disease, or complement receptor deficiency in type III disease.

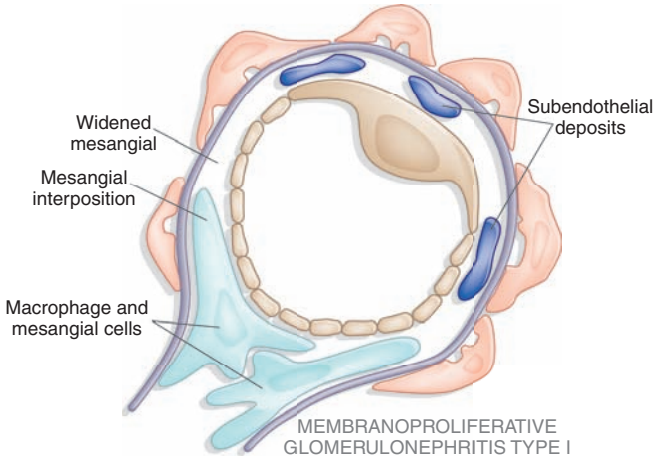
Type I MPGN, the most proliferative of the three types, shows mesangial proliferation with lobular segmentation on renal biopsy and mesangial interposition between the capillary basement membrane and endothelial cells, producing a double contour sometimes called *tramtracking* (Fig. 4-9). (See Glomerular Schematic 3.) Subendothelial deposits with low serum levels of C_3 are typical, although 50% of patients have normal levels of C_3 and occasional intramesangial deposits. Low serum C_3 and a dense thickening of the GBM containing ribbons of dense deposits and C_3 characterize type II MPGN, sometimes called *dense deposit disease* (Fig. 4-10). Classically, the glomerular tuft has a lobular appearance; intramesangial deposits are rarely present, and subendothelial deposits are generally absent. Proliferation in type III MPGN is less common than the other two types and is often focal; mesangial interposition is rare, and subepithelial deposits can occur along widened segments of the GBM that appear laminated and disrupted.

Type I MPGN is secondary to glomerular deposition of circulating immune complexes or their in situ formation. Types II and III MPGN may be related to "nephritic factors," which are autoantibodies that stabilize C_3 convertase and allow it to activate serum C_3.

TABLE 15-4

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS
Type I Disease (Most Common)
Idiopathic
Subacute bacterial endocarditis
Systemic lupus erythematosus
Hepatitis C ± cryoglobulinemia
Mixed cryoglobulinemia
Hepatitis B
Cancer: lung, breast, and ovary (germinal)
Type II Disease (Dense Deposit Disease)
Idiopathic
C_3 nephritic factor associated
Partial lipodystrophy
Type III Disease
Idiopathic
Complement receptor deficiency

Glomerular Schematic 3



Patients with MPGN present with proteinuria, hematuria, and pyuria (30%), systemic symptoms of fatigue and malaise that are most common in children with type I disease, or an acute nephritic picture with RPGN and a speedy deterioration in renal function in up to 25% of patients. Low serum C_3 levels are common. Fifty percent of patients with MPGN develop end-stage disease 10 years after diagnosis, and 90% have renal insufficiency after 20 years. Nephrotic syndrome, hypertension, and renal insufficiency all predict poor outcome. In the presence of proteinuria, treatment with inhibitors of the renin-angiotensin system is prudent. Evidence for treatment with dipyridamole, Coumadin (warfarin), or cyclophosphamide is not strongly established. There is some evidence supporting the efficacy of treatment of *primary MPGN* with steroids, particularly in children, as well as reports of efficacy with plasma exchange and other immunosuppressive drugs. In *secondary MPGN*, treating the associated infection, autoimmune disease, or neoplasms is of demonstrated benefit. In particular, pegylated interferon and ribavirin are useful in reducing viral load. Although all primary renal diseases can recur over time in transplanted renal allografts, patients with MPGN are well known to be at risk for not only a histologic recurrence but also a clinically significant recurrence with loss of graft function.

MESANGIOPROLIFERATIVE GLOMERULONEPHRITIS

Mesangioproliferative glomerulonephritis is characterized by expansion of the mesangium, sometimes associated with mesangial hypercellularity; thin, single contoured capillary walls; and mesangial immune deposits. Clinically, it can present with varying degrees of proteinuria and, commonly, hematuria. Mesangioproliferative disease may be seen in IgA nephropathy, *Plasmodium falciparum* malaria, resolving postinfectious glomerulonephritis, and class II nephritis from lupus, all of which can have a similar histologic appearance. With these secondary entities excluded, the diagnosis of *primary mesangioproliferative glomerulonephritis* is made in less than 15% of renal biopsies. As an immune-mediated renal lesion with deposits of IgM, C1q, and C_3, the clinical course is variable. Patients with isolated hematuria may have a very benign course, and those with heavy proteinuria occasionally progress to renal failure. There is little agreement on treatment, but some clinical reports suggest benefit from use of inhibitors of the renin-angiotensin system, steroid therapy, and even cytotoxic agents.

NEPHROTIC SYNDROME

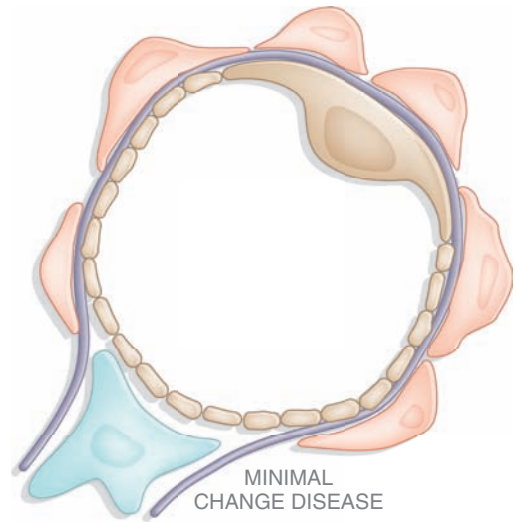
Nephrotic syndrome classically presents with heavy proteinuria, minimal hematuria, hypoalbuminemia, hypercholesterolemia, edema, and hypertension. If left undiagnosed or untreated, some of these syndromes will progressively damage enough glomeruli to cause a fall in GFR, producing renal failure.

Therapies for various causes of nephrotic syndrome are noted under individual disease headings later in the chapter. In general, all patients with hypercholesterolemia secondary to nephrotic syndrome should be treated with lipid-lowering agents because they are at increased risk for cardiovascular disease. Edema secondary to salt and water retention can be controlled with the judicious use of diuretics, avoiding intravascular volume depletion. Venous complications secondary to the hypercoagulable state associated with nephrotic syndrome can be treated with anticoagulants. The losses of various serum binding proteins, such as thyroid-binding globulin, lead to alterations in functional tests. Finally, proteinuria itself is hypothesized to be nephrotoxic, and treatment of proteinuria with inhibitors of the renin-angiotensin system can lower urinary protein excretion.

MINIMAL CHANGE DISEASE

Minimal change disease (MCD), sometimes known as *nil lesion*, causes 70–90% of nephrotic syndrome in childhood but only 10–15% of nephrotic syndrome in adults. Minimal change disease usually presents as a primary renal disease but can be associated with several other conditions, including Hodgkin's disease, allergies, or use of nonsteroidal anti-inflammatory agents; significant interstitial nephritis often accompanies cases associated with nonsteroidal use. Minimal change disease on renal biopsy shows no obvious glomerular lesion by light microscopy and is negative for deposits by immunofluorescent microscopy, or occasionally shows small amounts of IgM in the mesangium (Fig. 4-1). (See Glomerular Schematic 4.) Electron microscopy,

Glomerular Schematic 4



however, consistently demonstrates an effacement of the foot process supporting the epithelial podocytes with weakening of slit-pore membranes. The pathophysiology of this lesion is uncertain. Most agree there is a circulating cytokine, perhaps related to a T-cell response that alters capillary charge and podocyte integrity. The evidence for cytokine-related immune injury is circumstantial and is suggested by the presence of preceding allergies, altered cell-mediated immunity during viral infections, and the high frequency of remissions with steroids.

Minimal change disease presents clinically with the abrupt onset of edema and nephrotic syndrome accompanied by acellular urinary sediment. Average urine protein excretion reported in 24 hours is 10 g with severe hypoalbuminemia. Less common clinical features include hypertension (30% in children, 50% in adults), microscopic hematuria (20% in children, 33% in adults), atopy or allergic symptoms (40% in children, 30% in adults), and decreased renal function (<5% in children, 30% in adults). The appearance of acute renal failure in adults is often seen more commonly in patients with low serum albumin and intrarenal edema (nephrosarca) that is responsive to intravenous albumin and diuretics. This presentation must be distinguished from acute renal failure secondary to hypovolemia. Acute tubular necrosis and interstitial inflammation is also reported. In children, the abnormal urine principally contains albumin with minimal amounts of higher-molecular-weight proteins, and is sometimes called *selective proteinuria*. Although up to 30% of children have a spontaneous remission, all children today are treated with steroids; only children who are nonresponders are biopsied in this setting. Primary responders are patients who have a complete remission (<0.2 mg/24 h of proteinuria) after a single course of prednisone; steroid-dependent patients relapse as their steroid dose is tapered. Frequent relapsers have two or more relapses in the 6 months following taper, and steroid-resistant patients fail to respond to steroid therapy. Adults are not considered steroid resistant until after 4 months of therapy. Ninety to 95% of children will develop a complete remission after 8 weeks of steroid therapy, and 80–85% of adults will achieve complete remission, but only after a longer course of 20–24 weeks. Patients with steroid resistance may have FSGS on repeat biopsy. Some hypothesize that if the first renal biopsy does not have a sample of deeper corticomedullary glomeruli, then the correct early diagnosis of FSGS may be missed.

Relapses occur in 70–75% of children after the first remission, and early relapse predicts multiple subsequent relapses. The frequency of relapses decreases after puberty, although there is an increased risk of relapse following the rapid tapering of steroids in all groups. Relapses are less common in adults but are more resistant to subsequent therapy. Prednisone is first-line therapy, either given daily or on alternate days. Other immunosuppressive drugs and such as cyclophosphamide, chlorambucil, and mycophenolate mofetil, are saved for frequent relapsers and steroid-dependent or steroid-resistant patients. Cyclosporine can induce remission, but relapse is also common when cyclosporine is withdrawn. The long-term prognosis in adults is less favorable when acute renal failure or steroid resistance occurs.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Focal segmental glomerulosclerosis (FSGS) refers to a pattern of renal injury characterized by segmental glomerular scars that involve some but not all glomeruli; the clinical findings of FSGS largely manifest as proteinuria. When the secondary causes of FSGS are eliminated **(Table 15-5)**, the remaining patients are considered to have primary FSGS. The incidence of this disease is increasing, and it now represents up to one-third of cases of nephrotic syndrome in adults and one-half of cases of nephrotic syndrome in African Americans, in whom it is seen more commonly. The pathogenesis of FSGS is probably multifactorial. Possible mechanisms include a T-cell–mediated circulating permeability factor, TGF-β–mediated cellular proliferation and matrix synthesis, and podocyte abnormalities associated with genetic mutations. Risk polymorphisms at the *APOL1* locus encoding apolipoprotein L1 expressed in podocytes substantially explain

TABLE 15-5

FOCAL SEGMENTAL GLOMERULOSCLEROSIS
Primary focal segmental glomerulosclerosis
Secondary focal segmental glomerulosclerosis
Viruses: HIV/hepatitis B/parvovirus
Hypertensive nephropathy
Reflux nephropathy
Cholesterol emboli
Drugs: heroin/analgesics/pamidronate
Oligomeganephronia
Renal dysgenesis
Alport's syndrome
Sickle cell disease
Lymphoma
Radiation nephritis
Familial podocytopathies
NPHS1 mutation/nephrin
NPHS2 mutation/podocin
TRPC6 mutation/cation channel
ACTN4 mutation/actinin
α-Galactosidase A deficiency/Fabry's disease
N-acetylneuraminic acid hydrolase deficiency/ nephrosialidosis

the increased burden of FSGS among African Americans with or without HIV-associated disease.

The pathologic changes of FSGS are most prominent in glomeruli located at the corticomedullary junction (Fig. 4-2), so if the renal biopsy specimen is from superficial tissue, the lesions can be missed, which sometimes leads to a misdiagnosis of MCD. In addition to focal and segmental scarring, other variants have been described, including cellular lesions with *endocapillary hypercellularity* and heavy proteinuria; *collapsing glomerulopathy* (Fig. 4-3) with segmental or global glomerular collapse and a rapid decline in renal function; a hilar stalk lesion (Fig. 4-4) or the *glomerular tip lesion* (Fig. 4-5), which may have a better prognosis. (See Glomerular Schematic 5.)

FSGS can present with hematuria, hypertension, any level of proteinuria, or renal insufficiency. Nephrotic-range proteinuria, African-American race, and renal insufficiency are associated with a poor outcome, with 50% of patients reaching renal failure in 6–8 years. FSGS rarely remits spontaneously, but treatment-induced remission of proteinuria significantly improves prognosis. Treatment of patients with *primary FSGS* should include inhibitors of the renin-angiotensin system. Based on retrospective studies, patients with nephrotic-range proteinuria can be treated with steroids but respond far less often and after a longer course of therapy than patients with MCD. Proteinuria remits in only 20–45% of patients receiving a course of steroids over 6–9 months. Limited evidence suggests that the use of cyclosporine in steroid-responsive patients helps ensure remissions. Relapse frequently occurs after cessation of cyclosporine therapy, and cyclosporine itself can lead to a deterioration of renal function due to its nephrotoxic effects. A role for other agents that suppress the immune system has not been established. Primary FSGS recurs in 25–40% of patients given allografts at end-stage disease, leading to graft loss in half of those cases. The treatment of *secondary FSGS* typically involves treating the underlying cause and controlling proteinuria. There is no role for steroids or other immunosuppressive agents in secondary FSGS.

MEMBRANOUS GLOMERULONEPHRITIS

Membranous glomerulonephritis (MGN), or *membranous nephropathy* as it is sometimes called, accounts for approximately 30% of cases of nephrotic syndrome in

Glomerular Schematic 5

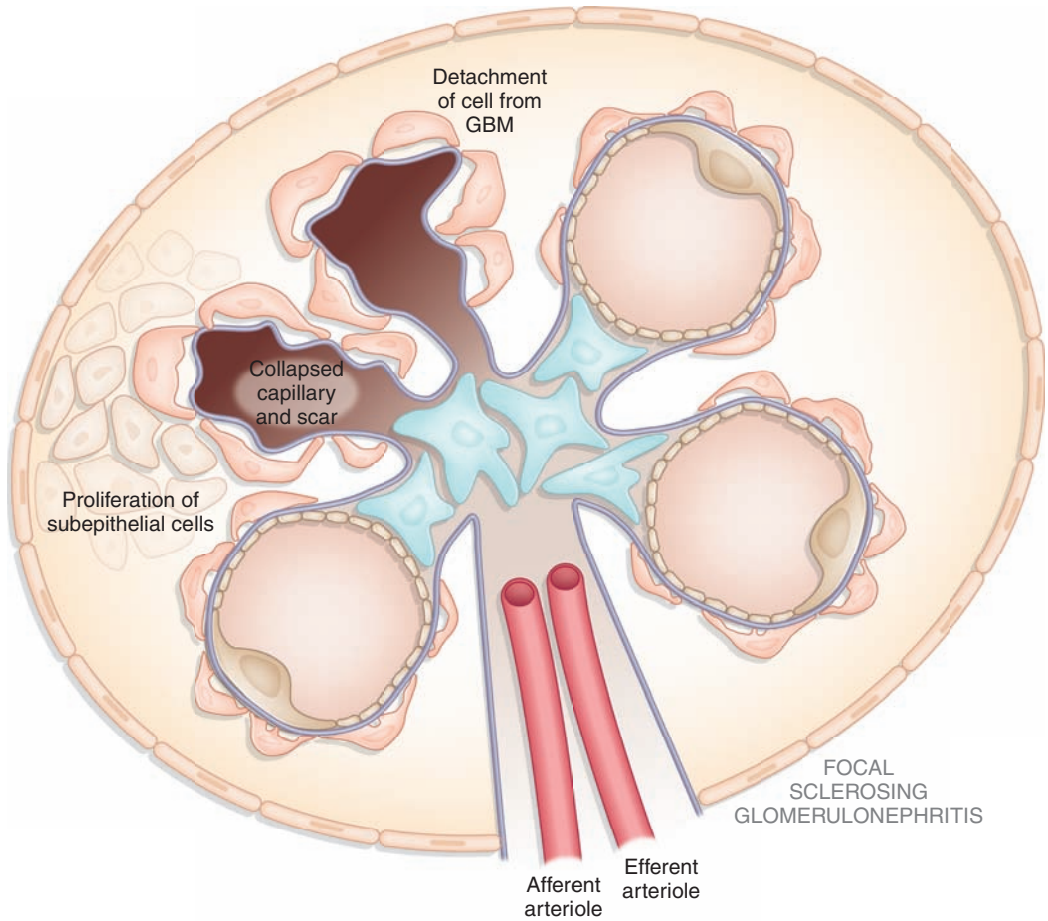


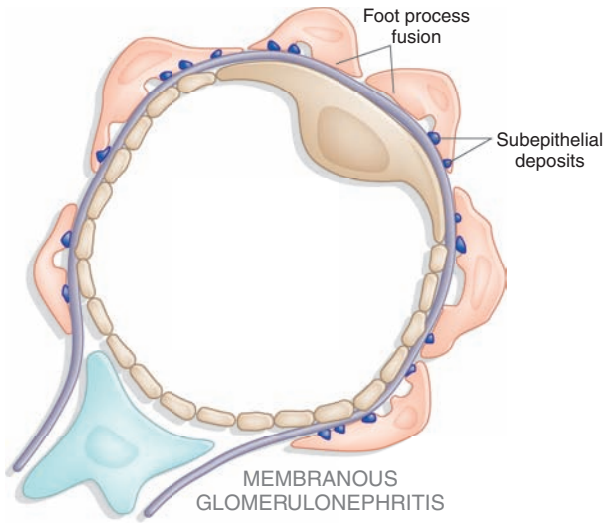
TABLE 15-6

MEMBRANOUS GLOMERULONEPHRITIS
Primary/idiopathic membranous glomerulonephritis
Secondary membranous glomerulonephritis
Infection: hepatitis B and C, syphilis, malaria, schistosomiasis, leprosy, filariasis
Cancer: breast, colon, lung, stomach, kidney, esophagus, neuroblastoma
Drugs: gold, mercury, penicillamine, nonsteroidal anti-inflammatory agents, probenecid
Autoimmune diseases: systemic lupus erythematosus, rheumatoid arthritis, primary biliary cirrhosis, dermatitis herpetiformis, bullous pemphigoid, myasthenia gravis, Sjögren's syndrome, Hashimoto's thyroiditis
Other systemic diseases: Fanconi's syndrome, sickle cell anemia, diabetes, Crohn's disease, sarcoidosis, Guillain-Barré syndrome, Weber-Christian disease, angiofollicular lymph node hyperplasia

adults, with a peak incidence between the ages of 30 and 50 years and a male to female ratio of 2:1. It is rare in childhood and the most common cause of nephrotic syndrome in the elderly. In 25–30% of cases, MGN is associated with a malignancy (solid tumors of the breast, lung, colon), infection (hepatitis B, malaria, schistosomiasis), or rheumatologic disorders like lupus or rarely rheumatoid arthritis **(Table 15-6)**.

Uniform thickening of the basement membrane along the peripheral capillary loops is seen by light microscopy on renal biopsy (Fig. 4-7); this thickening needs to be distinguished from that seen in diabetes and amyloidosis. (See Glomerular Schematic 6.) Immunofluorescence demonstrates diffuse granular deposits of IgG and C_3, and electron microscopy typically reveals electron-dense subepithelial deposits.

Glomerular Schematic 6



While different stages (I–V) of progressive membranous lesions have been described, some published analyses indicate that the degree of tubular atrophy or interstitial fibrosis is more predictive of progression than is the stage of glomerular disease. The presence of subendothelial deposits or the presence of tubuloreticular inclusions strongly points to a diagnosis of membranous lupus nephritis, which may precede the extrarenal manifestations of lupus. Work in Heyman nephritis, an animal model of MGN, suggests that glomerular lesions result from in situ formation of immune complexes with megalin receptor–associated protein as the putative antigen. This antigen is not found in human podocytes, but human antibodies have been described against neutral endopeptidase expressed by podocytes, hepatitis antigens B/C, *Helicobacter pylori* antigens, and tumor antigens. In a newer study, autoantibodies against the M-type phospholipase A_2 receptor (PLA_2R) circulate and bind to a conformational epitope present in the receptor on human podocytes, producing in situ deposits characteristic of idiopathic membranous nephropathy. Other renal diseases and secondary membranous nephropathy do not appear to involve such autoantibodies. Eighty percent of patients with MGN present with nephrotic syndrome and nonselective proteinuria. Microscopic hematuria is seen in up to 50% of patients but is seen less commonly than in IgA nephropathy or FSGS. Spontaneous remissions occur in 20–33% of patients and often occur late in the course after years of nephrotic syndrome, which make treatment decisions difficult. One-third of patients continue to have relapsing nephrotic syndrome but maintain normal renal function, and approximately another third of patients develop renal failure or die from the complications of nephrotic syndrome. Male gender, older age, hypertension, and the persistence of proteinuria are associated with worse prognosis. Although thrombotic complications are a feature of all nephrotic syndromes, MGN has the highest reported incidences of renal vein thrombosis, pulmonary embolism, and deep vein thrombosis. Prophylactic anticoagulation is controversial but has been recommended for patients with severe or prolonged proteinuria in the absence of risk factors for bleeding.

In addition to the treatment of edema, dyslipidemia, and hypertension, inhibition of the renin-angiotensin system is recommended. Therapy with immunosuppressive drugs is also recommended for patients with primary MGN and persistent proteinuria (>3.0 g/24 h). The choice of immunosuppressive drugs for therapy is controversial, but current recommendations based on small clinical studies are to treat with steroids and cyclophosphamide, chlorambucil, mycophenolate mofetil, or cyclosporine. In patients who relapse or fail to respond to this therapy there are case reports of beneficial effects

with the use of rituximab, an anti-CD20 antibody directed at B cells, or with synthetic adrenocorticotropic hormone.

DIABETIC NEPHROPATHY

Diabetic nephropathy is the single most common cause of chronic renal failure in the United States, accounting for 45% of patients receiving renal replacement therapy, and is a rapidly growing problem worldwide. The dramatic increase in the number of patients with diabetic nephropathy reflects the epidemic increase in obesity, metabolic syndrome, and type 2 diabetes mellitus. Approximately 40% of patients with type 1 or 2 diabetes develop nephropathy, but due to the higher prevalence of type 2 diabetes (90%) compared to type 1 (10%), the majority of patients with diabetic nephropathy have type 2 disease. Renal lesions are more common in African-American, Native American, Polynesian, and Maori populations. Risk factors for the development of diabetic nephropathy include hyperglycemia, hypertension, dyslipidemia, smoking, a family history of diabetic nephropathy, and gene polymorphisms affecting the activity of the renin-angiotensin-aldosterone axis.

Within 1–2 years after the onset of clinical diabetes, morphologic changes appear in the kidney. Thickening of the GBM is a sensitive indicator for the presence of diabetes but correlates poorly with the presence or absence of clinically significant nephropathy. The composition of the GBM is altered notably with a loss of heparan sulfate moieties that form the negatively charged filtration barrier. This change results in increased filtration of serum proteins into the urine, predominantly negatively charged albumin. The expansion of the mesangium due to the accumulation of extracellular matrix correlates with the clinical manifestations of diabetic nephropathy (see stages in Fig. 4-20). This expansion in mesangial matrix is associated with the development of *mesangial sclerosis*. Some patients also develop eosinophilic, PAS+ nodules called *nodular glomerulosclerosis* or *Kimmelstiel-Wilson nodules*. Immunofluorescence microscopy often reveals the nonspecific deposition of IgG (at times in a linear pattern) or complement staining without immune deposits on electron microscopy. Prominent vascular changes are frequently seen with hyaline and hypertensive arteriosclerosis. This is associated with varying degrees of chronic glomerulosclerosis and tubulointerstitial changes. Renal biopsies from patients with type 1 or 2 diabetes are largely indistinguishable.

These pathologic changes are the result of a number of postulated factors. Multiple lines of evidence support an important role for increases in glomerular capillary pressure (intraglomerular hypertension) in alterations in renal structure and function. Direct effects of hyperglycemia on the actin cytoskeleton of renal mesangial and vascular smooth-muscle cells as well as diabetes-associated changes in circulating factors such as atrial natriuretic factor, angiotensin II, and insulin-like growth factor (IGF) may account for this. Sustained glomerular hypertension increases matrix production, alterations in the GBM with disruption in the filtration barrier (and hence proteinuria), and glomerulosclerosis. A number of factors have also been identified that alter matrix production, including the accumulation of advanced glycosylation end products, circulating factors including growth hormone, IGF-I, angiotensin II, connective tissue growth factor, TGF-β, and dyslipidemia.

The natural history of diabetic nephropathy in patients with type 1 or 2 diabetes is similar. However, since the onset of type 1 diabetes is readily identifiable and the onset of type 2 diabetes is not, a patient newly diagnosed with type 2 diabetes may have renal disease for many years before nephropathy is discovered and presents as *advanced diabetic nephropathy*. At the onset of diabetes, renal hypertrophy and glomerular hyperfiltration are present. The degree of glomerular hyperfiltration correlates with the subsequent risk of clinically significant nephropathy. In the approximately 40% of patients with diabetes who develop diabetic nephropathy, the earliest manifestation is an increase in albuminuria detected by sensitive radioimmunoassay (Table 15-1). Albuminuria in the range of 30–300 mg/24 h is called *microalbuminuria*. In patients with types 1 or 2 diabetes, microalbuminuria appears 5–10 years after the onset of diabetes. It is currently recommended to test patients with type 1 disease for microalbuminuria 5 years after diagnosis of diabetes and yearly thereafter, and, because the time of onset of type 2 diabetes is often unknown, to test type 2 patients at the time of diagnosis of diabetes and yearly thereafter.

Patients with small rises in albuminuria increase their levels of urinary albumin excretion, typically reaching dipstick-positive levels of proteinuria (>300 mg albuminuria) 5–10 years after the onset of early albuminuria. Microalbuminuria is a potent risk factor for cardiovascular events and death in patients with type 2 diabetes. Many patients with type 2 diabetes and microalbuminuria succumb to cardiovascular events before they progress to proteinuria or renal failure. Proteinuria in frank diabetic nephropathy can be variable, ranging from 500 mg to 25 g/24 h, and is often associated with nephrotic syndrome. More than 90% of patients with type 1 diabetes and nephropathy have diabetic retinopathy, so the absence of retinopathy in type 1 patients with proteinuria should prompt consideration of a diagnosis other than diabetic nephropathy; only 60% of patients with type 2 diabetes with nephropathy have diabetic retinopathy. There is a highly significant correlation between the presence of retinopathy and the presence of Kimmelstiel-Wilson nodules (Fig. 4-20). Also, characteristically, patients with advanced diabetic nephropathy

have normal to enlarged kidneys, in contrast to other glomerular diseases where kidney size is usually decreased. Using the above epidemiologic and clinical data, and in the absence of other clinical or serologic data suggesting another disease, diabetic nephropathy is usually diagnosed without a renal biopsy. After the onset of proteinuria, renal function inexorably declines, with 50% of patients reaching renal failure over another 5–10 years; thus, from the earliest stages of microalbuminuria, it usually takes 10–20 years to reach end-stage renal disease. Hypertension may predict which patients develop diabetic nephropathy, as the presence of hypertension accelerates the rate of decline in renal function. Once renal failure appears, however, survival on dialysis is far shorter for patients with diabetes compared to other dialysis patients. Survival is best for patients with type 1 diabetes who receive a transplant from a living related donor.

Good evidence supports the benefits of blood sugar and blood pressure control as well as inhibition of the renin-angiotensin system in retarding the progression of diabetic nephropathy. In patients with type 1 diabetes, intensive control of blood sugar clearly prevents the development or progression of diabetic nephropathy. The evidence for benefit of intensive blood glucose control in patients with type 2 diabetes is less certain, with current studies reporting conflicting results. Some, but not all, trials have reported increased mortality rate associated with intensive blood glucose control, and the safety of $HgbA_1C$ goals less than 7% in patients with type 2 diabetes is currently unclear.

Controlling systemic blood pressure decreases renal and cardiovascular adverse events in this high-risk population. The vast majority of patients with diabetic nephropathy require three or more antihypertensive drugs to achieve this goal. Drugs that inhibit the renin-angiotensin system, independent of their effects on systemic blood pressure, have been shown in numerous large clinical trials to slow the progression of diabetic nephropathy at early (microalbuminuria) and late (proteinuria with reduced glomerular filtration) stages, independent of any effect they may have on systemic blood pressure. Since angiotensin II increases efferent arteriolar resistance, and hence glomerular capillary pressure, one key mechanism for the efficacy of ACE inhibitors or angiotensin receptor blockers (ARBs) is reducing glomerular hypertension. Patients with type 1 diabetes for 5 years who develop albuminuria or declining renal function should be treated with ACE inhibitors. Patients with type 2 diabetes and microalbuminuria or proteinuria may be treated with ACE inhibitors or ARBs. Less compelling evidence supports therapy with a combination of two drugs (ACE inhibitors, ARBs, renin inhibitors, or aldosterone antagonists) that suppress several components of the renin-angiotensin system.

GLOMERULAR DEPOSITION DISEASES

Plasma cell dyscrasias producing excess light chain immunoglobulin sometimes lead to the formation of glomerular and tubular deposits that cause heavy proteinuria and renal failure; the same is true for the accumulation of serum amyloid A protein fragments seen in several inflammatory diseases. This broad group of proteinuric patients have *glomerular deposition disease*.

Light chain deposition disease

The biochemical characteristics of nephrotoxic light chains produced in patients with light chain malignancies often confer a specific pattern of renal injury; that of either cast *nephropathy* (Fig. 4-17), which causes renal failure but not heavy proteinuria or amyloidosis, or light chain deposition disease (Fig. 4-16), which produces nephrotic syndrome with renal failure. These latter patients produce kappa light chains that do not have the biochemical features necessary to form amyloid fibrils. Instead, they self-aggregate and form granular deposits along the glomerular capillary and mesangium, tubular basement membrane, and Bowman's capsule. When predominant in glomeruli, nephrotic syndrome develops, and about 70% of patients progress to dialysis. Light chain deposits are not fibrillar and do not stain with Congo red, but they are easily detected with anti–light chain antibody using immunofluorescence or as granular deposits on electron microscopy. A combination of the light chain rearrangement, self-aggregating properties at neutral pH, and abnormal metabolism probably contribute to the deposition. Treatment for light chain deposition disease is treatment of the primary disease. As so many patients with light chain deposition disease progress to renal failure, the overall prognosis is grim.

Renal amyloidosis

Most *renal amyloidosis* is either the result of primary fibrillar deposits of immunoglobulin light chains known as amyloid L (AL) or secondary to fibrillar deposits of serum amyloid A (AA) protein fragments. Even though both occur for different reasons, their clinicopathophysiology is quite similar and will be discussed together. Amyloid infiltrates the liver, heart, peripheral nerves, carpal tunnel, upper pharynx, and kidney, producing restrictive cardiomyopathy, hepatomegaly, macroglossia, and heavy proteinuria sometimes associated with renal vein thrombosis. In systemic AL amyloidosis, also called *primary amyloidosis*, light chains produced in excess by clonal plasma cell dyscrasias are made into fragments by macrophages so they can self-aggregate at acid pH. A disproportionate number of these light chains (75%) are of the *lambda* class. About 10% of these patients have overt myeloma with lytic bone lesions

and infiltration of the bone marrow with >30% plasma cells; nephrotic syndrome is common, and about 20% of patients progress to dialysis. AA amyloidosis is sometimes called *secondary amyloidosis* and also presents as nephrotic syndrome. It is due to deposition of β-pleated sheets of serum amyloid A protein, an acute phase reactant whose physiologic functions include cholesterol transport, immune cell attraction, and metalloprotease activation. Forty percent of patients with AA amyloid have rheumatoid arthritis, and another 10% have ankylosing spondylitis or psoriatic arthritis; the rest derive from other lesser causes. Less common in Western countries but more common in Mediterranean regions, particularly in Sephardic and Iraqi Jews, is familial Mediterranean fever (FMF). FMF is caused by a mutation in the gene encoding pyrin, while Muckle-Wells syndrome, a related disorder, results from a mutation in cryopyrin; both proteins are important in the apoptosis of leukocytes early in inflammation; such proteins with pyrin domains are part of a new pathway called the *inflammasome*. Receptor mutations in tumor necrosis factor receptor 1 (TNFR1)-associated periodic syndrome also produce chronic inflammation and secondary amyloidosis. Fragments of serum amyloid A protein increase and self-aggregate by attaching to receptors for advanced glycation end products in the extracellular environment; nephrotic syndrome is common, and about 40–60% of patients progress to dialysis. AA and AL amyloid fibrils are detectable with Congo red or in more detail with electron microscopy (Fig. 4-15). Currently developed serum free light chain nephelometry assays are useful in the early diagnosis and follow-up of disease progression. Biopsy of involved liver or kidney is diagnostic 90% of the time when the pretest probability is high; abdominal fat pad aspirates are positive about 70% of the time, but apparently less so when looking for AA amyloid. Amyloid deposits are distributed along blood vessels and in the mesangial regions of the kidney. The treatment for primary amyloidosis is not particularly effective; melphalan and autologous hematopoietic stem cell transplantation can delay the course of disease in about 30% of patients. Secondary amyloidosis is also relentless unless the primary disease can be controlled. Some new drugs in development that disrupt the formation of fibrils may be available in the future.

Fibrillary-immunotactoid glomerulopathy

Fibrillary-immunotactoid glomerulopathy is a rare (<1.0% of renal biopsies) morphologically defined disease characterized by glomerular accumulation of nonbranching randomly arranged fibrils. Some classify amyloid and nonamyloid fibril-associated renal disease all as fibrillary glomerulopathies with immunotactoid glomerulopathy reserved for nonamyloid fibrillary disease not associated with a systemic illness. Others define fibrillary glomerulonephritis as a nonamyloid fibrillary disease with fibrils 12–24 nm and immunotactoid glomerulonephritis with fibrils >30 nm. In either case, fibrillar/microtubular deposits of oligoclonal or oligotypic immunoglobulins and complement appear in the mesangium and along the glomerular capillary wall. Congo red stains are negative. The cause of this "nonamyloid" glomerulopathy is mostly idiopathic; reports of immunotactoid glomerulonephritis describe an occasional association with chronic lymphocytic leukemia or B-cell lymphoma. Both disorders appear in adults in the fourth decade with moderate to heavy proteinuria, hematuria, and a wide variety of histologic lesions, including DPGN, MPGN, MGN, or mesangioproliferative glomerulonephritis. Nearly half of patients develop renal failure over a few years. There is no consensus on treatment of this uncommon disorder. The disease has been reported to recur following renal transplantation in a minority of cases.

FABRY'S DISEASE

Fabry's disease is an X-linked inborn error of globotriaosylceramide metabolism secondary to deficient lysosomal α-galactosidase A activity, resulting in excessive intracellular storage of globotriaosylceramide. Affected organs include the vascular endothelium, heart, brain, and kidneys. Classically, Fabry's disease presents in childhood in males with acroparesthesias, angiokeratoma, and hypohidrosis. Over time male patients develop cardiomyopathy, cerebrovascular disease, and renal injury, with an average age of death around 50 years of age. Hemizygotes with hypomorphic mutations sometimes present in the fourth to sixth decade with single-organ involvement. Rarely, dominant-negative α-galactosidase A mutations or female heterozygotes with unfavorable X inactivation present with mild single-organ involvement. Rare females develop severe manifestations including renal failure but do so later in life than males. Renal biopsy reveals enlarged glomerular visceral epithelial cells packed with small clear vacuoles containing globotriaosylceramide; vacuoles may also be found in parietal and tubular epithelia (Fig. 4-18). These vacuoles of electron-dense materials in parallel arrays (zebra bodies) are easily seen on electron microscopy. Ultimately, renal biopsies reveal FSGS. The nephropathy of Fabry's disease typically presents in the third decade as mild to moderate proteinuria, sometimes with microscopic hematuria or nephrotic syndrome. Urinalysis may reveal oval fat bodies and birefringent glycolipid globules under polarized light (Maltese cross). Renal biopsy is necessary for definitive diagnosis. Progression to renal failure occurs by the fourth or fifth decade. Treatment with inhibitors of the renin-angiotensin system is recommended. Treatment with recombinant α-galactosidase A clears microvascular endothelial deposits of globotriaosylceramide from the

kidneys, heart, and skin. The degree of organ involvement at the time when enzyme replacement is initiated is crucial. In patients with advanced organ involvement, progression of disease occurs despite enzyme replacement therapy. Variable responses to enzyme therapy may be due to the occurrence of neutralizing antibodies or differences in uptake of the enzyme. Graft and patient survival following renal transplantation in patients with Fabry's are similar to other causes of end-stage renal disease.

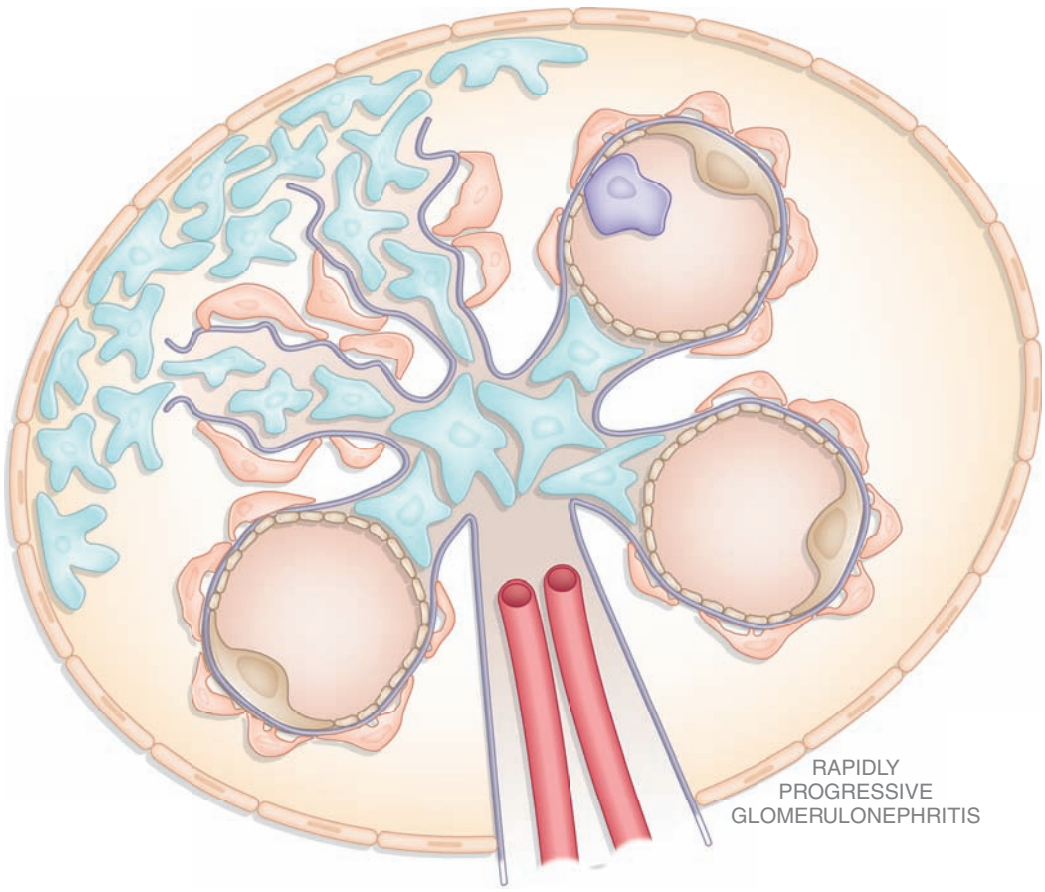
PULMONARY-RENAL SYNDROMES

Several diseases can present with catastrophic hemoptysis and glomerulonephritis associated with varying degrees of renal failure. The usual causes include Goodpasture's syndrome, granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis, Churg-Strauss vasculitis, and, rarely, Henoch-Schönlein purpura or cryoglobulinemia. Each of these diseases can also present without hemoptysis and are discussed in detail in the section "Acute Nephritic Syndromes." (See Glomerular Schematic 7.) Pulmonary bleeding in this setting is life threatening and often results in airway intubation, and acute renal failure requires dialysis. Diagnosis is difficult initially because biopsies and serologic testing take time. Treatment with plasmapheresis and methylprednisolone is often empirical and temporizing until results of testing are available.

BASEMENT MEMBRANE SYNDROMES

All kidney epithelia, including podocytes, rest on basement membranes assembled into a planar surface through the interweaving of collagen IV with laminins, nidogen, and sulfated proteoglycans. Structural abnormalities in GBM associated with hematuria are characteristic of several familial disorders related to the expression of collagen IV genes. The extended family of collagen IV contains six chains, which are expressed in different tissues at different stages of embryonic development. All epithelial basement membranes early in human development are composed of interconnected triple-helical protomers rich in $\alpha1.\alpha1.\alpha2$(IV) collagen. Some specialized tissues undergo a developmental switch replacing $\alpha1.\alpha1.\alpha2$(IV) protomers with an $\alpha3.\alpha4.\alpha5$(IV) collagen network; this switch occurs in the kidney (glomerular and tubular basement membrane), lung, testis, cochlea, and eye, while an $\alpha5.\alpha5.\alpha6$(IV) network appears in skin, smooth muscle, and esophagus and along Bowman's capsule in the

Glomerular Schematic 7



kidney. This switch probably occurs because the α3.α4.α5(IV) network is more resistant to proteases and ensures the structural longevity of critical tissues. When basement membranes are the target of glomerular disease, they produce moderate proteinuria, some hematuria, and progressive renal failure.

ANTI-GBM DISEASE

Autoimmune disease where antibodies are directed against the α3 NC1 domain of collagen IV produces an *anti-GBM disease* often associated with RPGN and/or a pulmonary-renal syndrome called *Goodpasture's syndrome*. Discussion of this disease is covered in the section "Acute Nephritic Syndromes."

ALPORT'S SYNDROME

Classically, patients with Alport's syndrome develop hematuria, thinning and splitting of the GBMs, and mild proteinuria (<1–2 g/24 h), which appears late in the course, followed by chronic glomerulosclerosis leading to renal failure in association with sensorineural deafness. Some patients develop lenticonus of the anterior lens capsule, "dot and fleck" retinopathy, and, rarely, mental retardation or leiomyomatosis. Approximately 85% of patients with Alport's syndrome have an X-linked inheritance of mutations in the α5(IV) collagen chain on chromosome Xq22–24. Female carriers have variable penetrance depending on the type of mutation or the degree of mosaicism created by X inactivation. Fifteen percent of patients have autosomal recessive disease of the α3(IV) or α4(IV) chains on chromosome 2q35–37. Rarely, some kindred have an autosomal dominant inheritance of dominant-negative mutations in α3(IV) or α4(IV) chains.

Pedigrees with the X-linked syndrome are quite variable in their rate and frequency of tissue damage leading to organ failure. Seventy percent of patients have the juvenile form with nonsense or missense mutations, reading frame shifts, or large deletions and generally develop renal failure and sensorineural deafness by age 30. Patients with splice variants, exon skipping, or missense mutations of α-helical glycines generally deteriorate after the age of 30 (adult form) with mild or late deafness. Early severe deafness, lenticonus, or proteinuria suggests a poorer prognosis. Usually females from X-linked pedigrees have only microhematuria, but up to 25% of carrier females have been reported to have more severe renal manifestations. Pedigrees with the autosomal recessive form of the disease have severe early disease in both females and males with asymptomatic parents.

Clinical evaluation should include a careful eye examination and hearing tests. However, the absence of extrarenal symptoms does not rule out the diagnosis. Since α5(IV) collagen is expressed in the skin, some X-linked Alport patients can be diagnosed with a skin biopsy revealing the lack of the α5(IV) collagen chain on immunofluorescent analysis. Other patients with suspected disease require a renal biopsy. Alport's patients early in their disease typically have thin basement membranes on renal biopsy (Fig. 4-19), which thicken over time into multilamellations surrounding lucent areas that often contain granules of varying density—the so-called split basement membrane. In any Alport kidney there are areas of thinning mixed with splitting of the GBM. Tubules drop out, glomeruli scar, and the kidney eventually succumbs to interstitial fibrosis. Primary treatment is control of systemic hypertension and use of ACE inhibitors to slow renal progression. Although patients who receive renal allografts usually develop anti-GBM antibodies directed toward the collagen epitopes absent in their native kidney, overt Goodpasture's syndrome is rare and graft survival is good.

THIN BASEMENT MEMBRANE DISEASE

Thin basement membrane disease (TBMD) characterized by persistent or recurrent hematuria is not typically associated with proteinuria, hypertension, or loss of renal function or extrarenal disease. Although not all cases are familial (perhaps a founder effect), it usually presents in childhood in multiple family members and is also called *benign familial hematuria*. Cases of TBMD have genetic defects in type IV collagen, but in contrast to Alport behave as an autosomal dominant disorder that in ~40% of families segregates with the *COL(IV) α3/COL(IV) α4* loci. Mutations in these loci can result in a spectrum of disease ranging from TBMD to autosomal dominant or recessive Alport's. The GBM shows diffuse thinning compared to normal values for the patient's age in otherwise normal biopsies (Fig. 4-19). The vast majority of patients have a benign course.

NAIL-PATELLA SYNDROME

Patients with nail-patella syndrome develop iliac horns on the pelvis and dysplasia of the dorsal limbs involving the patella, elbows, and nails, variably associated with neural-sensory hearing impairment, glaucoma, and abnormalities of the GBM and podocytes, leading to hematuria, proteinuria, and FSGS. The syndrome is autosomal dominant, with haploinsufficiency for the *LIM* homeodomain transcription factor LMX1B; pedigrees are extremely variable in the penetrance for all features of the disease. LMX1B regulates the expression of genes encoding α3 and α4 chains of collagen IV, interstitial type III collagen, podocin, and CD2AP that help form the slit-pore membranes connecting podocytes. Mutations in the LIM domain region of *LMX1B*

associate with glomerulopathy, and renal failure appears in as many as 30% of patients. Proteinuria or isolated hematuria is discovered throughout life, but usually by the third decade, and is inexplicably more common in females. On renal biopsy there is lucent damage to the lamina densa of the GBM, an increase in collagen III fibrils along glomerular capillaries and in the mesangium, and damage to the slit-pore membrane, producing heavy proteinuria not unlike that seen in congenital nephrotic syndrome. Patients with renal failure do well with transplantation.

GLOMERULAR-VASCULAR SYNDROMES

A variety of diseases result in classic vascular injury to the glomerular capillaries. Most of these processes also damage blood vessels elsewhere in the body. The group of diseases discussed here lead to vasculitis, renal endothelial injury, thrombosis, ischemia, and/or lipid-based occlusions.

ATHEROSCLEROTIC NEPHROPATHY

Aging in the developed world is commonly associated with the occlusion of coronary and systemic blood vessels. The reasons for this include obesity, insulin resistance, smoking, hypertension, and diets rich in lipids that deposit in the arterial and arteriolar circulation, producing local inflammation and fibrosis of small blood vessels. When the renal arterial circulation is involved, the glomerular microcirculation is damaged, leading to *chronic nephrosclerosis*. Patients with GFRs <60 mL/min have more cardiovascular events and hospitalizations than those with higher filtration rates. Several aggressive lipid disorders can accelerate this process, but most of the time atherosclerotic progression to chronic nephrosclerosis is associated with poorly controlled hypertension. Approximately 10% of glomeruli are normally sclerotic by age 40, rising to 20% by age 60 and 30% by age 80. Serum lipid profiles in humans are greatly affected by *apolipoprotein E* polymorphisms; the E4 allele is accompanied by increases in serum cholesterol and is more closely associated with atherogenic profiles in patients with renal failure. Mutations in E2 alleles, particularly in Japanese patients, produce a specific renal abnormality called *lipoprotein glomerulopathy* associated with glomerular lipoprotein thrombi and capillary dilation.

HYPERTENSIVE NEPHROSCLEROSIS

Uncontrolled systemic hypertension causes permanent damage to the kidneys in about 6% of patients with elevated blood pressure. As many as 27% of patients with end-stage kidney disease have hypertension as a primary cause. Although there is not a clear correlation between the extent or duration of hypertension and the risk of end-organ damage, *hypertensive nephrosclerosis* is fivefold more frequent in African Americans than whites. Risk alleles associated with *APOL1*, a functional gene for apolipoprotein L1 expressed in podocytes, substantially explains the increased burden of end-stage renal disease among African Americans. Associated risk factors for progression to end-stage kidney disease include age, sex, race, smoking, hypercholesterolemia, duration of hypertension, low birth weight, and preexisting renal injury. Kidney biopsies in patients with hypertension, microhematuria, and moderate proteinuria demonstrate arteriolosclerosis, chronic nephrosclerosis, and interstitial fibrosis in the absence of immune deposits (Fig. 4-21). Today, based on a careful history, physical examination, urinalysis, and some serologic testing, the diagnosis of chronic nephrosclerosis is usually inferred without a biopsy. Treating hypertension is the best way to avoid progressive renal failure; most guidelines recommend lowering blood pressure to <130/80 mmHg if there is preexisting diabetes or kidney disease. In the presence of kidney disease, most patients begin therapy with two drugs, classically a thiazide diuretic and an ACE inhibitor; most will require three drugs. There is strong evidence in African Americans with hypertensive nephrosclerosis that therapy initiated with an ACE inhibitor can slow the rate of decline in renal function independent of effects on systemic blood pressure. Malignant acceleration of hypertension complicates the course of chronic nephrosclerosis, particularly in the setting of scleroderma or cocaine use (Fig. 4-24). The hemodynamic stress of malignant hypertension leads to fibrinoid necrosis of small blood vessels, thrombotic microangiography, a nephritic urinalysis, and acute renal failure. In the setting of renal failure, chest pain, or papilledema, the condition is treated as a hypertensive emergency. Slightly lowering the blood pressure often produces an immediate reduction in GFR that improves as the vascular injury attenuates and autoregulation of blood vessel tone is restored.

CHOLESTEROL EMBOLI

Aging patients with clinical complications from atherosclerosis sometimes shower cholesterol crystals into the circulation—either spontaneously or, more commonly, following an endovascular procedure with manipulation of the aorta—or with use of systemic anticoagulation. Spontaneous emboli may shower acutely or shower subacutely and somewhat more silently. Irregular emboli trapped in the microcirculation produce ischemic damage that induces an inflammatory reaction. Depending on the location of the atherosclerotic plaques releasing these cholesterol fragments, one may

see cerebral transient ischemic attacks; livedo reticularis in the lower extremities; Hollenhorst plaques in the retina with visual field cuts; necrosis of the toes; and acute glomerular capillary injury leading to *focal segmental glomerulosclerosis* sometimes associated with hematuria, mild proteinuria, and loss of renal function, which typically progresses over a few years. Occasional patients have fever, eosinophilia, or eosinophiluria. A skin biopsy of an involved area may be diagnostic. Since tissue fixation dissolves the cholesterol, one typically sees only residual, biconvex clefts in involved vessels (Fig. 4-22). There is no therapy to reverse embolic occlusions, and steroids do not help. Controlling blood pressure and lipids and cessation of smoking are usually recommended for prevention.

SICKLE CELL DISEASE

Although individuals with SA-hemoglobin are usually asymptomatic, most will gradually develop hyposthenuria due to subclinical infarction of the renal medulla, thus predisposing them to volume depletion; interestingly, there is an unexpectedly high prevalence of sickle trait among dialysis patients who are African American. Patients with homozygous SS-sickle cell disease develop chronic vasoocclusive disease in many organs. Polymers of deoxygenated SS-hemoglobin distort the shape of red blood cells. These cells attach to endothelia and obstruct small blood vessels, producing frequent, random, and painful sickle cell crises over time. Vessel occlusions in the kidney produce glomerular hypertension, FSGS, interstitial nephritis, and renal infarction associated with hyposthenuria, microscopic hematuria, and even gross hematuria; some patients also present with MPGN. By the second or third decade of life, persistent vasoocclusive disease in the kidney leads to varying degrees of renal failure, and some patients end up on dialysis. Treatment is directed to reducing the frequency of painful crises and administering ACE inhibitors in the hope of delaying a progressive decline in renal function. In sickle cell patients undergoing renal transplantation, renal graft survival is comparable to that of African Americans in the general transplant population.

THROMBOTIC MICROANGIOPATHIES

Thrombotic thrombocytopenic purpura (TTP) and *hemolytic-uremic syndrome* (HUS) represent a spectrum of thrombotic microangiopathies. Thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome share the general features of idiopathic thrombocytopenic purpura, hemolytic anemia, fever, renal failure, and neurologic disturbances. When patients, particularly children, have more evidence of renal injury, their condition tends to be called HUS. In adults with neurologic disease, it is considered to be TTP. In adults there is often a mixture of both, which is why they are often called TTP/HUS. On examination of kidney tissue there is evidence of *glomerular capillary endotheliosis* associated with platelet thrombi, damage to the capillary wall, and formation of fibrin material in and around glomeruli (Fig. 4-23). These tissue findings are similar to what is seen in preeclampsia/HELLP (hemolysis, elevated liver enzymes, and low platelet count syndrome), malignant hypertension, and the antiphospholipid syndrome. Thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome is also seen in pregnancy; with the use of oral contraceptives or quinine; in renal transplant patients given OKT3 for rejection; in patients taking the calcineurin inhibitors, cyclosporine and tacrolimus, or in patients taking the antiplatelet agents, ticlopidine and clopidogrel; or following HIV infection.

Although there is no agreement on how much they share a final common pathophysiology, two general groups of patients are recognized: childhood HUS associated with enterohemorrhagic diarrhea and TTP/HUS in adults. Childhood HUS is caused by a toxin released by *Escherichia coli* 0157:H7 and occasionally by *Shigella dysenteriae*. This shiga toxin (verotoxin) directly injures endothelia, enterocytes, and renal cells, causing apoptosis, platelet clumping, and intravascular hemolysis by binding to the glycolipid receptors (Gb3). These receptors are more abundant along endothelia in children compared to adults. Shiga toxin also inhibits the endothelial production of ADAMTS13. In familial cases of adult TTP/HUS, there is a genetic deficiency of the ADAMTS13 metalloprotease that cleaves large multimers of von Willebrand's factor. Absent ADAMTS13, these large multimers cause platelet clumping and intravascular hemolysis. An antibody to ADAMTS13 is found in many sporadic cases of adult TTP/HUS, but not all; many patients also have antibodies to the thrombospondin receptor on selected endothelial cells in small vessels or increased levels of plasminogen-activator inhibitor 1 (PAI-1). Some children with complement protein deficiencies express atypical HUS (aHUS), which can be treated with liver transplant. The treatment of adult TTP/HUS is daily plasmapheresis, which can be lifesaving. Plasmapheresis is given until the platelet count rises, but in relapsing patients it normally is continued well after the platelet count improves, and in resistant patients twice-daily exchange may be helpful. Most patients respond within 2 weeks of daily plasmapheresis. Since TTP/HUS often has an autoimmune basis, there is an anecdotal role in relapsing patients for using splenectomy, steroids, immunosuppressive drugs, or rituximab, an anti-CD20 antibody. Patients with childhood HUS from infectious diarrhea are not given antibiotics, as antibiotics are thought to accelerate the release of the toxin and the diarrhea is usually self-limited. No intervention appears superior to supportive therapy in children with postdiarrheal HUS.

INFECTIOUS DISEASE–ASSOCIATED SYNDROMES

A number of infectious diseases will injure the glomerular capillaries as part of a systemic reaction producing an immune response or from direct infection of renal tissue. Evidence of this immune response is collected by glomeruli in the form of immune deposits that damage the kidney, producing moderate proteinuria and hematuria. Some of these infectious diseases represent the most common causes of glomerulonephritis in many parts of the world.

POST-STREPTOCOCCAL GLOMERULONEPHRITIS

This form of glomerulonephritis is one of the classic complications of streptococcal infection. The discussion of this disease can be found in the section "Acute Nephritic Syndromes."

SUBACUTE BACTERIAL ENDOCARDITIS

Renal injury from persistent bacteremia absent the continued presence of a foreign body, regardless of cause, is treated presumptively as if the patient has endocarditis. The discussion of this disease can be found in the section "Acute Nephritic Syndromes."

HUMAN IMMUNODEFICIENCY VIRUS

Renal disease is an important complication of HIV disease. The risk of development of end-stage renal disease is much higher in HIV-infected African Americans than in HIV-infected whites. About 50% of HIV-infected patients with kidney disease have HIV-associated nephropathy (HIVAN) on biopsy. The lesion in HIVAN is FSGS, characteristically revealing a collapsing glomerulopathy (Fig. 4-3) with visceral epithelial cell swelling, microcystic dilatation of renal tubules, and tubuloreticular inclusion. Renal epithelial cells express replicating HIV virus, but host immune responses also play a role in the pathogenesis. MPGN and DPGN have also been reported but more commonly in HIV-infected whites and in patients coinfected with hepatitis B or C. HIV-associated TTP has also been reported. Other renal lesions include DPGN, IgA nephropathy, and MCD. Renal biopsy may be indicated to distinguish between these lesions.

HIV patients with FSGS typically present with nephrotic-range proteinuria and hypoalbuminemia, but unlike patients with other etiologies for nephrotic syndrome, they do not commonly have hypertension, edema, or hyperlipidemia. Renal ultrasound also reveals large, echogenic kidneys despite the finding that renal function in some patients declines rapidly. Treatment with inhibitors of the renin-angiotensin system decreases the proteinuria. Effective antiretroviral therapy benefits both the patient and the kidney and improves survival of HIV-infected patient with chronic kidney disease (CKD) or end-stage renal disease. In HIV-infected patients not yet on therapy, the presence of HIVAN is an indication to initiate therapy. Following the introduction of antiretroviral therapy, survival on dialysis for HIV-infected patients has improved dramatically and is equivalent in patients treated with hemodialysis or peritoneal dialysis. Renal transplants in HIV-infected patients without detectable viral loads or histories of opportunistic infections have a better survival benefit over dialysis. Following transplantation, patient and graft survival are similar to that in the general transplant population despite frequent rejections.

HEPATITIS B AND C

Typically, infected patients present with microscopic hematuria, nonnephrotic or nephrotic-range proteinuria, and hypertension. There is a close association between hepatitis B infection and polyarteritis nodosa, with vasculitis appearing generally in the first 6 months following infection. Renal manifestations include renal artery aneurysms, renal infarction, and ischemic scars. Alternatively, the hepatitis B carrier state can produce an MGN that is more common in children than adults, or MPGN that is more common in adults than in children. Renal histology is indistinguishable from idiopathic MGN or type I MPGN. Viral antigens are found in the renal deposits. There are no good treatment guidelines, but interferon α-2b and lamivudine have been used to some effect in small studies. Children have a good prognosis, with 60–65% achieving spontaneous remission within 4 years. In contrast, 30% of adults have renal insufficiency and 10% have renal failure 5 years after diagnosis.

Up to 30% of patients with chronic hepatitis C infection have some renal manifestations. Patients often present with type II mixed cryoglobulinemia, nephrotic syndrome, microscopic hematuria, abnormal liver function tests, depressed C_3 levels, anti–hepatitis C virus (HCV) antibodies, and viral RNA in the blood. The renal lesions most commonly seen, in order of decreasing frequency, are *cryoglobulinemic glomerulonephritis*, *MGN*, and *type I MPGN*. Treatment with pegylated interferon and ribavirin is typical to reduce the viral load.

OTHER VIRUSES

Other viral infections are occasionally associated with glomerular lesions, but cause and effect are not well established. These viral infections and their respective glomerular lesions include cytomegalovirus producing MPGN; influenza and anti-GBM disease;

measles-associated endocapillary proliferative glomerulonephritis, with measles antigen in the capillary loops and mesangium; parvovirus causing mild proliferative or mesangioproliferative glomerulonephritis or FSGS; mumps and mesangioproliferative glomerulonephritis; Epstein-Barr virus producing MPGN, diffuse proliferative nephritis, or IgA nephropathy; dengue hemorrhagic fever causing endocapillary proliferative glomerulonephritis; and coxsackievirus producing *focal glomerulonephritis* or DPGN.

SYPHILIS

Secondary syphilis, with rash and constitutional symptoms, develops weeks to months after the chancre first appears and occasionally presents with the nephrotic syndrome from MGN caused by subepithelial immune deposits containing treponemal antigens. Other lesions have also rarely been described including interstitial syphilitic nephritis. The diagnosis is confirmed with nontreponemal and treponemal tests for *Treponema pallidum*. The renal lesion responds to treatment with penicillin or an alternative drug, if allergic. Additional testing for other sexually transmitted diseases is an important part of disease management.

LEPROSY

Despite aggressive eradication programs, approximately 400,000 new cases of leprosy appear annually worldwide. The diagnosis is best made in patients with multiple skin lesions accompanied by sensory loss in affected areas using skin smears showing paucibacillary or multibacillary infection (WHO criteria). Leprosy is caused by infection with *Mycobacterium leprae* and can be classified by Ridley-Jopling criteria into various types: tuberculoid, borderline tuberculoid, mid-borderline and borderline lepromatous, and lepromatous. Renal involvement in leprosy is related to the quantity of bacilli in the body, and the kidney is one of the target organs during splanchnic localization. In some series, all cases with borderline lepromatous and lepromatous types of leprosy have various forms of renal involvement including FSGS, mesangioproliferative glomerulonephritis, or renal amyloidosis; much less common are the renal lesions of DPGN and MPGN. Treatment with dapsone, rifampicin, and clofazimine can eradicate the infection in nearly all patients.

MALARIA

There are 300–500 million incident cases of malaria each year worldwide, and the kidney is commonly involved. Glomerulonephritis is due to immune complexes containing malarial antigens that are implanted in the glomerulus. In malaria from *P. falciparum,* mild proteinuria is associated with subendothelial deposits, mesangial deposits, and mesangioproliferative glomerulonephritis that usually resolve with treatment. In quartan malaria from infection with *P. malariae*, children are more commonly affected and renal involvement is more severe. Transient proteinuria and microscopic hematuria can resolve with treatment of the infection. However, resistant nephrotic syndrome with progression to renal failure over 3–5 years does happen, as <50% of patients respond to steroid therapy. Affected patients with nephrotic syndrome have thickening of the glomerular capillary walls, with subendothelial deposits of IgG, IgM, and C_3 associated with a sparse membranoproliferative lesion. The rare mesangioproliferative glomerulonephritis reported with *P. vivax* or *P. ovale* typically has a benign course.

SCHISTOSOMIASIS

Schistosomiasis affects more than 300 million people worldwide and primarily involves the urinary and gastrointestinal tracts. Glomerular involvement varies with the specific strain of schistosomiasis; *Schistosoma mansoni* is most commonly associated with clinical renal disease, and the glomerular lesions can be classified: Class I is a *mesangioproliferative glomerulonephritis*; class II is an *extracapillary proliferative glomerulonephritis*; class III is a *membranoproliferative glomerulonephritis*; class IV is a *focal segmental glomerulonephritis*; and class V lesions have *amyloidosis*. Classes I–II often remit with treatment of the infection, but classes III and IV lesions are associated with IgA immune deposits and progress despite antiparasitic and/or immunosuppressive therapy.

OTHER PARASITES

Renal involvement with toxoplasmosis infections is rare. When it occurs, patients present with nephrotic syndrome and have a histologic picture of MPGN. Fifty percent of patients with leishmaniasis will have mild to moderate proteinuria and microscopic hematuria, but renal insufficiency is rare. Acute DPGN, MGN, and mesangioproliferative glomerulonephritis have all been observed on biopsy. Filariasis and trichinosis are caused by nematodes and are sometimes associated with glomerular injury presenting with proteinuria, hematuria, and a variety of histologic lesions that typically resolve with eradication of the infection.

CHAPTER 16

POLYCYSTIC KIDNEY DISEASE AND OTHER INHERITED TUBULAR DISORDERS

David J. Salant ■ Craig E. Gordon

INTRODUCTION

The polycystic kidney diseases are among the most common life-threatening inherited diseases worldwide and frequently cause kidney failure. Autosomal dominant polycystic kidney disease (ADPKD) is seen predominantly in adults **(Fig. 16-1)**, whereas autosomal recessive polycystic kidney disease (ARPKD) is mainly a disease of childhood. Renal cysts also are seen in several other hereditary kidney diseases **(Table 16-1)**, some of which may have defects in a common signaling pathway with ADPKD and ARPKD. Other inherited tubular diseases manifest primarily with alterations in fluid, electrolyte, acid-base, and mineral balance **(Table 16-2)**.

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Etiology and pathogenesis

ADPKD is a systemic disorder resulting from mutations in either the *PKD-1* or the *PKD-2* gene. The *PKD-1*-encoded protein, polycystin-1, is a large receptor-like molecule, whereas the *PKD-2* gene product, polycystin-2, has features of a calcium channel protein. Both are transmembrane proteins that are present throughout all segments of the nephron. They have been localized to the luminal surface of tubular cells in primary cilia, where they appear to serve as flow sensors; on the basal surface in focal adhesion complexes; and on the lateral surface in adherens junctions. The proteins are thought to function independently, or as a complex, to regulate fetal and adult epithelial cell gene transcription, apoptosis, differentiation, and cell-matrix interactions. Disruption of these processes leads to epithelial dedifferentiation, unregulated proliferation and apoptosis, altered cell polarity, disorganization of surrounding extracellular matrix, excessive fluid secretion, and abnormal expression of several genes, including some that encode growth factors. Vasopressin-mediated elevation of cyclic AMP levels in cyst epithelia plays a major role in cystogenesis by stimulating cell proliferation and fluid secretion into the cyst lumen through apical chloride and aquaporin channels. Cyst formation begins in utero from any point along the nephron, although <5% of total nephrons are thought to be involved. As the cysts accumulate fluid, they enlarge, separate entirely from the nephron, compress the neighboring renal parenchyma, and progressively compromise renal function.

GENETIC CONSIDERATIONS

ADPKD occurs in 1:400–1:1000 individuals worldwide and accounts for ~4% of end-stage renal disease (ESRD) in the United States. ADPKD is equally prevalent in all ethnic and racial groups. Over 90% of cases are inherited as an autosomal dominant trait, with the remainder probably representing spontaneous mutations. Mutations in the *PKD-1* gene on chromosome 16 (ADPKD-1) account for 85% of cases, and mutations in the *PKD-2* gene on chromosome 4 (ADPKD-2) account for the remainder. A few families appear to have a defect at a site that is different from either of these loci. Direct mutation analysis of isolated cysts suggests that there is loss of heterozygosity, whereby a somatic mutation in the normal allele of a small number of tubular epithelial cells leads to unregulated clonal proliferation of the cells that ultimately form the cyst lining.

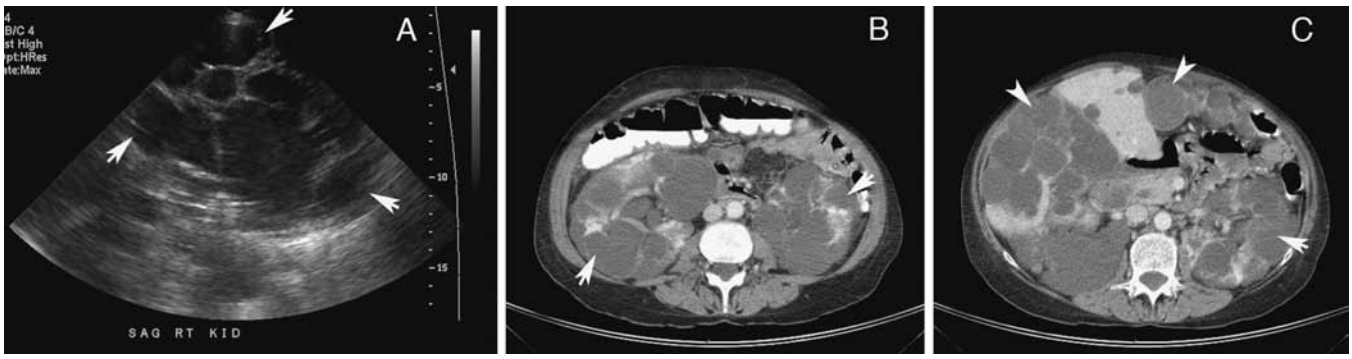


FIGURE 16-1

Renal ultrasonogram and contrast-enhanced abdominal CT scan in a 56-year-old woman with autosomal dominant polycystic kidney disease. ***A***. Sonogram of the right kidney showing numerous cysts of varying sizes (*arrows*). ***B***. Abdominal CT scan demonstrating bilaterally enlarged kidneys with large cysts (*arrows*). ***C***. Multiple liver cysts (*arrowheads*) and renal cysts (*arrow*) are seen in an upper abdominal image.

Clinical features

Phenotypic heterogeneity is a hallmark of ADPKD, as evidenced by family members who have the same mutation but have a different clinical course. Affected individuals are often asymptomatic into the fourth or fifth decade. Presenting symptoms and signs include abdominal discomfort, hematuria, urinary tract infection, incidental discovery of hypertension, abdominal masses, elevated serum creatinine, and cystic kidneys on imaging studies (Fig. 16-1*A* and *B*). Frequently, the diagnosis is made before the onset of symptoms, when asymptomatic members in affected families request screening. In most patients, renal function declines progressively over the course of 10–20 years from the time of diagnosis, but not everyone with ADPKD develops ESRD; it occurs in about 60% of these patients by age 70. Those with ADPKD-2 tend to have later onset and slower progression. Hypertension is common and often precedes renal dysfunction, perhaps mediated by increased activity of the renin-angiotensin system. There is only mild proteinuria, and impaired urinary concentrating ability manifests early as polyuria and nocturia. Risk factors for progressive kidney disease include younger age at diagnosis, black race, male sex, presence of polycystin-1 mutation, and hypertension. There is a close correlation between the rate of kidney expansion, as measured by magnetic resonance imaging (MRI) scanning, and the rate of decline in kidney function. Dull, persistent flank and abdominal pain and early satiety are common due to the mass effect of the enlarged kidneys or liver. Cyst rupture or hemorrhage into a cyst may produce acute flank pain or symptoms and signs of localized peritonitis. Gross hematuria may result from cyst rupture into the collecting system or from uric acid or calcium oxalate kidney stones. Nephrolithiasis occurs in about 20% of patients. Urinary tract infection, including acute pyelonephritis, occurs with increased frequency in ADPKD. Infection in a kidney cyst is a particularly serious complication. It is most often due to gram-negative bacteria and presents with flank pain, fever, and chills. Blood cultures are frequently positive, but urine culture may be negative because infected kidney cysts do not communicate directly with the collecting system. Distinguishing between infection and cyst hemorrhage is often challenging, and the diagnosis relies mainly on clinical and bacteriologic findings. Radiologic and nuclear imaging studies are generally not helpful.

Numerous extrarenal manifestations of ADPKD highlight the systemic nature of the disease. Patients with ADPKD have a twofold to fourfold increased risk of subarachnoid or cerebral hemorrhage from a ruptured intracranial aneurysm compared with the general population. Saccular aneurysms of the anterior cerebral circulation may be detected in up to 10% of asymptomatic patients on magnetic resonance angiography (MRA) screening, but most are small, have a low risk of spontaneous rupture, and do not merit the risk of intervention. In general, hemorrhage tends to occur before age 50 years, in patients with a family history of intracranial hemorrhage, and in those who have survived a previous bleed, have aneurysms >10 mm, and have uncontrolled hypertension. Other vascular abnormalities include aortic root and annulus dilation. Cardiac valvular abnormalities occur in 25% of patients, most commonly mitral valve prolapse and aortic regurgitation. Although most valvular lesions are asymptomatic, some may progress over time and warrant valve replacement. The incidence of hepatic cysts is 83% by MRI in patients aged 15–46 years. Most patients are asymptomatic with normal liver function tests, but hepatic cysts may bleed, become infected, rupture, and cause pain. Although the frequency of liver cysts is equal between the sexes, women are more likely to have massive cysts (Fig. 16-1*C*). Colonic diverticulae are common, with a higher incidence of perforation

TABLE 16-1

INHERITED CYSTIC KIDNEY DISEASES

DISEASE (OMIM)	MODE OF INHERITANCE	LOCUS	GENE	PROTEIN	RENAL ABNORMALITIES	EXTRARENAL ABNORMALITIES
Autosomal dominant polycystic kidney disease (601313, 173910)	AD	16p13	*PKD1*	Polycystin-1	Cortical and medullary cysts	Cerebral aneurysms; liver cysts, other[a]
	AD	4q21	*PKD2*	Polycystin-2	Cortical and medullary cysts	Cerebral aneurysms; liver cysts, other[a]
Autosomal recessive polycystic kidney disease (263200)	AR	6p21	*PKHD1*	Fibrocystin (polyductin)	Distal tubule and collecting duct cysts	Hepatic fibrosis; Caroli's disease
Nephronophthisis I (juvenile/adolescent, 256100)[b]	AR	2q13	*NPHP1*	Nephrocystin	Small fibrotic kidneys; medullary cysts	Retinitis pigmentosa
Nephronophthisis II (infantile, 602088)[b]	AR	9q31	*NPHP2 (INVS)*	Inversin	Large kidneys; widespread cysts	Situs inversus
Nephronophthisis III (juvenile/adolescent, 604387)[b]	AR	3q22	*NPHP3*	Nephrocystin-3	Small fibrotic kidneys; medullary cysts	Retinitis pigmentosa; hepatic fibrosis
Medullary cystic kidney disease (174000, 603860)	AD	1q21	*MCKD1*	Unknown	Small fibrotic kidneys; medullary cysts	None
	AD	16p12	*MCKD2 (UMOD)*	Uromodulin (Tamm-Horsfall protein)	Small fibrotic kidneys; medullary cysts	Hyperuricemia and gout
Tuberous sclerosis (191100)	AD	9q34	*TSC1*	Hamartin	Renal cysts; angiomyolipomas; renal cell carcinoma	Facial angiofibromas; CNS hamartomas
	AD	16p13	*TSC2*	Tuberin	Renal cysts; angiomyolipomas; renal cell carcinoma	Facial angiofibromas; CNS hamartomas
Von Hippel-Lindau disease (608537)	AD	3p26-p25	*VHL*	pVHL	Renal cysts; renal cell carcinoma	Retinal angiomas; CNS hemangioblastomas; pheochromocytomas

[a]See text for details.
[b]The three variants of nephronophthisis listed are the most prevalent of the currently described 11 forms of nephronophthisis. Each variant has similar renal abnormalities but varying extrarenal phenotypes.
Abbreviations: AD, autosomal dominant; AR, autosomal recessive; OMIM, online Mendelian inheritance in man.

in patients with ADPKD. Abdominal wall and inguinal hernias also occur with a higher frequency than in the general population.

Diagnosis and screening

Most often, the diagnosis of ADPKD is made from a positive family history and imaging studies showing large kidneys with multiple bilateral cysts and possibly liver cysts (Fig. 16-1). Criteria for the diagnosis of ADPKD by ultrasonography in asymptomatic individuals account for the later onset of ADPKD-2 and assume that the genotype of the individual and family being tested is unknown. The presence of three or more cysts in one or both kidneys is required to diagnose ADPKD in patients aged 15–39 years with a specificity and positive predictive value of 100%; sensitivity varies from 82 to 96% for persons aged 15–29 and 30–39 years, respectively. The presence of two or more cysts in each kidney is associated with a sensitivity and specificity of 90% and 100%, respectively, in patients aged 40–59 years. In subjects older than 60 years, the presence of four or more cysts in each kidney is required to diagnose ADPKD because of the increased frequency of benign simple cysts,

TABLE 16-2

INHERITED TUBULAR DISORDERS

DISEASE (OMIM)	MODE OF INHERITANCE	LOCUS	GENE	PROTEIN	RENAL ABNORMALITIES	EXTRARENAL ABNORMALITIES
Bartter's syndrome						
Type 1 (601678)	AR	15q15	*SLC12A1*	NKCC2	Salt wasting; hypokalemia	
Type 2 (241200)	AR	11q24	*KCNJ1*	ROMK	Salt wasting; hypokalemia	
Type 3 (607364)	AR	1p36	*ClCNKb*	CLC-Kb	Salt wasting; hypokalemia	
Type 4 (602023)	AR	1p31	*BSND*	Barttin	Salt wasting; hypokalemia	Sensorineural deafness
Type 5 (601199)	AD	3q13	*CASR*	CASR	Salt wasting; hypokalemia	
Gitelman's syndrome (263800)	AR	16q13	*SLC12A3*	NCCT	Salt wasting; hypokalemia; hypomagnesemia	
Pseudohypoaldosteronism type I (264350, 177735)	AR	16p13 16p13 12p13	*SCNN1B* *SCNN1G* *SCNN1A*	α, β, or γ subunit of ENaC	Hyperkalemia; salt wasting	Increased lung secretions and lung infections
	AD	4q31	*NR3C2*	Mineralocorticoid receptor (type I)	Hyperkalemia; salt wasting	
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) (248250, 248190)	AR	3q27 1p34	*CLDN16* *CLDN19*	Claudin 16 Claudin 19	Hypomagnesemia; nephrocalcinosis	Ocular abnormalities (claudin 19 defect only)
Hypomagnesemia with secondary hypocalcemia (HSH) (602014)	AR	9q22	*TRPM6*	TRPM6	Hypomagnesemia; hypocalcemia	
Autosomal dominant hypomagnesemia (154020)	AD	11q23	*FXYD2*	γ subunit of basolateral Na/K-ATPase of DCT	Hypomagnesemia; hypocalciuria	
Autosomal dominant hypoparathyroidism (601199)	AD	3q13	*CASR*	CASR	Hypocalcemia; hypercalciuria; hypomagnesemia	
Isolated autosomal recessive hypomagnesemia (611718)	AR	4q25	*EGF*	EGF	Hypomagnesemia	
Liddle's syndrome (177200)	AD	16p13	*SCNN1B* *SCNN1G*	β and γ subunits of ENaC	Hypertension; hypokalemia; alkalosis	
Pseudohypoaldosteronism type II (Gordon's syndrome, 145260)	AD	12p13 17q21	*WNK1* *WNK4*	WNK 1 WNK 4	Hypertension; hyperkalemia	
Nephrogenic DI type 1 (304800)	XL	Xq28	*AVPR2*	AVPR2	Renal concentrating defect	
Nephrogenic DI type 2 (125800)	AR, AD	12q13	*AQP2*	AQP2	Renal concentrating defect	

(*continued*)

TABLE 16-2

INHERITED TUBULAR DISORDERS (*CONTINUED*)

DISEASE (OMIM)	MODE OF INHERITANCE	LOCUS	GENE	PROTEIN	RENAL ABNORMALITIES	EXTRARENAL ABNORMALITIES
Nephrogenic syndrome of inappropriate antidiuresis (300539)	XL	Xq28	*AVPR2*	AVPR2	Hyponatremia	
Distal renal tubular acidosis (267300, 602722, 259730, 179800)	AR	2cenq13 7q33	*ATP6V1B1* *ATP6VOA4*	H^+-ATPase (B1) H^+-ATPase (α4)	Hyperchloremic metabolic acidosis; nephrocalcinosis	Sensorineural deafness (B1 defect only); growth retardation
	AR	8q22	*CA2*	CA2	Proximal and distal RTA	Osteopetrosis, short stature, mental retardation
	AD	17q21	*SLC4A1*	AE1	Distal RTA	
Proximal renal tubular acidosis (604278)	AR	4q21	*SLC4A4*	NBC-1	Moderate hyperchloremic metabolic acidosis	Glaucoma; band keratopathy
Cystinuria (220100)	AR	2p16 19q13	*SLC3A1* *SLC7A9*	rBAT$b^{o,+}$AT1	Cystine stones; dibasic aminoaciduria	
Hartnup disease (234500)	AR	5p15	*SLC6A19*	B^oAT1	Neutral aminoaciduria	Dermatitis, ataxia; dementia
Dent's disease (300009)	XL	Xp11	*CLCN5*	CLC-5	Fanconi syndrome; nephrocalcinosis	Osteomalacia; rickets
Cystinosis (219800)	AR	17p13	*CTNS*	Cystinosin	Fanconi syndrome; progressive kidney failure	Ocular, muscular, liver, gonadal, and thyroid involvement
Renal glucosuria (233100)	AR	16p11	*SLC5A2*	SGLT2	Glucosuria	
Hereditary hypophosphatemic rickets with hypercalciuria (HHRH, 241530)	AR	9q34	*SLC34A3*	Sodium-phosphate co-transporter	Hypophosphatemia; hypercalciuria	Rickets
Vitamin D–dependent rickets type I (VDDR I, 264700)	AR	12q14.1	*CYP27B1*	25-vitamin D_3-1-α-hydroxylase	Hypocalcemia	Rickets

Abbreviations: AD, autosomal dominant; AE1, anion exchanger 1; AR, autosomal recessive; AT1, amino acid transporter; AVPR2, arginine vasopressin receptor 2; CA2, carbonic anhydrase II; CASR, calcium-sensing receptor; CLC-5, chloride channel 5; CLC-Kb, chloride channel Kb; DI, diabetes insipidus; ENaC, amiloride-sensitive epithelial sodium channel; NBC, sodium-bicarbonate co-transporter; NCCT, thiazide-sensitive Na-Cl co-transporter; NKCC2, Na-K-2Cl co-transporter; OMIM, online Mendelian inheritance in man; rBAT, renal basic amino acid transport glycoprotein; ROMK, renal outer medullary potassium channel; SGLT2, sodium/glucose co-transporter;TRPM6, transient receptor potential cation channel, subfamily M, member 6; WNK, with no lysine (K); XL, X-linked.

whereas fewer than two renal cysts in at-risk individuals aged ≥40 years is sufficient to exclude the disease. Computed tomography (CT) scan and T2-weighted MRI are more sensitive for detecting presymptomatic disease in young patients. Genetic linkage analysis and mutational screening for *ADPKD-1* and *ADPKD-2* is available for equivocal cases, especially when a young adult from an affected family is being considered as a potential kidney donor. Genetic counseling is essential for those being screened. Screening for asymptomatic intracranial aneurysms should be restricted to patients with a personal or family history of intracranial hemorrhage and those in high-risk occupations. Intervention should be limited to aneurysms larger than 10 mm.

TREATMENT **Autosomal Dominant Polycystic Kidney Disease**

No treatment has been proved to prevent cyst growth or the decline in kidney function. Hypertension control with a target blood pressure of 130/80 mmHg or less is recommended according to Joint National Committee (JNC) VII guidelines. A multidrug approach that includes agents to inhibit the renin-angiotensin system is frequently required. Studies are investigating the role of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in slowing growth of kidney volume and loss of glomerular filtration rate (GFR). Lipid-soluble antimicrobials such as trimethoprim-sulfamethoxazole and fluoroquinolones that have good cyst penetration are the preferred therapy for infected kidney and liver cysts. Pain management occasionally requires cyst drainage by percutaneous aspiration, sclerotherapy with alcohol, or, rarely, surgical drainage. Patients with ADPKD appear to have a survival advantage on either peritoneal dialysis or hemodialysis compared with patients with other causes of ESRD. Those undergoing kidney transplantation may require bilateral nephrectomy if the kidneys are massively enlarged or have been the site of infected cysts. Posttransplantation survival rates are similar to those of patients with other causes of kidney failure, but these patients remain at risk for the extrarenal complications of ADPKD. Studies in animal models of inherited cystic diseases have identified promising therapeutic strategies, including vasopressin V_2 receptor antagonists that suppress cyst growth by lowering intracellular cAMP, and inhibitors of cell dedifferentiation and proliferation that target the epidermal growth factor receptor tyrosine kinase and the mammalian target of rapamycin (mTOR). Clinical trials of these agents are ongoing.

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

Genetic Considerations

ARPKD is primarily a disease of infants and children. The incidence is 1:20,000 births. The kidneys are enlarged, with small cysts, <5 mm, limited to the collecting tubules. The ARPKD gene on chromosome 6p21, *PKHD1*, encodes several alternatively spliced transcripts (Table 16-1). The largest transcript produces a multidomain transmembrane protein termed *fibrocystin (polyductin)* that is found in the cortical and medullary collecting ducts and the thick ascending limb of Henle's loop in the kidney as well as in biliary and pancreatic duct epithelia. Like the polycystins, fibrocystin has receptor-like features and may be involved in cell-cell and cell-matrix interactions. Fibrocystin, the polycystins, and several proteins involved in animal models of PKD are located in association with primary cilia on the tubular epithelial cell apical surface; this suggests that they may cooperate in a mechanosensory pathway. A large number of different mutations have been identified throughout *PKHD1* and are unique to individual families. Most patients are compound heterozygotes. Those with two truncating mutations frequently die shortly after birth, whereas those who survive beyond the neonatal period generally have at least one missense mutation. Mutations in *PKHD1* have also been identified in about 30% of children with congenital hepatic fibrosis (Caroli's syndrome) without evident kidney involvement.

Clinical features

The clinical presentation of ARPKD is highly variable. Up to 50% of affected neonates die of pulmonary hypoplasia, the result of oligohydramnios from severe intrauterine kidney disease. About 80% of those who survive the neonatal period are still alive after 10 years; however, one-third will have developed ESRD. Enlarged kidneys may be detected soon after birth as bilateral abdominal masses. Impaired urinary concentrating ability and metabolic acidosis ensue as tubular function deteriorates. Hypertension often occurs in the first few years of life. Kidney function deteriorates progressively from childhood into early adult life. Longer-term survivors frequently develop complications of portal hypertension from periportal fibrosis.

Diagnosis

Ultrasonography reveals large, echogenic kidneys. The diagnosis can be made in utero after 24 weeks of gestation in severe cases, but cysts generally become visible only after birth. The absence of renal cysts in either parent on ultrasonography helps distinguish ARPKD from ADPKD in older patients. The wide range of different mutations and the large size of the gene complicate molecular diagnosis, although prenatal diagnosis is possible by gene linkage to the *PKHD1* locus in families with a previous confirmed ARPKD birth.

TREATMENT **Autosomal Recessive Polycystic Kidney Disease**

There is no specific therapy for ARPKD. Improvements in neonatal intensive care, blood pressure management, dialysis, and kidney transplantation have led to survival into adulthood. Complications of hepatic fibrosis may necessitate liver transplantation. Future therapies may target aberrant cell signaling mechanisms, as in ADPKD.

NEPHRONOPHTHISIS

Genetics and pathogenesis

Nephronophthisis (NPHP) is the most common genetic cause of ESRD in childhood and adolescence. Eleven distinct genetic mutations with autosomal recessive inheritance have been identified to date and produce different renal and extrarenal manifestations of NPHP (Table 16-1). Although their precise functions are unclear, the defective protein products, named nephrocystins and inversin, localize to the primary cilium and associated basal body of renal epithelial cells, similar to the polycystins and fibrocystin. NPHP is classified into infantile, juvenile, and adolescent forms based on the age of ESRD onset. In juvenile NPHP, the most common form, the kidneys are shrunken and histology shows tubular atrophy, thickening of tubular basement membranes, diffuse interstitial fibrosis, and microscopic medullary cysts. In the infantile form, the kidneys are large with histology similar to that of the juvenile form except that medullary cysts are more prominent and develop earlier.

Clinical features

In juvenile NPHP symptoms typically appear after 1 year of age. Impaired tubular function causes salt wasting and defective urinary concentration and acidification. Patients may present with polyuria, polydipsia, volume depletion, or systemic acidosis. Hypertension is usually absent due to salt wasting. Progressive kidney failure and volume depletion lead to growth retardation. On average, ESRD occurs by age 3 in the infantile form, age 13 in the juvenile form, and age 19 in the adolescent form. Up to 15% of patients with juvenile NPHP have extrarenal manifestations (Table 16-1), most commonly retinitis pigmentosa (Senior-Loken syndrome). Other abnormalities include blindness from amaurosis, oculomotor apraxia, cerebellar ataxia (Joubert syndrome), polydactyly, mental retardation, hepatic fibrosis, and ventricular septal defect. Situs inversus is seen in some cases of infantile NPHP, consistent with mutation in *INVS (NPHP2)*, a gene critical for left-right patterning in the embryo.

Diagnosis

The diagnosis of NPHP should be considered in patients with a family history of kidney disease, early-onset progressive renal failure, and a bland urine sediment with minimal proteinuria. Ultrasonography reveals small hyperechoic kidneys in juvenile NPHP and large kidneys with cysts in the infantile form.

TREATMENT **Nephronophthisis**

There is no specific therapy to prevent loss of kidney function in NPHP. Salt and water replacement are required for patients with salt wasting and polyuria. Therapy should include sodium bicarbonate or citrate for acidosis, management of chronic kidney disease, and timely institution of dialysis and kidney transplantation. NPHP does not recur in transplanted kidneys.

MEDULLARY CYSTIC KIDNEY DISEASE

Genetic Considerations

The medullary cystic kidney diseases (MCKDs) generally present in young adults. Two genetic loci have been defined, both with autosomal dominant transmission (Table 16-1). The locus for MCKD1 has been mapped to chromosome 1q21. Mutations in the uromodulin gene (*UMOD*) that encodes the Tamm-Horsfall mucoprotein on chromosome 16p12 have been identified in MCKD2.

Clinical features

As with NPHP, patients with MCKD have atrophic kidneys with diffuse interstitial fibrosis, cysts restricted to the renal medulla, salt wasting, and polyuria. Disease onset is later than in NPHP. Consequently, there is no growth retardation, salt wasting is milder, and ESRD occurs later, usually between ages 20 and 70. There are no extrarenal manifestations in MCKD1, but most patients with MCKD2 have severe hyperuricemia and precocious onset of gout.

Diagnosis

MCKD should be considered in young adults with a family history suggesting dominant inheritance of kidney disease who present with progressive renal failure, bland urinalysis with little or no proteinuria, and small, dense kidneys with medullary cysts on radiographic imaging. The presence of hyperuricemia and gout is a further clue to the diagnosis of MCKD2, which can be confirmed by mutation analysis of *UMOD*.

TREATMENT **Medullary Cystic Kidney Disease**

There is no specific therapy for MCKD. Allopurinol is indicated for patients with gout and is reasonable for those with asymptomatic hyperuricemia, although there is no evidence that it prevents progressive renal failure in MCKD2. Dialysis and transplantation outcomes appear to be favorable. The disease does not recur in transplanted kidneys.

TUBEROUS SCLEROSIS

Tuberous sclerosis (TS) is an autosomal dominant disorder that affects 1 in 6000 people. It results from mutations in either the *TSC1* gene encoding hamartin or the *TSC2* gene encoding tuberin (Table 16-1). Hamartin and tuberin form a complex that is thought to negatively regulate cell growth and proliferation through inhibition of mTOR. The presence of either mutation produces uncontrolled proliferation in numerous tissues, including the kidneys, skin, central nervous system, and heart. The kidneys are affected in 80% of patients. Renal TS occurs in three forms: renal angiomyolipomas, renal cysts, and renal cell carcinoma. Angiomyolipomas are the most common renal abnormality. They occur bilaterally, are often multiple, and are usually asymptomatic; however, they may cause spontaneous bleeding, flank pain, hematuria, and life-threatening retroperitoneal hemorrhage. Large lesions, >4 cm, are more likely to be symptomatic and may require transcatheter arterial embolization or surgical excision. Cysts are usually asymptomatic and are not evident on imaging studies until adulthood. Rarely, cysts may be large and numerous, sometimes leading to ESRD and producing a clinical scenario that can be confused with ADPKD, especially if there are few other systemic manifestations of TS. Multicentric renal cell carcinomas occur with increased frequency in TS. Patients with TS should be screened for renal involvement at initial diagnosis with ultrasonography or CT. Those with cysts or angiomyolipomas require regular imaging to monitor for the development of renal cell carcinoma.

VON HIPPEL-LINDAU DISEASE

Von Hippel-Lindau disease (VHL) is a rare autosomal dominant disease characterized by abnormal angiogenesis with benign and malignant tumors that affect multiple tissues. The disease is inherited as a mutation in one allele of the *VHL* tumor-suppressor gene. Somatic mutation of the normal allele leads to retinal angiomas, central nervous system (CNS) hemangioblastomas, pheochromocytomas and multicentric clear cell cysts, hemangiomas, and adenomas of the kidney. The kidneys are affected in three-quarters of patients, and half of these patients develop clear cell carcinomas in the renal cysts. It is noteworthy that *VHL* mutations also account for 60% of spontaneous clear cell carcinomas of the kidney. The mean age of diagnosis of renal cell carcinoma in VHL disease is 44 years, and 70% of patients who survive to age 60 develop renal cell carcinoma. The high risk of renal cell carcinoma mandates periodic surveillance (usually yearly in adults) by CT or MRI. Routine screening and awareness of the natural history of lesions has enabled renal-sparing approaches to disease management. Tumors <3 cm in size require careful monitoring for growth, whereas partial nephrectomy is indicated in those >3 cm in the absence of metastasis. Nonsurgical renal-sparing strategies, including percutaneous radio frequency ablation and selective arterial embolization, have shown promise in short-term trials.

MEDULLARY SPONGE KIDNEY

Pathology and clinical features

Medullary sponge kidney (MSK) is a relatively common benign condition of unknown cause characterized by ectasia of the papillary collecting ducts of one or both kidneys. Urinary stasis in the dilated ducts, hypocitraturia, and occasionally incomplete distal renal tubular acidosis (dRTA) contribute to the formation of small calcium-containing calculi. Most cases are asymptomatic or are discovered during investigation of hematuria. Symptomatic patients typically present as young adults with renal colic and nephrolithiasis or recurrent urinary tract infections; however, MSK also may affect children. Most cases are sporadic, although MSK has been found rarely in association with other congenital anomalies of the urinary tract and with congenital hepatic ductal ectasia (Caroli's disease).

Diagnosis

MSK is characteristically seen as hyperdense papillae with clusters of small stones on renal ultrasonography or abdominal x-ray **(Fig. 16-2)**. The classical "paintbrush-like" features of MSK, representing the ectatic collecting ducts, are best seen on intravenous urography. However, this procedure has been supplanted by contrast-enhanced, high-resolution helical CT with digital reconstruction (Fig. 16-2).

TREATMENT **Medullary Sponge Kidney**

No treatment is necessary in asymptomatic individuals, aside from maintaining high fluid intake to reduce the risk of nephrolithiasis. Recurrent stone formation should prompt a metabolic evaluation and treatment as in any stone former (Chap. 9). In patients with hypocitraturia and incomplete dRTA, treatment with potassium citrate helps prevent new stone formation. Urinary tract infections should be treated promptly.

HEREDITARY DISORDERS OF SODIUM, POTASSIUM, AND MAGNESIUM HANDLING WITHOUT HYPERTENSION

Inherited forms of hypochloremic metabolic alkalosis and hypokalemia without hypertension are due to genetic mutations of various ion transporters and

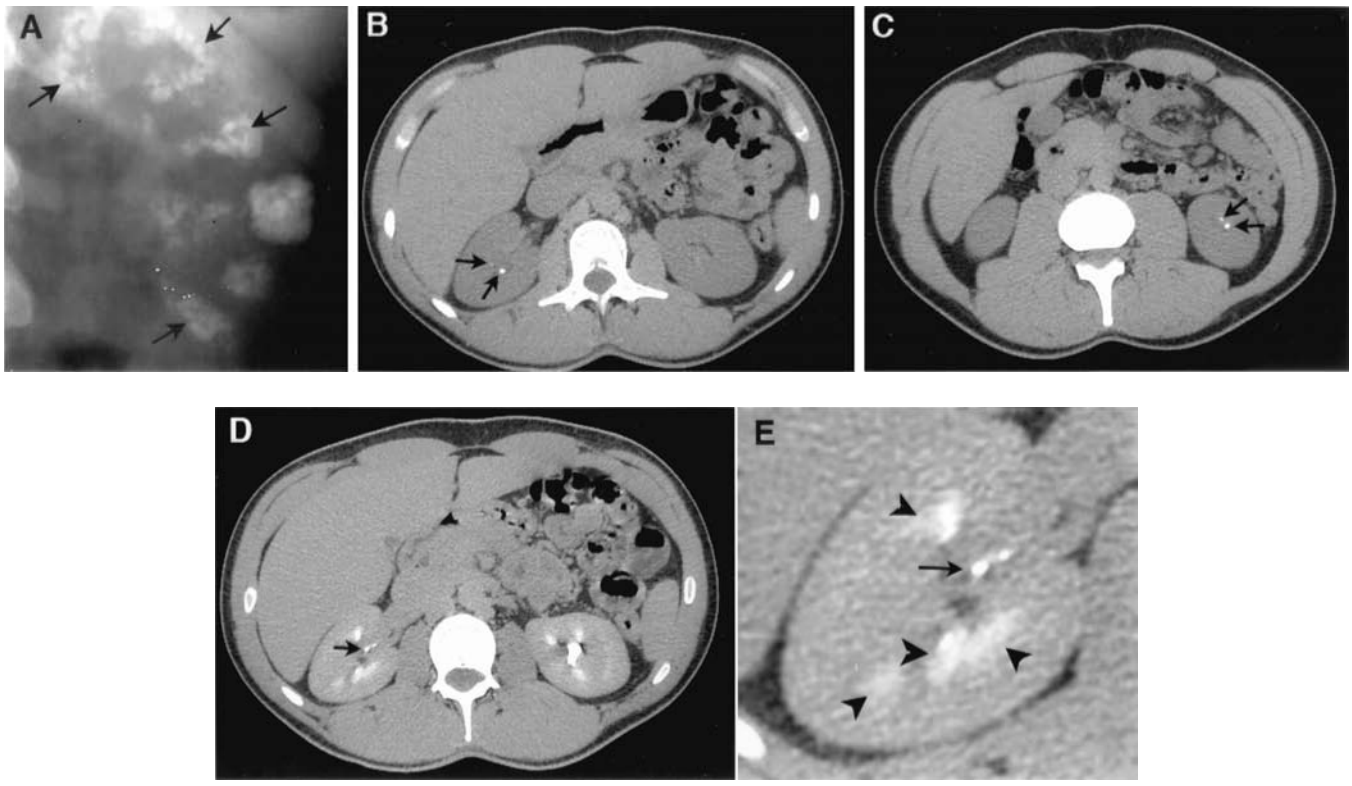


FIGURE 16-2

Radiographs of medullary sponge kidney disease. *A.* Plain x-ray film of a patient with a history of recurrent nephrolithiasis showing clusters of stones in the papillae (arrows). ***B–E.*** CT scan of an 18-year-old male patient investigated for persistent microscopic hematuria. ***B*** and ***C.*** CT without contrast showing a few small stones in the papillae (*arrows*). ***D*** and ***E.*** Contrast-enhanced CT of the same region shown in ***B.*** In addition to the stone (*arrow*), a blush of contrast is seen filling the ectatic collecting ducts (*arrowheads*).

channels of the thick ascending limb of Henle's loop (TAL) and distal convoluted tubule (DCT) (Table 16-2 and Fig. 16-3). In 1962 Bartter described two patients with a syndrome of metabolic alkalosis, hypovolemia, and failure to thrive associated with juxtaglomerular apparatus hyperplasia, hyperaldosteronism, and normal blood pressure. Subsequently, Gitelman identified a similar but milder syndrome accompanied by hypomagnesemia from urinary magnesium wasting and presenting in later childhood and adolescence. These disorders are now known to occur sporadically or result from genetically heterogeneous loss-of-function autosomal recessive mutations that cause salt-losing tubulopathy.

BARTTER'S SYNDROME AND GITELMAN'S SYNDROME

Genetics and pathogenesis

Bartter's syndrome may result from mutations affecting any of five ion transport proteins in the TAL. The proteins affected include the apical loop diuretic–sensitive sodium-potassium-chloride co-transporter NKCC2 (type 1), the apical potassium channel ROMK (type 2), and the basolateral chloride channel ClC-Kb (type 3). Bartter's type 4 results from mutations in barttin, an essential subunit of ClC-Ka and ClC-Kb that enables transport of the chloride channels to the cell surface. Barttin is also expressed in the inner ear; this accounts for the deafness invariably associated with Bartter's type 4. A Bartter-like phenotype (type 5) with associated hypocalcemia has been described in patients with autosomal dominant gain-of-function mutations in the extracellular calcium-sensing receptor (CaSR). Unregulated activation of this G protein–coupled receptor inhibits sodium reabsorption in the TAL. The TAL transporters function in an integrated manner to maintain both the electrical potential difference and the sodium gradient between the lumen and the cell (Fig. 16-3). Loss of the lumen-positive electrical transport potential that normally drives the paracellular reabsorption of sodium, calcium, and magnesium causes NaCl wasting, hypercalciuria, and mild hypomagnesemia. As expected, the clinical syndrome mimics the effects of chronic ingestion of a loop diuretic.

Gitelman's syndrome is due to mutations in the thiazide-sensitive Na-Cl co-transporter, NCCT, in the DCT. Defects in NCCT in Gitelman's syndrome impair sodium and chloride reabsorption in the DCT (Fig. 16-3) and thus resemble the effects of thiazide

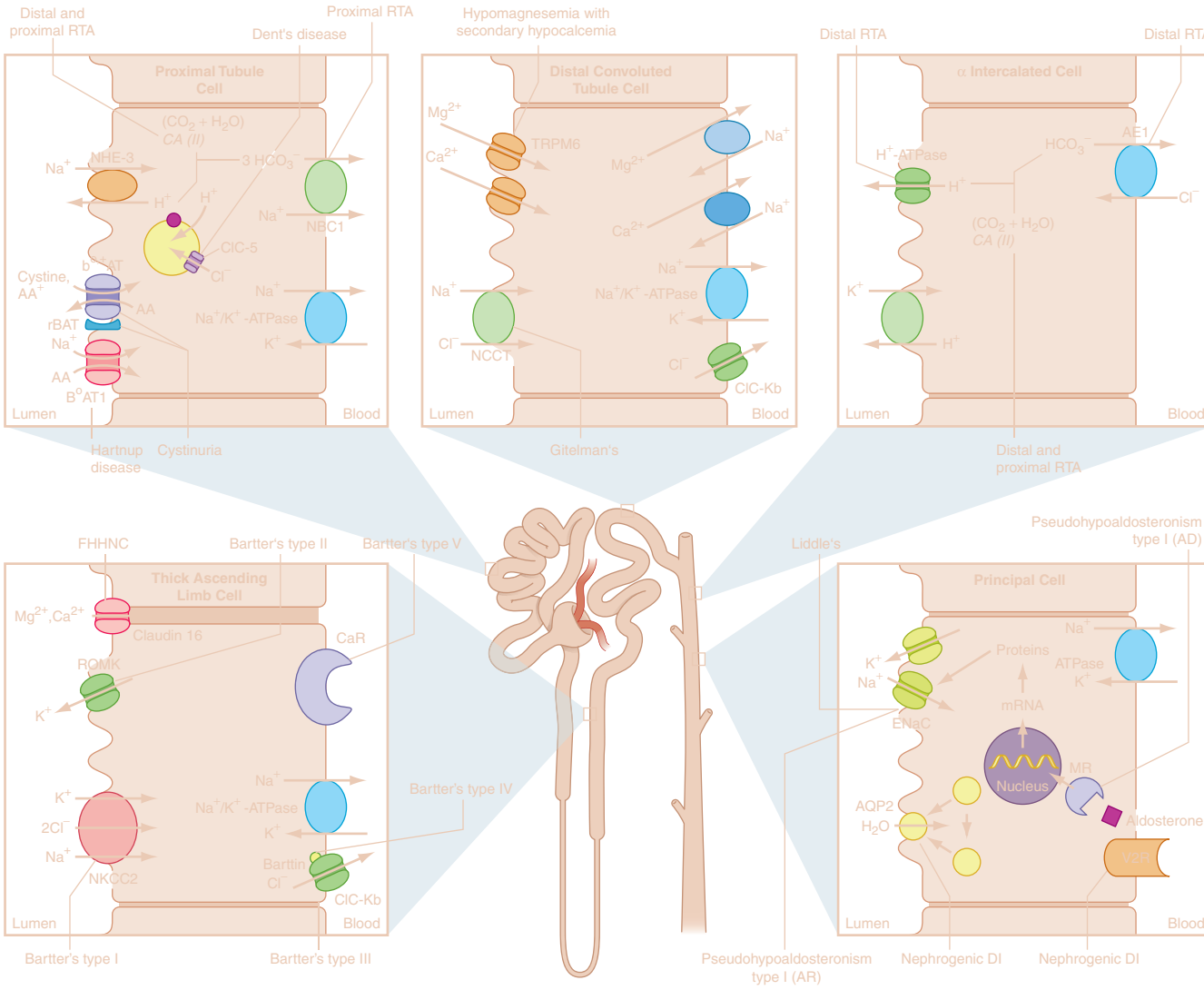


FIGURE 16-3

Schematic representation of channels, transporters, and enzymes associated with hereditary renal tubular disorders. AA, amino acids; AD, autosomal dominant; AE1, anion exchanger 1; AQP2, aquaporin-2; AR, autosomal recessive; AT1, amino acid transporter; CA (II), carbonic anhydrase II; CaR, calcium-sensing receptor; CLC-5, chloride channel 5; CLC-Kb, chloride channel Kb; DI, diabetes insipidus; ENaC, amiloride-sensitive epithelial sodium channel; MR, mineralocorticoid receptor; NBC1, sodium-bicarbonate co-transporter; NCCT, thiazide-senstitive Na-Cl co-transporter; NKCC2, Na-K-2Cl co-transporter; rBAT, renal basic amino acid transport glycoprotein; ROMK, renal outer medullary potassium channel; RTA, renal tubular acidosis; TRPM6, transient receptor potential cation channel, subfamily M, member 6; V2R, arginine vasopressin receptor 2; WNK, with no lysine (K).

diuretics. It remains unclear how this defect leads to severe magnesium wasting.

In both Bartter's and Gitelman's syndromes, hypovolemia from impaired sodium and chloride reabsorption in either the TAL or the DCT activates the renin-angiotensin-aldosterone system (RAAS). The consequent hyperaldosteronism, together with increased distal flow and sodium delivery, stimulates increased sodium reabsorption in the collecting tubules via the epithelial sodium channel (ENaC). This promotes increased potassium and hydrogen ion secretion, causing hypokalemia and metabolic alkalosis. Additionally, in Bartter's syndrome, RAAS activation causes increased levels of cyclooxygenase 2 (COX-2) and marked overproduction of renal prostaglandins (PGE2), and this exacerbates the polyuria and electrolyte abnormalities.

Clinical features

Bartter's syndrome

Bartter's syndrome is a rare disease that most often presents in the neonatal period or early childhood with polyuria, polydipsia, salt craving, and growth retardation. Blood pressure is normal or low. Metabolic abnormalities include hypokalemia, hypochloremic metabolic alkalosis, decreased urinary concentrating and diluting

ability, hypercalciuria with nephrocalcinosis, mild hypomagnesemia, and increased urinary prostaglandin excretion. Hyperprostaglandin E syndrome is a particularly severe form of Bartter's syndrome in which neonates present with pronounced volume depletion and failure to thrive, as well as fever, vomiting, and diarrhea from PGE_2 overproduction. In the antenatal period, fetal polyuria may cause maternal polyhydramnios and premature labor. Sensorineural deafness occurs in patients with barttin gene mutations (type 4). Patients with severe Bartter's syndrome who survive early childhood may develop chronic kidney disease from nephrocalcinosis or from tubular atrophy and interstitial fibrosis from severe persistent hypokalemia. Patients with Bartter's syndrome type 3 have a phenotype intermediate between those of Bartter's and Gitelman's syndromes, consistent with mutation of the ClC-Kb chloride channel in both the TAL and the DCT with preservation of the ClC-Ka chloride channel in the TAL. This disease occurs predominantly in African-American patients and resembles most closely the classic syndrome described by Bartter. Onset is generally later in childhood, patients have mild or no nephrocalcinosis, and prostaglandin excretion is normal.

Gitelman's syndrome

Gitelman's syndrome is more common than Bartter's syndrome and has a generally milder clinical course with a later age of presentation. It is characterized by prominent neuromuscular symptoms and signs, including fatigue, weakness, carpopedal spasm, cramps, and tetany.

Diagnosis

Hypokalemia and hypochloremic metabolic alkalosis without hypertension are more often due to surreptitious vomiting or diuretic abuse than to Bartter's or Gitelman's syndrome. In contrast to Bartter's and Gitelman's syndromes, urinary chloride levels are very low in patients with surreptitious vomiting. Diuretic abuse can be diagnosed by screening the urine for the offending agents. Gitelman's syndrome is distinguished from most forms of Bartter's syndrome by the presence of severe hypomagnesemia and hypocalciuria.

TREATMENT **Bartter's Syndrome and Gitelman's Syndrome**

Both conditions require lifelong therapy with potassium and magnesium supplements and liberal salt intake. High doses of spironolactone or amiloride treat the hypokalemia, alkalosis, and magnesium wasting. Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the polyuria and salt wasting in Bartter's syndrome but are ineffective in Gitelman's syndrome. They may be lifesaving in hyperprostaglandin E syndrome and can be given in the form of a COX-2 inhibitor to avoid the gastrointestinal side effects of long-term high-dose NSAIDs. In Gitelman's syndrome, magnesium repletion is essential to correct the hypokalemia and control muscle weakness, tetany, and metabolic alkalosis; however, it may prove difficult in patients wasting large amounts of magnesium.

PSEUDOHYPOALDOSTERONISM TYPE 1

Patients with type 1 pseudohypoaldosteronism present with severe renal salt wasting and hyperkalemia. Although these findings resemble mineralocorticoid deficiency, plasma renin activity and aldosterone levels are elevated. Defective salt handling is the result of autosomal recessive loss-of-function mutations of the α, β, or γ subunit of the ENaC or autosomal dominant mutations of one allele of the mineralocorticoid receptor (Table 16-2 and Fig. 16-3). The autosomal recessive form is a multisystem disorder with a severe phenotype, often manifesting in the neonatal period with renal salt wasting, vomiting, hyponatremia, hyperkalemia, acidosis, and failure to thrive. Impaired channel activity in the skin and lungs can produce excess sodium and chloride loss in sweat, excess fluid in the airways, and a propensity for lower respiratory tract infections that mimic cystic fibrosis. In contrast, the autosomal dominant form has a more benign course that is limited mainly to renal salt wasting and hyperkalemia. Aggressive salt replacement and management of hyperkalemia can lead to survival into adulthood, and symptoms may become less severe with time, especially in the dominant form. In the latter, high-dose fludrocortisone or carbenoxolone provides additional benefit by increasing mineralocorticoid activity and partly restoring the functional defect in the mutant receptor.

MAGNESIUM WASTING DISORDERS

In addition to Gitelman's syndrome, several hereditary disorders cause urinary magnesium wasting (Table 16-2 and Fig. 16-3). These disorders include autosomal recessive familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC), autosomal recessive hypomagnesemia with secondary hypocalcemia (HSH), autosomal dominant hypomagnesemia, autosomal dominant hypoparathyroidism, and isolated autosomal recessive hypomagnesemia. Common clinical features are the early onset of spasms, tetany, and seizures as well as associated or secondary disturbances in calcium homeostasis.

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis

FHHNC is the first example of a disorder attributable to a defective protein involved in paracellular ion

transport. *CLDCN16* encodes claudin 16 (previously known as paracellin-1), a member of the claudin family of proteins that are involved in tight junction formation. Claudin 16 is expressed in the TAL of Henle's loop and the DCT. Claudin 16 is thought to be an essential component of the paracellular pathway for Mg, and Ca to a lesser extent, reabsorption in the TAL. Clinical manifestations begin in infancy and include hypomagnesemia that is refractory to oral supplementation, hypercalciuria, and nephrocalcinosis. Recurrent urinary tract infections and nephrolithiasis have also been observed. Patients with mutations of claudin 19 have a similar phenotype but also manifest ocular defects, including corneal calcifications and chorioretinitis.

Hypomagnesemia with secondary hypocalcemia

Hypomagnesemia in HSH results from a defect in the TRPM6 channel, a member of the transient receptor potential (TRP) family of cation transport channels. TRPM6 is expressed in intestinal epithelia and the DCT and is thought to mediate transepithelial magnesium transport. Symptoms are attributable to hypomagnesemia with secondary impairment of parathyroid function and hypocalcemia. Seizures and muscle spasms occur in infancy, and restoration of magnesium and calcium levels requires high doses of oral magnesium supplementation.

Other hereditary hypomagnesemic disorders

Mutations of the sodium-potassium-ATPase γ subunit can cause an autosomal dominant hypomagnesemia. Activating mutations of the CaSR in autosomal dominant hypoparathyroidism primarily manifest as hypocalcemia, but hypomagnesemia has been reported in 50% of these patients. Mutations in epidermal growth factor (EGF) result in isolated autosomal recessive hypomagnesemia due to impaired activation of the EGF receptor and consequent failure to activate TRPM6.

HEREDITARY TUBULAR DISORDERS CAUSING HYPERTENSION DUE TO SALT RETENTION

LIDDLE'S SYNDROME

Liddle's syndrome mimics a state of aldosterone excess by the presence of early and severe hypertension, often accompanied by hypokalemia and metabolic alkalosis, but plasma aldosterone and renin levels are low. This disorder is due to unregulated sodium reabsorption by an overactive ENaC in the cortical collecting duct (Fig. 16-3). Deletional mutations of the intracellular domain of the β or γ subunit of ENaC (Table 16-2) prevent binding of the ubiquitin ligase Nedd4-2 that normally targets the channel for proteasomal degradation. This results in an inability to downregulate the number of channels despite a high intracellular sodium concentration. Increased potassium and hydrogen ion secretion follow the lumen-negative electrical potential that results from chloride-independent sodium reabsorption. Amiloride or triamterene blocks ENaC and, combined with salt restriction, provides effective therapy for the hypertension and hypokalemia.

PSEUDOHYPOALDOSTERONISM TYPE II (FAMILIAL HYPERKALEMIC HYPERTENSION; GORDON'S SYNDROME)

Pseudohypoaldosteronism type II is a rare autosomal dominant disease that manifests in adolescence or early adulthood with thiazide-responsive low-renin hypertension, hyperkalemia, and metabolic acidosis with normal renal function. Mutations have been identified in the WNK kinases 1 and 4 that lead to increased activity of the thiazide-sensitive sodium chloride channel, NCCT. This causes hypertension from enhanced salt reabsorption in the DCT and impaired distal secretion of potassium and hydrogen ion, all of which can be corrected with thiazide diuretics.

INHERITED DISORDERS OF WATER HANDLING

HEREDITARY NEPHROGENIC DIABETES INSIPIDUS

Hereditary nephrogenic diabetes insipidus (NDI) is a rare monogenic disease that usually presents in infancy with severe vasopressin-resistant polyuria, dehydration, failure to thrive, and dilute urine despite the presence of hypernatremia.

Genetics and pathogenesis

Vasopressin [antidiuretic hormone (ADH)]-stimulated water reabsorption in the collecting duct is mediated by the type 2 vasopressin receptor (V2R) on the basal surface of principal cells. Activation of the adenylyl cyclase–cAMP pathway phosphorylates vesicle-associated aquaporin-2 (AQP2) water channels and stimulates their insertion into the apical plasma membrane. Water enters the cells from the tubular lumen through AQP2 and exits along an osmotic gradient into the hypertonic medulla and vasa rectae via basal AQP3/4 channels (Fig. 16-3). X-linked mutations of *AVPR2*, the gene that encodes V2R, account for about 90% of cases of hereditary NDI, such that the expression of the receptor on the cell surface is impaired. The remaining cases are due to various autosomal recessive or dominant mutations of *AQP2* that

cause the water channels to be retained within the cytosol (Table 16-2). The effect of these mutations is an inability to concentrate the urine and conserve water despite high plasma levels of vasopressin. Penetrance is variable in heterozygous female carriers of X-linked NDI, and some have a moderate concentrating defect that may be exacerbated in pregnancy due to placental vasopressinase.

Clinical features

Whereas NDI in adults is most often acquired from lithium therapy, hypercalcemia, and partial chronic urinary obstruction, hereditary NDI typically presents in infancy. Unlike other polyuric syndromes such as Bartter's and Gitelman's syndromes, conservation of electrolytes is normal, and hypernatremia is entirely from the loss of water. Recurrent episodes of dehydration and hypernatremia can lead to seizures and mental retardation. Although renal function is otherwise normal, chronically high urine flow causes dilation of the ureters and bladder and may cause bladder dysfunction and obstructive uropathy.

Diagnosis

The diagnosis in infants and children with hereditary NDI is usually apparent from the family history and clinical presentation. The diagnosis can be confirmed by the presence of high plasma levels of vasopressin in the face of polyuria and hypotonic urine. This may be especially useful in adults with partial NDI to distinguish the polyuric state from central diabetes insipidus or psychogenic polydipsia. Genetic screening for mutations in *AVPR2* and *AQP2* is available in research centers and can be performed to identify affected infants from families at risk of NDI to begin treatment and avoid dehydration and its consequences.

TREATMENT **Hereditary Nephrogenic Diabetes Insipidus**

Early diagnosis and treatment with abundant water intake have enabled many patients to live to adulthood with normal mental and physical development. Exogenous vasopressin is ineffective, and because these patients can excrete up to 20 L of urine per day, maintaining adequate water intake is challenging. Thiazide diuretics and salt restriction can reduce urine output by inducing a state of mild volume contraction, thereby promoting increased proximal reabsorption of isotonic fluid and inhibiting the delivery of free water to the collecting duct. A combination thiazide-amiloride formulation will avoid thiazide-induced hypokalemia, and indomethacin may further reduce urine output by inhibiting prostaglandin synthesis.

NEPHROGENIC SYNDROME OF INAPPROPRIATE ANTIDIURESIS

Activating mutations of the V2R result in hyponatremia, inappropriately elevated urinary osmolality, and undetectable arginine vasopressin (AVP) levels in affected males. This syndrome results from missense mutations of *AVPR2* on the X chromosome, which cause constitutive activation of V2R and inappropriate water reabsorption. Heterozygous female carriers may be at risk of hyponatremia when exposed to large volumes of hypotonic fluids.

INHERITED RENAL TUBULAR ACIDOSIS

Non-anion-gap (hyperchloremic) metabolic acidosis from proximal tubular bicarbonate wasting or impaired distal net acid excretion may be a primary (sporadic or inherited) tubular disorder or may be acquired secondary to a variety of conditions (Chap. 5). There are three forms of renal tubular acidosis (RTA). Types 1 and 2 may be acquired or primary, whereas the most common form, type 4 RTA, usually is acquired in association with moderate renal dysfunction and is characterized by hyperkalemia.

TYPE 1 (DISTAL) RTA

Clinical features and diagnosis

In distal RTA the kidneys are unable to acidify the urine to pH <5.5 in the presence of systemic metabolic acidosis or after acid loading as a result of impaired hydrogen ion secretion or bicarbonate reabsorption in the distal nephron. Other features include hypokalemia, hypocitraturia, hypercalciuria, nephrocalcinosis, and/or nephrolithiasis. Chronic untreated acidosis may cause rickets or osteomalacia. Inheritance of primary dRTA includes autosomal dominant and autosomal recessive forms with a broad spectrum of clinical expression. Autosomal recessive dRTA most often presents in infancy with severe acidosis, failure to thrive, impaired growth, and impaired kidney function from nephrocalcinosis. Many patients with autosomal dominant dRTA, and some with recessive disease, are asymptomatic, and RTA is discovered incidentally in adolescence or adulthood during evaluation for kidney stones. In the absence of systemic acidosis, the diagnosis of incomplete dRTA is suggested by hypocitraturia and hypercalciuria and can be confirmed by failure of the urine to acidify to pH <5.5 after acid loading.

Genetics and pathophysiology

Primary dRTA may be hereditary or sporadic with autosomal recessive and autosomal dominant forms. Several kindreds with autosomal recessive dRTA have

been identified in Southeast Asia and in areas of the world where parental consanguinity is high. The cellular basis for dRTA lies in dysfunction at the level of the α type intercalated cell of the cortical collecting duct (Fig. 16-3). Mutations affecting subunits of the H^+-ATPase proton pump on the luminal surface impair hydrogen ion secretion and account for most forms of autosomal recessive dRTA and are often associated with early-onset sensorineural hearing loss (Table 16-2). Autosomal dominant dRTA results from mutations involving the chloride-bicarbonate exchanger, AE1, on the basolateral membrane. Anion exchange by the mutant AE1 is normal, but aberrant targeting of AE1 from the basal to the apical plasma membrane is believed to cause bicarbonate loss into the urine instead of reabsorption. Bi-allelic mutations of AE1 may impair transport activity and account for some cases of recessive disease (Table 16-2). A syndrome of osteopetrosis, short stature, and mental retardation, so-called marble-brain disease with dRTA, is due to mutations in carbonic anhydrase II. Urinary potassium wasting and defective urinary concentration are characteristic of dRTA. Calcium is released from bone in the process of buffering of acid and results in hypercalciuria. Enhanced proximal citrate absorption accounts for hypocitraturia and, together with hypercalciuria, predisposes to nephrocalcinosis and formation of calcium phosphate stones.

TREATMENT **Type 1 (Distal) RTA**

Early initiation of alkali replacement at doses equivalent to 1–3 mmol/kg per day of bicarbonate in divided doses will usually correct the acidosis, hypokalemia, and hypocitraturia, maintaining growth and preventing bone disease in early-onset dRTA. Citrate is generally tolerated better than sodium bicarbonate and can be given as the potassium or sodium salt, depending on the severity of hypokalemia. In patients who present later with kidney stones, large fluid intake and sufficient alkali to restore normal acid-base balance correct the hypocitraturia and reduce hypercalciuria, thereby inhibiting the formation of new stones.

TYPE 2 (PROXIMAL) RTA

Proximal RTA (pRTA) is the result of impaired bicarbonate reabsorption in the proximal tubule, where the bulk of filtered bicarbonate is recovered (Fig. 16-3). It is most often secondary to various autoimmune, drug-induced, infiltrative, or other tubulopathies (Chap. 5) or results from tubular injury from inherited diseases in which endogenous metabolites accumulate and produce tubular injury. Such inherited disorders include Wilson's disease, cystinosis, tyrosinemia, galactosemia, hereditary fructose intolerance, glycogen storage disease type I, and Lowe's syndrome. In this situation pRTA is only one of several abnormalities that constitute Fanconi syndrome. Other features are hyperphosphaturia, hyperuricosuria, hypercalciuria, nonselective aminoaciduria, and glycosuria. In addition to hyperchloremic acidosis, rickets and osteomalacia are the predominant effects of Fanconi syndrome.

A rare infantile form of primary pRTA with isolated proximal tubular bicarbonate wasting is due to homozygous mutations of the proximal tubule basolateral sodium-bicarbonate co-transporter NBC1 (Table 16-2). This co-transporter is the main mechanism by which bicarbonate moves from the proximal tubule cell back into the blood. Other manifestations include short stature and mental retardation. An ocular phenotype that includes bilateral glaucoma, cataracts, and band keratopathy reflects a role of NBC1 in maintaining normal fluid balance in the eye and clarity of the lens.

TREATMENT **Type 2 (Proximal) RTA**

It is difficult to restore normal acid-base balance in patients with pRTA despite large amounts of alkali. This is the case because they continue to waste bicarbonate (fractional excretion >15%) until the serum level falls below a threshold, usually about 15–17 mmol/L, at which time bicarbonate is completely reabsorbed distally and the urine is maximally acidified with pH <5.5. When the serum bicarbonate concentration is raised above the threshold with alkali therapy, bicarbonate wasting recurs and causes hypokalemia as potassium is secreted to maintain luminal electroneutrality. Thus, treatment of pRTA requires 5–15 mmol/kg per day of bicarbonate together with supplemental potassium.

OTHER MONOGENIC DISORDERS OF PROXIMAL TUBULAR FUNCTION (FIG. 16-3)

CYSTINURIA

Cystinuria is an autosomal recessive disorder of cystine and dibasic amino acid (ornithine, arginine, and lysine) transport in the proximal tubule and intestinal epithelial cells. With a prevalence of about 1 in 10,000, it represents one of the more common heritable diseases. Impaired tubular absorption leads to high concentrations of cystine, which is insoluble in the acid environment of the renal tubules. Clinical severity varies from asymptomatic cystine crystalluria in heterozygous carriers to the frequent passage of gravel and cystine stones, ureteral obstruction, recurrent urinary infections, formation of staghorn calculi, and progressive kidney failure in homozygotes. The median onset of

nephrolithiasis is 12 years. The disease is due to mutations in one of two genes, *SLC3A1* and *SLC7A9* (Table 16-2). *SLC3A1* encodes rBAT, a high-affinity, sodium-independent transporter for dibasic amino acids. The protein product of *SLC7A9*, $b^{0,+}$AT, is a catalytic subunit that associates with rBAT to form the active transporter. Diagnosis of cystinuria is established by a positive family history, the finding of hexagonal cystine crystals on urinalysis, and 24-h urinary cystine excretion that exceeds 400 mg (normal is less than 30 mg/d).

TREATMENT **Cystinuria**

The mainstay of treatment is hydration to achieve a urine output of 2.5 L/d or more to reduce urine cystine concentration to <300 mg/L, together with urine alkalinization to pH 7.0–7.5 with potassium citrate, and sodium restriction. Cystine is an oxidized dimer that is formed by linking two cysteine residues via a disulfide bond between the -SH groups. Thus, in intractable cases, thiol derivatives such as penicillamine, tiopronin, and captopril may be added as chelation therapy to dissociate the cystine molecule into more soluble disulfide compounds. Various stone removal and urinary drainage procedures are often required.

HARTNUP DISEASE

Hartnup disease is an autosomal recessive condition caused by a defect in intestinal and renal transport of neutral amino acids. The major clinical manifestations are cerebellar ataxia and a pellagra-like skin rash. Other than aminoaciduria, the kidneys are unaffected. The defective gene, *SLC6A19*, encodes a sodium-dependent and chloride-independent neutral amino acid transporter (B^0AT1), which is expressed predominantly in the small intestine and proximal tubule of the kidney (Table 16-2). Amino acids such as tryptophan that are retained in the intestinal lumen are converted to indole compounds that are toxic to the CNS. Abnormal tryptophan metabolism also leads to a niacin deficiency that accounts for the skin manifestations. Symptoms are aggravated by a protein-deficient diet and are alleviated with a high-protein diet and nicotinamide supplements.

DENT'S DISEASE

Dent's disease and X-linked recessive nephrolithiasis are unusual forms of Fanconi syndrome due to X-linked mutations of the gene encoding CLC-5, a voltage-gated chloride channel (Table 16-2). The disorders are characterized by childhood onset of low-molecular-weight proteinuria, hypercalciuria, nephrocalcinosis, and nephrolithiasis. Rickets or osteomalacia occurs in 25% of patients, and progressive renal failure from interstitial fibrosis, tubular atrophy, and glomerulosclerosis commonly develops in adulthood. CLC-5 serves to maintain the electrical gradient and acid environment established in proximal tubular cell endosomes by proton-ATPase, which is necessary for the degradation of low-molecular-weight proteins normally filtered by the glomerulus. Defects in CLC-5 appear to disrupt this process and lead to tubular cell dysfunction.

TREATMENT **Dent's Disease**

Treatment is directed at controlling hypercalciuria by dietary salt restriction and thiazide diuretics, which favor calcium reabsorption. Restriction of dietary calcium is not recommended.

CYSTINOSIS

Cystinosis is a rare multisystem autosomal recessive disease caused by mutations of cystinosin, a hydrogen ion–driven transporter responsible for exporting cystine from lysosomes. Accumulation of insoluble cystine leads to crystal formation in proximal tubular cells and other organs. Cystinosis occurs in infantile (nephropathic), adolescent, and adult forms. The nephropathic form is the most common, with clinical signs developing between 3 and 6 months of age, including Fanconi syndrome, salt and water wasting, growth retardation, rickets, vomiting, constipation, and unexplained fever. End-stage renal disease occurs by age 10 in the infantile form of the disease but after age 15 in the intermediate form. Extrarenal manifestations result from cystine accumulation in organs and include photophobia and blindness, muscular weakness from carnitine deficiency, hepatomegaly, hypothyroidism, delayed pubertal development, and late-onset neurologic disease. The adult form of cystinosis is largely asymptomatic except for photophobia. The diagnosis is made by measuring elevated cystine content of peripheral blood leukocytes.

TREATMENT **Cystinosis**

Treatment includes replacement of fluid and electrolyte losses related to Fanconi syndrome and polyuria. L-Carnitine supplementation is recommended to achieve normal plasma carnitine levels. Cysteamine provides a direct treatment of the disease that converts cystine to cysteine, which can exit the lysosome. Cysteamine should be started promptly upon the diagnosis of cystinosis as it preserves kidney function, prevents hypothyroidism, and improves growth. Kidney transplantation is the treatment of choice for ESRD as cystinosis does not recur in transplanted kidneys, but the extrarenal manifestations persist and may progress.

RENAL GLUCOSURIA

Isolated glucosuria in the presence of a normal blood glucose concentration is due to mutations in *SLC5A2*, the gene that encodes the high-capacity sodium-glucose co-transporter SGLT2 in the proximal renal tubule (Table 16-2). Subjects with this disorder are usually asymptomatic and do not have other features of proximal tubular dysfunction. Depending on the severity of the defect, the tubular maximum for glucose reabsorption may fall well within normal blood glucose levels and lead to >50 g/d of glucosuria. Such patients may have polyuria from osmotic diuresis.

RENAL PHOSPHATE WASTING

Renal phosphate wasting resulting in hypophosphatemia, and rickets or osteomalacia may be part of a generalized disorder of proximal tubular function, as in Fanconi syndrome, or an isolated phenomenon. Isolated phosphaturia is most often due to the inhibition of renal tubular phosphate reabsorption by one or another phosphaturic hormone, with FGF-23 playing a major role. An exception is hereditary hypophosphatemic rickets with hypercalciuria (HHRH), an autosomal recessive disorder due to mutations in *SLC34A3*, the gene encoding the proximal tubule sodium-phosphate co-transporter, NPT-2c (Table 16-2). Defective phosphate reabsorption causes renal phosphate wasting and stunted growth from rickets. The low serum phosphorus levels stimulate 1-hydroxylation of vitamin D, which increases intestinal calcium absorption, suppresses parathyroid hormone (PTH) secretion, and results in hypercalciuria. High levels of 1,25-dihydroxyvitamin D help distinguish HHRH from hormonal causes of hyperphosphaturia. Treatment is directed at phosphate repletion.

VITAMIN D–DEPENDENT RICKETS

Vitamin D–dependent rickets exists in two forms that manifest with hypocalcemia, hypophosphatemia, elevated PTH levels, and the skeletal abnormalities of rickets and osteomalacia. Tetany may be present in severe cases. Vitamin D–dependent rickets type I is an autosomal recessive disease that results from mutations in *CYP27B1*, the gene that encodes 25(OH)D_3-1α-hydroxylase, an enzyme in the proximal tubule that catalyzes the hydroxylation and activation of 25(OH)D_3 into 1,25$(OH)_2D_3$ (Table 16-2). It can be treated with physiologic replacement doses of 1,25$(OH)_2D_3$. In contrast, autosomal recessive vitamin D–dependent rickets type II is due to end organ resistance to 1,25$(OH)_2D_3$ as a result of mutations in the vitamin D receptor.

CHAPTER 17

TUBULOINTERSTITIAL DISEASES OF THE KIDNEY

Laurence H. Beck ■ David J. Salant

Inflammation or fibrosis of the renal interstitium and atrophy of the tubular compartment are common consequences of diseases that target the glomeruli or vasculature. Distinct from these secondary phenomena, however, are a group of disorders that primarily affect the tubules and interstitium, with relative sparing of the glomeruli and renal vessels. Such disorders are conveniently divided into acute and chronic tubulointerstitial nephritis (TIN) **(Table 17-1)**.

Acute TIN most often presents with acute renal failure (Chap. 10). The acute nature of this group of disorders may be caused by aggressive inflammatory infiltrates that lead to tissue edema, tubular cell injury, and compromised tubular flow, or by frank obstruction of the tubules with casts, cellular debris, or crystals. There is sometimes flank pain due to distention of the renal capsule. Urinary sediment is often active with leukocytes and cellular casts, but depends on the exact nature of the disorder in question.

The clinical features of chronic TIN are more indolent and may manifest with disorders of tubular function, including polyuria from impaired concentrating ability (nephrogenic diabetes insipidus), defective proximal tubular reabsorption leading to features of Fanconi syndrome [glycosuria, phosphaturia, aminoaciduria, hypokalemia, and type II renal tubular acidosis (RTA) from bicarbonaturia], or non-anion-gap metabolic acidosis and hyperkalemia (type IV RTA) due to impaired ammoniagenesis, as well as progressive azotemia [rising creatinine and blood urea nitrogen (BUN)]. There is often modest proteinuria (rarely >2 g/d) attributable to decreased tubular reabsorption of filtered proteins; however, nephrotic-range albuminuria may occur in some conditions due to the development of secondary focal segmental glomerulosclerosis (FSGS). Renal ultrasonography may reveal changes of "medical renal disease," such as increased echogenicity of the renal parenchyma with loss of corticomedullary differentiation, prominence of the renal pyramids, and cortical scarring in some conditions. The predominant pathology in chronic TIN is interstitial fibrosis with patchy mononuclear cell infiltration and widespread tubular atrophy, luminal dilation, and thickening of tubular basement membranes. Because of the nonspecific nature of the histopathology, biopsy specimens rarely provide a specific diagnosis. Thus, diagnosis relies on careful analysis of history, drug or toxin exposure, associated symptoms, and imaging studies.

ACUTE INTERSTITIAL NEPHRITIS

In 1897 Councilman reported on eight cases of acute interstitial nephritis (AIN) in the Medical and Surgical Reports of the Boston City Hospital; three as a postinfectious complication of scarlet fever and two from diphtheria. Later, he described the lesion as "an acute inflammation of the kidney characterized by cellular and fluid exudation in the interstitial tissue, accompanied by, but not dependant on, degeneration of the epithelium; the exudation is not purulent in character, and the lesions may be both diffuse and focal." Today AIN is far more often encountered as an allergic reaction to a drug (Table 17-1). Immune-mediated AIN may also occur as part of a known autoimmune syndrome, but in some cases there is no identifiable cause despite features suggestive of an immunological etiology (Table 17-1).

ALLERGIC INTERSTITIAL NEPHRITIS

Although biopsy-proven AIN accounts for no more than ~15% of cases of unexplained acute renal failure, this is likely a substantial underestimate of the true incidence.

TABLE 17-1

CLASSIFICATION OF THE CAUSES OF TUBULOINTERSTITIAL DISEASES OF THE KIDNEY

Acute Tubulointerstitial Disorders

Acute Interstitial Nephritis

Therapeutic agents

- Antibiotics (β-lactams, sulfonamides, quinolones, vancomycin, erythromycin, minocycline, rifampin, ethambutol, acyclovir)
- Nonsteroidal anti-inflammatory drugs, COX-2 inhibitors
- Diuretics (rarely thiazides, loop diuretics, triamterene)
- Anticonvulsants (phenytoin, valproate, carbamazepine, phenobarbital)
- Miscellaneous (proton pump inhibitors, H_2 blockers, captopril, mesalazine, indinavir, allopurinol)

Infection

- Bacteria (*Streptococcus*, *Staphylococcus*, *Legionella*, *Salmonella*, *Brucella*, *Yersinia*, *Corynebacterium diphtheriae*)
- Viruses (EBV, CMV, hantavirus, polyomavirus, HIV)
- Miscellaneous (*Leptospira*, *Rickettsia*, *Mycoplasma*)

Autoimmune

- Tubulointerstitial nephritis with uveitis (TINU)
- Sjögren's syndrome
- Systemic lupus erythematosus
- Granulomatous interstitial nephritis
- IgG4-related systemic disease
- Idiopathic autoimmune interstitial nephritis

Acute obstructive disorders

- Light chain cast nephropathy ("myeloma kidney")
- Acute phosphate nephropathy
- Acute urate nephropathy

Chronic Tubulointerstitial Disorders

- Vesicoureteral reflux/reflux nephropathy
- Sickle cell disease
- Chronic exposure to toxins or therapeutic agents
  - Analgesics, especially those containing phenacetin
  - Lithium
  - Heavy metals (lead, cadmium)
  - Aristolochic acid (Chinese herbal and Balkan endemic nephropathies)
  - Calcineurin inhibitors (cyclosporine, tacrolimus)

Metabolic Disturbances

- Hypercalcemia and/or nephrocalcinosis
- Hyperuricemia
- Prolonged hypokalemia
- Hyperoxaluria
- Cystinosis (see Chap. 16)

Cystic and Hereditary Disorders (see Chap. 16)

- Polycystic kidney disease
- Nephronophthisis
- Adult medullary cystic disease
- Medullary sponge kidney

Miscellaneous

- Aging
- Chronic glomerulonephritis
- Chronic urinary tract obstruction
- Ischemia and vascular disease
- Radiation nephritis (rare)

Abbreviations: CMV, cytomegalovirus; COX, cyclooxygenase; EBV, Epstein-Barr virus.

This is because potentially offending medications are more often identified and empirically discontinued in a patient noted to have a rising serum creatinine, without the benefit of a renal biopsy to establish the diagnosis of AIN.

Clinical features

The classic presentation of AIN, namely, fever, rash, peripheral eosinophilia, and oliguric renal failure occurring after 7–10 days of treatment with methicillin or another β-lactam antibiotic, is the exception rather than the rule. More often, patients are found incidentally to have a rising serum creatinine or present with symptoms attributable to acute renal failure (Chap. 10). Atypical reactions can occur; most notably nonsteroidal anti-inflammatory drug (NSAID)-induced AIN, in which fever, rash and eosinophilia are rare, but acute renal failure with heavy proteinuria is common. A particularly severe and rapid-onset AIN may occur upon reintroduction of rifampin after a drug-free period. More insidious reactions to the agents listed in Table 17-1 may lead to progressive tubulointerstitial damage. Examples include proton pump inhibitors and, rarely, sulfonamide and 5-aminosalicylate (mesalazine and sulfasalazine) derivatives and antiretrovirals.

Diagnosis

Finding otherwise unexplained renal failure with or without oliguria and exposure to a potentially offending agent usually points to the diagnosis. Peripheral blood eosinophilia adds supporting evidence but is present in only a minority of patients. Urinalysis reveals pyuria with white blood cell casts and hematuria. Urinary eosinophils are neither sensitive nor specific for AIN; therefore, testing is not recommended. Renal biopsy is generally not required for diagnosis but reveals extensive interstitial and tubular infiltration of leukocytes, including eosinophils.

TREATMENT **Allergic Interstitial Nephritis**

Discontinuation of the offending agent often leads to reversal of the renal injury. However, depending on the duration of exposure and degree of tubular atrophy and interstitial fibrosis that has occurred, the renal damage may not be completely reversible. Glucocorticoid therapy may accelerate renal recovery, but does not appear to impact long-term renal survival. It is best reserved for those cases with severe renal failure in which dialysis is imminent or if renal function continues to deteriorate despite stopping the offending drug (Fig. 17-1 and Table 17-2).

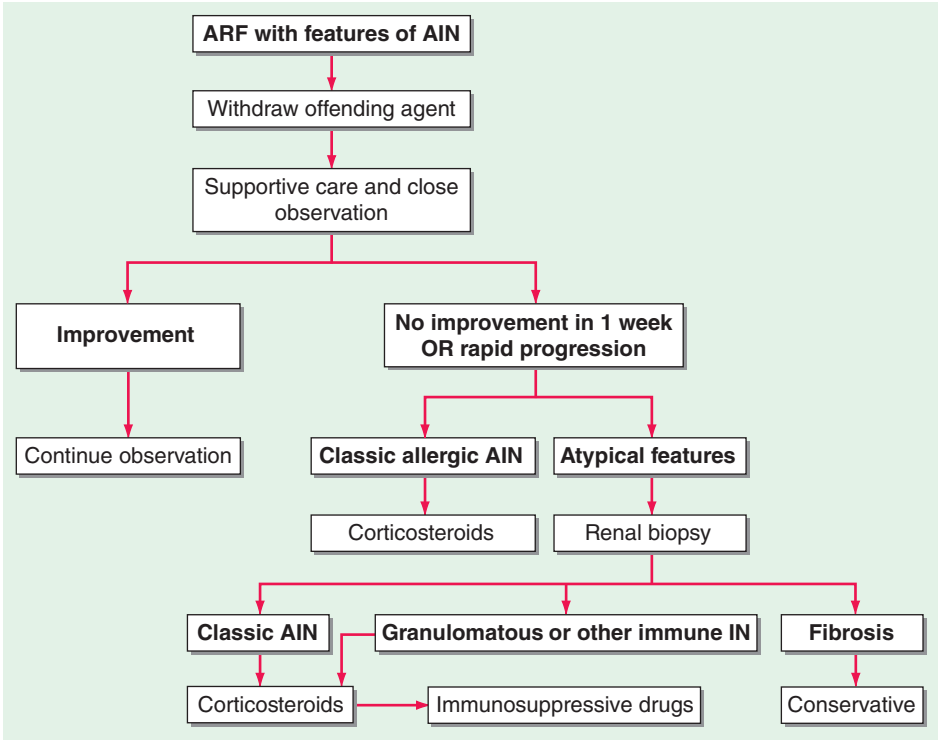


FIGURE 17-1
Algorithm for the treatment of allergic and other immune-mediated acute interstitial nephritis (AIN). ARF, acute renal failure. See text for immunosuppressive drugs used for refractory or relapsing AIN. (*Modified from S Reddy, DJ Salant: Ren Fail 20:829, 1998.*)

SJÖGREN'S SYNDROME

Sjögren's syndrome is a systemic autoimmune disorder that primarily targets the exocrine glands, especially the lacrimal and salivary glands, and thus results in symptoms, such as dry eyes and mouth, that constitute the "sicca syndrome". Tubulointerstitial nephritis with a predominant lymphocytic infiltrate is the most common renal manifestation of Sjögren's syndrome and can be associated with distal RTA, nephrogenic diabetes insipidus, and moderate renal failure. Diagnosis is strongly supported by positive serologic testing for anti-Ro (SS-A) and anti-La (SS-B) antibodies. A large proportion of patients with Sjögren's syndrome also have polyclonal hypergammaglobulinemia. Treatment is initially with glucocorticoids, although patients may require maintenance therapy with azathioprine or mycophenolate mofetil to prevent relapse (Fig. 17-1 and Table 17-2).

TABLE 17-2
INDICATIONS FOR CORTICOSTEROIDS AND IMMUNOSUPPRESSIVES IN INTERSTITIAL NEPHRITIS

Absolute Indications
• Sjögren's syndrome
• Sarcoidosis
• SLE interstitial nephritis
• Adults with TINU
• Idiopathic and other granulomatous interstitial nephritis
Relative Indications
• Drug-induced or idiopathic AIN with: Rapid progression of renal failure Diffuse infiltrates on biopsy Impending need for dialysis Delayed recovery
• Children with TINU
• Postinfectious AIN with delayed recovery (?)

Abbreviations: AIN, acute interstitial nephritis; SLE, systemic lupus erythematosus; TINU, tubulointerstitial nephritis with uveitis.
Source: Modified from S Reddy, DJ Salant: Ren Fail 20:829, 1998.

TUBULOINTERSTITIAL NEPHRITIS WITH UVEITIS (TINU)

TINU is a systemic autoimmune disease of unknown etiology. It accounts for fewer than 5% of all cases of AIN, affects females three times more often than males, and has a median age of onset of 15 years. Its hallmark feature, in addition to a lymphocyte-predominant interstitial nephritis **(Fig. 17-2)**, is a painful anterior uveitis, often bilateral and accompanied by blurred vision and photophobia. Diagnosis is often confounded by the fact that the ocular symptoms precede or accompany the renal disease in only one-third of cases. Additional extrarenal features include fever, anorexia, weight loss,

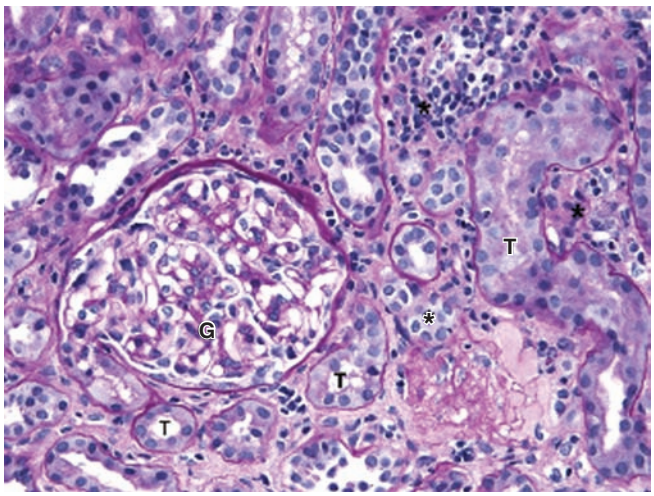


FIGURE 17-2

Acute interstitial nephritis (AIN) in a patient who presented with acute iritis, low-grade fever, erythrocyte sedimentation rate of 103, pyuria and cellular casts on urinalysis, and a newly elevated serum creatinine of 2.4 mg/dL. Both the iritis and AIN improved after intravenous methylprednisolone. This PAS-stained renal biopsy shows a mononuclear cell interstitial infiltrate (asterisks) and edema separating the tubules (T) and a normal glomerulus (G). Some of the tubules contain cellular debris and infiltrating inflammatory cells. The findings in this biopsy are indistinguishable from those that would be seen in a case of drug-induced AIN. PAS, periodic acid–Schiff.

abdominal pain, and arthralgia. The presence of such symptoms as well as elevated creatinine, sterile pyuria, mild proteinuria, features of the Fanconi syndrome, and elevated erythrocyte sedimentation rate should raise suspicion for this disorder. Serologies suggestive of the more common autoimmune diseases are usually negative, and TINU is often a diagnosis of exclusion after other causes of uveitis and renal disease, such as Sjögren's syndrome, Behçet's disease, sarcoidosis, and systemic lupus erythematosus, have been considered. Clinical symptoms are typically self-limited in children, but are more apt to follow a relapsing course in adults. The renal and ocular manifestations generally respond well to oral glucocorticoids, although maintenance therapy with agents such as methotrexate, azathioprine, or mycophenolate may be necessary to prevent relapses (Fig. 17-1 and Table 17-2).

SYSTEMIC LUPUS ERYTHEMATOSUS

An interstitial mononuclear cell inflammatory reaction often accompanies the glomerular lesion in most cases of class III or IV lupus nephritis (Chap. 15), and deposits of immune complexes can be identified in tubule basement membranes in about 50%. Occasionally, however, the tubulointerstitial inflammation predominates and may manifest with azotemia and type IV RTA rather than features of glomerulonephritis.

GRANULOMATOUS INTERSTITIAL NEPHRITIS

Some patients may present with features of AIN but follow a protracted and relapsing course. Renal biopsy in such patients reveals a more chronic inflammatory infiltrate with granulomas and multinucleated giant cells. Most often, no associated disease or cause is found; however, some of these cases may have or subsequently develop the pulmonary, cutaneous, or other systemic manifestations of *sarcoidosis* such as hypercalcemia. Most patients experience some improvement in renal function if treated early with glucocorticoids before the development of significant interstitial fibrosis and tubular atrophy (Table 17-2). Other immunosuppressive agents may be required for those who relapse frequently upon steroid withdrawal (Fig. 17-1). Tuberculosis should be ruled out before starting treatment because this too is a rare cause of granulomatous interstitial nephritis.

IgG4-RELATED SYSTEMIC DISEASE

A form of AIN characterized by a dense inflammatory infiltrate containing IgG4-expressing plasma cells can occur as a part of a recently described syndrome known as IgG4-related systemic disease. Autoimmune pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, and a chronic sclerosing sialadenitis (mimicking Sjögren's syndrome) may variably be present as well. Fibrotic lesions that form pseudotumors in the affected organs soon replace the initial inflammatory infiltrates and often lead to biopsy or excision for fear of true malignancy. Although the involvement of IgG4 in the pathogenesis is not understood, glucocorticoids have been successfully used as first-line treatment in this group of disorders, once they are correctly diagnosed.

IDIOPATHIC AIN

Some patients present with typical clinical and histologic features of AIN but have no evidence of drug exposure or clinical or serologic features of an autoimmune disease. The presence in some cases of autoantibodies to a tubular antigen, similar to that identified in rats with an induced form of interstitial nephritis, suggests that an autoimmune response may be involved. Like TINU and granulomatous interstitial nephritis, idiopathic AIN is responsive to glucocorticoid therapy but may follow a relapsing course requiring maintenance treatment with another immunosuppressive agent (Fig. 17-1 and Table 17-2).

INFECTION-ASSOCIATED AIN

AIN may also occur as a local inflammatory reaction to microbial infection (Table 17-1) and should be distinguished from acute bacterial pyelonephritis (Chap. 20). Acute bacterial pyelonephritis does not generally cause acute renal failure unless it affects both kidneys or causes septic shock. Presently, infection-associated AIN is most often seen in immunocompromised patients, particularly renal transplant recipients with reactivation of polyomavirus BK (Chaps. 13 and 14).

CRYSTAL DEPOSITION DISORDERS AND OBSTRUCTIVE TUBULOPATHIES

Acute renal failure may occur when crystals of various types are deposited in tubular cells and interstitium or when they obstruct tubules. Oliguric acute renal failure, often accompanied by flank pain from tubular obstruction, may occur in patients treated with sulfadiazine for toxoplasmosis, indinavir for HIV, and intravenous acyclovir for severe herpesvirus infections. Urinalysis reveals "sheaf of wheat" sulfonamide crystals, individual or parallel clusters of needle-shaped indinavir crystals, or red-green birefringement needle-shaped crystals of acyclovir. This adverse effect is generally precipitated by hypovolemia and is reversible with saline volume repletion and drug withdrawal. Distinct from the obstructive disease, a frank AIN from indinavir crystal deposition has also been reported.

Acute tubular obstruction is also the cause of oliguric renal failure in patients with *acute urate nephropathy*. It typically results from severe hyperuricemia from tumor lysis syndrome in patients with lympho- or myeloproliferative disorders treated with cytotoxic agents, but also may occur spontaneously before the treatment has been initiated. Uric acid crystallization in the tubules and collecting system leads to partial or complete obstruction of the collecting ducts, renal pelvis, or ureter. A dense precipitate of birefringent uric acid crystals is found in the urine, usually in association with microscopic or gross hematuria. Prophylactic allopurinol reduces the risk of uric acid nephropathy but is of no benefit once tumor lysis has occurred. Once oliguria has developed, attempts to increase tubular flow and solubility of uric acid with alkaline diuresis may be of some benefit; however, emergent treatment with hemodialysis or rasburicase, a recombinant urate oxidase, is usually required to rapidly lower uric acid levels and restore renal function.

Calcium oxalate crystal deposition in tubular cells and interstitium may lead to permanent renal dysfunction in patients who survive ethylene glycol intoxication, in patients with enteric hyperoxaluria from ileal resection or small-bowel bypass surgery, and in patients with hereditary hyperoxaluria (Chap. 9). *Acute phosphate nephropathy* is an uncommon but serious complication of oral Phospho-soda used as a laxative or for bowel preparation for colonoscopy. It is the result of calcium phosphate crystal deposition in tubules and interstitium and occurs especially in subjects with underlying renal impairment and hypovolemia. Consequently, Phospho-soda should be avoided in patients with chronic kidney disease.

LIGHT CHAIN CAST NEPHROPATHY

Patients with multiple myeloma may develop acute renal failure in the setting of hypovolemia, infection, or hypercalcemia or after exposure to NSAIDs or radiographic contrast media. The diagnosis of light chain cast nephropathy (LCCN)—commonly known as *myeloma kidney*—should be considered in patients who fail to recover when the precipitating factor is corrected or in any elderly patient with otherwise unexplained acute renal failure.

In this disorder, filtered monoclonal immunoglobulin light chains (Bence-Jones proteins) form intratubular aggregates with secreted Tamm-Horsfall protein in the distal tubule. Casts, in addition to obstructing the tubular flow in affected nephrons, incite a giant cell or foreign body reaction and can lead to tubular rupture, resulting in interstitial fibrosis **(Fig. 17-3)**. Although LCCN generally occurs in patients with known multiple myeloma and a large plasma cell burden, the disorder should also be considered as a possible diagnosis in patients who have known monoclonal gammopathy even in the absence of frank myeloma. Filtered monoclonal light chains may also cause less pronounced renal manifestations in the absence of obstruction, due to direct toxicity to proximal tubular cells and intracellular crystal

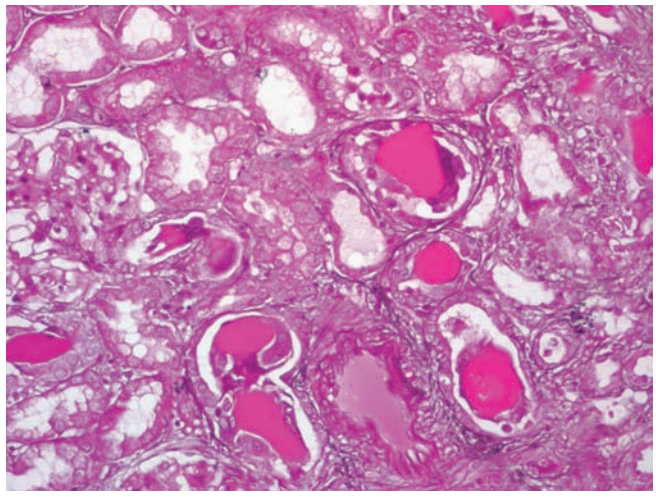


FIGURE 17-3
Histologic appearance of myeloma cast nephropathy. A hematoxylin-eosin-stained kidney biopsy shows many atrophic tubules filled with eosinophilic casts (consisting of Bence-Jones protein), which are surrounded by giant cell reactions. (*Courtesy of Dr. Michael N. Koss, University of Southern California Keck School of Medicine; with permission.*)

formation. This may result in isolated tubular disorders such as RTA or the full Fanconi syndrome.

Diagnosis

Clinical clues to the diagnosis include anemia, bone pain, hypercalcemia, and an abnormally narrow anion gap due to hypoalbuminemia and hypergammaglobulinemia. Urinary dipsticks detect albumin but not immunoglobulin light chains; however, laboratory detection of increased amounts of protein in a spot urine specimen and a negative dipstick result are highly suggestive that the urine contains Bence-Jones protein. Serum and urine should both be sent for protein electrophoresis and for immunofixation for the detection and identification of a potential monoclonal band. A sensitive method is now clinically available to detect urine and serum free light chains.

TREATMENT **Light Chain Cast Nephropathy**

The goals of treatment are to correct precipitating factors such as hypovolemia and hypercalcemia, discontinue potential nephrotoxic agents, and treat the underlying plasma cell dyscrasia; plasmapheresis to remove light chains is of questionable value for LCCN.

LYMPHOMATOUS INFILTRATION OF THE KIDNEY

Interstitial infiltration by malignant B lymphocytes is a common autopsy finding in patients dying of chronic lymphocytic leukemia and non-Hodgkin's lymphoma; however, this is usually an incidental finding. Rarely, such infiltrates may cause massive enlargement of the kidneys and oliguric acute renal failure. Although high-dose glucocorticoids and subsequent chemotherapy often results in recovery of renal function, the prognosis in such cases is generally poor.

CHRONIC TUBULOINTERSTITIAL DISEASES

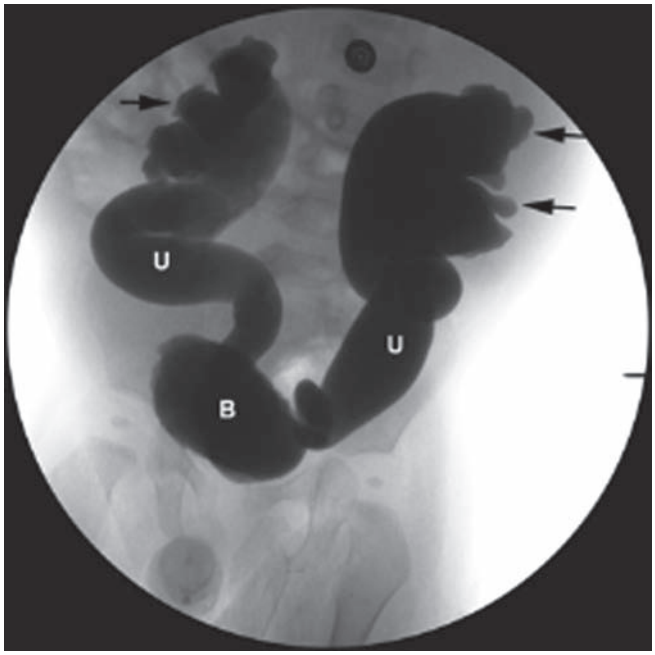
Improved occupational and public health measures, together with the banning of over-the-counter phenacetin-containing analgesics, has led to a dramatic decline in the incidence of chronic interstitial nephritis (CIN) from heavy metal—particularly lead and cadmium—exposure and analgesic nephropathy in North America. Today, CIN is most often the result of renal ischemia or secondary to a primary glomerular disease (Chap. 15). Other important forms of CIN are the result of developmental anomalies or inherited diseases such as reflux nephropathy or sickle cell nephropathy and may not be recognized until adolescence or adulthood. Whereas it is impossible to reverse damage that has already occurred, further deterioration may be prevented or at least slowed in such cases by treating glomerular hypertension, a common denominator in the development of secondary FSGS and progressive loss of functioning nephrons. Therefore, awareness and early detection of patients at risk may prevent them from developing end-stage renal disease (ESRD).

VESICOURETERAL REFLUX AND REFLUX NEPHROPATHY

Reflux nephropathy is the consequence of vesicoureteral reflux (VUR) or other urologic anomalies in early childhood. It was previously called *chronic pyelonephritis* because it was believed to result from recurrent urinary tract infections (UTIs) in childhood. VUR stems from abnormal retrograde urine flow from the bladder into one or both ureters and kidneys because of mislocated and incompetent ureterovesical valves **(Fig. 17-4)**. Although high-pressure sterile reflux may impair normal growth of the kidneys, when coupled with recurrent UTIs in early childhood, the result is patchy interstitial scarring and tubular atrophy. Loss of functioning nephrons leads to hypertrophy of the remnant glomeruli and eventual secondary FSGS. Reflux nephropathy often goes unnoticed until early adulthood when chronic kidney disease is detected during routine evaluation or during pregnancy. Affected adults are frequently asymptomatic, but may give a history of prolonged bed-wetting or recurrent UTIs during childhood, and exhibit variable renal insufficiency, hypertension, mild to moderate proteinuria, and unremarkable urine sediment. When both kidneys are affected, the disease often progresses inexorably over several years to end-stage kidney disease, despite the absence of ongoing urinary infections or reflux. A single affected kidney may go undetected, except for the presence of hypertension. Renal ultrasound in adults characteristically shows asymmetric, small kidneys with irregular outlines, thinned cortices, and regions of compensatory hypertrophy (Fig. 17-4).

TREATMENT **Vesicoureteral Reflux and Reflux Nephropathy**

Maintenance of a sterile urine in childhood has been shown to limit scarring of the kidneys. Surgical reimplantation of the ureters into the bladder to restore competency is indicated in young children with persistent high-grade reflux but is ineffective and is not indicated in adolescents or adults after scarring has occurred. Aggressive control of blood pressure with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) and other agents is effective in reducing proteinuria and may significantly forestall further deterioration of renal function.



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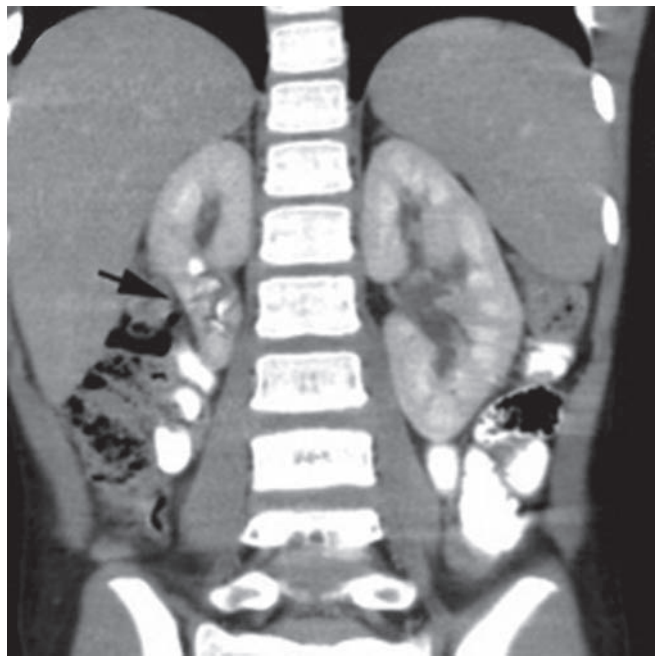

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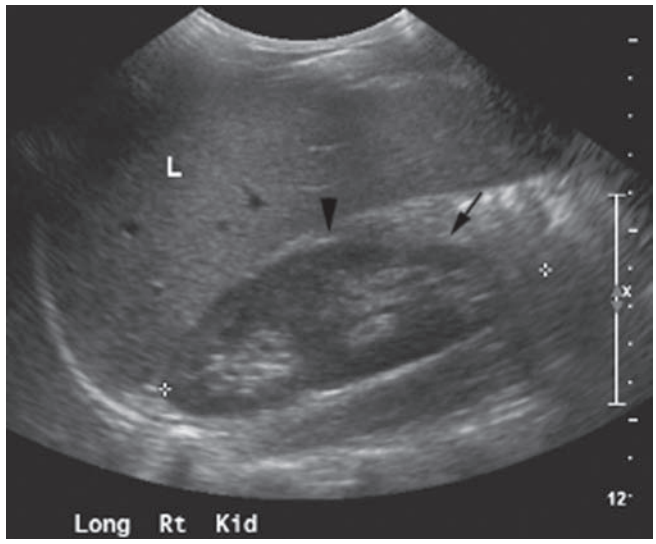

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FIGURE 17-4
Radiographs of vesicoureteral reflux (VUR) and reflux nephropathy. *A*. Voiding cystourethrogram in a 7-month-old baby with bilateral high-grade VUR evidenced by clubbed calyces (*arrows*) and dilated tortuous ureters (U) entering the bladder (B). ***B*.** Abdominal CT scan (coronal plane reconstruction) in a child showing severe scarring of the lower portion of the right kidney (*arrow*). ***C*.** Sonogram of the right kidney showing loss of parenchyma at the lower pole due to scarring (*arrow*) and hypertrophy of the mid-region (*arrowhead*). (*Courtesy of Dr. George Gross, University of Maryland Medical Center; with permission.*)

SICKLE CELL NEPHROPATHY

The pathogenesis and clinical manifestations of sickle cell nephropathy are described in Chap. 18. Evidence of tubular injury may be evident in childhood and early adolescence in the form of polyuria due to decreased concentrating ability or type IV renal tubular acidosis years before there is significant nephron loss and proteinuria from secondary FSGS. Early recognition of these subtle renal abnormalities or development of microalbuminuria in a child with sickle cell disease may warrant consultation with a nephrologist and/or therapy with low-dose ACEIs. Papillary necrosis may result from ischemia due to sickling of red cells in the relatively hypoxemic and hypertonic medullary vasculature and present with gross hematuria and ureteric obstruction by sloughed ischemic papillae **(Table 17-3)**.

TABLE 17-3

MAJOR CAUSES OF PAPILLARY NECROSIS
Analgesic nephropathy
Sickle cell nephropathy
Diabetes with urinary tract infection
Prolonged NSAID use (rare)

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

TUBULOINTERSTITIAL ABNORMALITIES ASSOCIATED WITH GLOMERULONEPHRITIS

Primary glomerulopathies are often associated with damage to tubules and interstitium. This may occasionally be due to the same pathologic process affecting the glomerulus and tubulointerstitium, as is the case with immune-complex deposition in lupus nephritis. More often, however, chronic tubulointerstitial changes occur as a secondary consequence of prolonged glomerular dysfunction. Potential mechanisms by which glomerular disease might cause tubulointerstitial injury include proteinuria-mediated damage to the epithelial cells, activation of tubular cells by cytokines and complement, or reduced peritubular blood flow leading to downstream tubulointerstitial ischemia, especially in the case of glomeruli that are globally obsolescent due to severe glomerulonephritis. It is often difficult to discern the initial cause of injury by renal biopsy in a patient who presents with advanced renal disease in this setting.

ANALGESIC NEPHROPATHY

Analgesic nephropathy results from the long-term use of compound analgesic preparations containing phenacetin (banned in the United States since 1983), aspirin, and caffeine. In its classic form, analgesic nephropathy is characterized by renal insufficiency, papillary necrosis (Table 17-3) attributable to the presumed concentration of the drug to toxic levels in the inner medulla, and a radiographic constellation of small, scarred kidneys with papillary calcifications best appreciated by computed tomography **(Fig. 17-5)**. Patients may also have polyuria due to impaired concentrating ability and non-anion-gap metabolic acidosis from tubular damage. Shedding of a sloughed necrotic papilla can cause gross hematuria and ureteric colic due to ureteral obstruction. Individuals with end-stage kidney disease as a result of analgesic nephropathy are at increased risk of a urothelial malignancy compared to patients with other causes of renal failure. Recent cohort studies in individuals with normal baseline renal function suggest that the moderate chronic use of current analgesic preparations available in the United States, including acetaminophen and NSAIDs, does not seem to cause the constellation of findings known as analgesic nephropathy, although volume-depleted individuals and those with chronic kidney disease are at higher risk of NSAID-related renal toxicity. Nonetheless, it is recommended that heavy users of acetaminophen and NSAIDs be screened for evidence of renal disease.

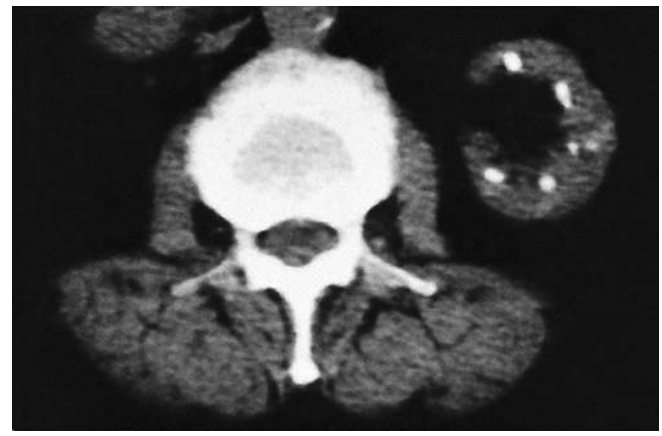

FIGURE 17-5

Radiologic appearance of analgesic nephropathy. A noncontrast CT scan shows an atrophic left kidney with papillary calcifications in a garland pattern. (*Reprinted by permission from Macmillan Publishers, Ltd., MM Elseviers et al: Kidney International 48:1316, 1995.*)

CHINESE HERBAL NEPHROPATHY AND BALKAN NEPHROPATHY

Nontraditional (alternative or herbal) medications can also lead to progressive tubulointerstitial disease. In Chinese herbal nephropathy, first described in young women taking Chinese herbal preparations as part of a weight-loss regimen, one of the offending agents has been identified as aristolochic acid, a botanical product and known rodent carcinogen from the plant *Aristolochia*. This chemical, after prolonged exposure, produces renal interstitial fibrosis with a relative paucity of cellular infiltrates. The urine sediment is bland, with rare leukocytes and only mild proteinuria. Anemia may be disproportionately severe relative to the level of renal dysfunction. Like analgesic nephropathy, Chinese herbal nephropathy has been associated with a long-term increased risk of bladder and ureteral malignancies. There is recent evidence that Balkan endemic nephropathy, a chronic tubulointerstitial nephritis found primarily in towns along the tributaries of the Danube River, may also be linked to aristolochic acid as a result of contamination of local grain preparations. Although other environmental factors for Balkan endemic nephropathy, such as the mycotoxin ochratoxin A or water-soluble hydrocarbons leached from the coal deposits in the area, have been proposed as causative agents, current evidence appears to be strongest for aristolochic acid. It has been proposed that Chinese herbal nephropathy and Balkan endemic nephropathy be collectively known as aristolochic acid nephropathy.

LITHIUM-ASSOCIATED NEPHROPATHY

The use of lithium salts for the treatment of manic-depressive illness may have several renal sequelae, the most common of which is nephrogenic diabetes insipidus manifesting as polyuria and polydipsia. Lithium accumulates in principal cells of the collecting duct by entering through the epithelial sodium channel (ENaC), where it inhibits glycogen synthase kinase 3β and down-regulates vasopressin-regulated aquaporin water channels. Less frequently, chronic tubulointerstitial nephritis develops after prolonged (greater than 10–20 years) lithium use and is most likely to occur in patients that have experienced repeated episodes of toxic lithium levels. Findings on renal biopsy include interstitial fibrosis and tubular atrophy that are out of proportion to the degree of glomerulosclerosis or vascular disease, a sparse lymphocytic infiltrate, and small cysts or dilation of the distal tubule and collecting duct that are highly characteristic of this disorder. The degree of interstitial fibrosis correlates both with duration and cumulative dose of lithium. Individuals with lithium-associated nephropathy are typically asymptomatic, with minimal proteinuria, few urinary leukocytes, and normal blood pressure. Some patients develop more severe proteinuria due to secondary FSGS, which may contribute to further loss of renal function.

TREATMENT **Lithium-Associated Nephropathy**

Renal function should be followed regularly in patients taking lithium, and caution should be exercised in patients with underlying renal disease. The use of amiloride to inhibit lithium entry via ENaC has been effective to prevent and treat lithium-induced nephrogenic diabetes insipidus, but it is not clear if it will prevent lithium-induced CIN. Once lithium-associated nephropathy is detected, the discontinuation of lithium in an attempt to forestall further renal deterioration can be problematic, as lithium is an effective mood stabilizer that is often incompletely substituted by other agents. Furthermore, despite discontinuation of lithium, chronic renal disease in such patients is often irreversible and can slowly progress to end-stage kidney disease. The most prudent approach is to monitor lithium levels frequently and adjust dosing to avoid toxic levels (preferably <1 meq/L). This is especially important as lithium is cleared less effectively as renal function declines. In those cases that develop significant proteinuria, ACEI or ARB treatment should be initiated.

CALCINEURIN-INHIBITOR NEPHROTOXICITY

The calcineurin inhibitor (CNI) immunosuppressive agents cyclosporine and tacrolimus can cause both acute and chronic renal injury. Acute forms can result from vascular causes such as vasoconstriction or the development of thrombotic microangiopathy, or can be due to a toxic tubulopathy. Chronic CNI-induced renal injury is typically seen in solid organ (including heart-lung and liver) transplant recipients and manifests with a slow but irreversible reduction of glomerular filtration rate, with mild proteinuria and arterial hypertension. Hyperkalemia is a relatively common complication and is caused, in part, by tubular resistance to aldosterone. The histologic changes in renal tissue include patchy interstitial fibrosis and tubular atrophy, often in a "striped" pattern. In addition, the intrarenal vasculature often demonstrates hyalinosis, and focal glomerulosclerosis can be present as well. Similar changes may occur in patients receiving CNIs for autoimmune diseases, although the doses are generally lower than those used for organ transplantation. Dose reduction or CNI avoidance appears to mitigate the chronic tubulointerstitial changes, but may increase the risk of rejection and graft loss.

HEAVY METAL (LEAD) NEPHROPATHY

Heavy metals, such as lead or cadmium, can lead to a chronic tubulointerstitial process after prolonged exposure. The disease entity is no longer commonly diagnosed, because such heavy metal exposure has been greatly reduced due to the known health risks from lead and the consequent removal of lead from most commercial products and fuels. Nonetheless, occupational exposure is possible in workers involved in the manufacture or destruction of batteries, removal of lead paint, or manufacture of alloys and electrical equipment (cadmium) in countries where industrial regulation is less stringent. In addition, ingestion of moonshine whiskey distilled in lead-tainted containers has been one of the more frequent sources of lead exposure.

Early signs of chronic lead intoxication are attributable to proximal tubule dysfunction, particularly hyperuricemia as a result of diminished urate secretion. The triad of "saturnine gout," hypertension, and renal insufficiency should prompt a practitioner to ask specifically about lead exposure. Unfortunately, evaluating lead burden is not as straightforward as ordering a blood test; the preferred methods involve measuring urinary lead after infusion of a chelating agent or by radiographic fluoroscopy of bone. Several recent studies have shown an association between chronic low-level lead exposure and decreased renal function, although either of these two factors may have been the primary event. In those patients who have CIN of unclear origin and an elevated total body lead burden, repeated treatments of lead chelation therapy have been shown to slow the decline in renal function.

METABOLIC DISORDERS

Disorders leading to excessively high or low levels of certain electrolytes and products of metabolism can also lead to chronic kidney disease if untreated.

CHRONIC URIC ACID NEPHROPATHY

The constellation of pathologic findings that represent *gouty nephropathy* are very uncommon nowadays and are more of historical interest than clinical importance, as gout is typically well managed with allopurinol and other agents. However, there is emerging evidence that hyperuricemia is an independent risk factor for the development of chronic kidney disease, perhaps through endothelial damage. The complex interactions of hyperuricemia, hypertension, and renal failure are still incompletely understood.

Presently, gouty nephropathy is most likely to be encountered in patients with severe tophaceous gout and prolonged hyperuricemia from a hereditary disorder of purine metabolism (Chap. 8). Histologically, the distinctive feature of gouty nephropathy is the presence of crystalline deposits of uric acid and monosodium urate salts in the kidney parenchyma. These deposits not only cause intrarenal obstruction but also incite an inflammatory response, leading to lymphocytic infiltration, foreign-body giant cell reaction, and eventual fibrosis, especially in the medullary and papillary regions of the kidney. Since patients with gout frequently suffer from hypertension and hyperlipidemia, degenerative changes of the renal arterioles may constitute a striking feature of the histologic abnormality, out of proportion to the other morphologic defects. Clinically, gouty nephropathy is an insidious cause of chronic kidney disease. Early in its course, glomerular filtration rate may be near normal, often despite morphologic changes in medullary and cortical interstitium, proteinuria, and diminished urinary concentrating ability. Treatment with allopurinol and urine alkalinization is generally effective in preventing uric acid nephrolithiasis and the consequences of recurrent kidney stones; however, gouty nephropathy may be intractable to such measures. Furthermore, the use of allopurinol in asymptomatic hyperuricemia has not been consistently shown to improve renal function.

HYPERCALCEMIC NEPHROPATHY

Chronic hypercalcemia, as occurs in primary hyperparathyroidism, sarcoidosis, multiple myeloma, vitamin D intoxication, or metastatic bone disease, can cause tubulointerstitial disease and progressive renal failure. The earliest lesion is a focal degenerative change in renal epithelia, primarily in collecting ducts, distal tubules, and loops of Henle. Tubular cell necrosis leads to nephron obstruction and stasis of intrarenal urine, favoring local precipitation of calcium salts and infection. Dilation and atrophy of tubules eventually occurs, as does interstitial fibrosis, mononuclear leukocyte infiltration, and interstitial calcium deposition (nephrocalcinosis). Calcium deposition may also occur in glomeruli and the walls of renal arterioles.

Clinically, the most striking defect is an inability to maximally concentrate the urine, due to reduced collecting duct responsiveness to AVP and defective transport of sodium and chloride in the loop of Henle. Reductions in both glomerular filtration rate and renal blood flow can occur, both in acute and in prolonged hypercalcemia. Eventually, uncontrolled hypercalcemia leads to severe tubulointerstitial damage and overt renal failure. Abdominal x-rays may demonstrate nephrocalcinosis as well as nephrolithiasis, the latter due to the hypercalciuria that often accompanies hypercalcemia.

Treatment consists of reducing the serum calcium concentration toward normal and correcting the primary abnormality of calcium metabolism. Renal dysfunction of acute hypercalcemia may be completely reversible. Gradual progressive renal insufficiency related to chronic hypercalcemia, however, may not improve even with correction of the calcium disorder.

HYPOKALEMIC NEPHROPATHY

Patients with prolonged and severe hypokalemia from chronic laxative or diuretic abuse, surreptitious vomiting, or primary aldosteronism may develop a reversible tubular lesion characterized by vacuolar degeneration of proximal and distal tubular cells. Eventually, tubular atrophy and cystic dilation accompanied by interstitial fibrosis may ensue, leading to irreversible chronic kidney disease. Timely correction of the hypokalemia will prevent further progression, but persistent hypokalemia can cause ESRD.

GLOBAL PERSPECTIVE

The causes of acute and chronic interstitial nephritis vary widely across the globe. Analgesic nephropathy continues to be seen in countries where phenacetin-containing compound analgesic preparations are readily available. Adulterants in unregulated herbal and traditional medicaments pose a threat of toxic interstitial nephritis, as exemplified by aristolochic acid contamination of herbal slimming preparations. Contamination of food sources with toxins, such as the recent outbreak of nephrolithiasis and acute renal failure from

melamine contamination of infant milk formula, poses a continuing risk. Likewise, Balkan endemic nephropathy appears likely to be the result of aristolochic acid contamination of grain preparations. While industrial exposure to lead and cadmium has largely disappeared as a cause of chronic interstitial nephritis in developed nations, it remains a risk for nephrotoxicity in countries where such exposure is less well controlled. Conversely, the widespread use of proton pump inhibitors for gastroesophageal reflux disease (GERD) and Phospho-soda prior to screening colonoscopy has introduced a new spectrum of drug-induced kidney diseases to wealthier nations.

Acknowledgment

We are grateful to Drs. Alan Yu and Barry Brenner, authors of "Tubulointerstitial Diseases of the Kidney" in the 17th edition of Harrison's Principles of Internal Medicine, for contributions to this chapter.

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SECTION V

RENAL VASCULAR DISEASE

CHAPTER 18

VASCULAR INJURY TO THE KIDNEY

Stephen C. Textor ■ Nelson Leung

The renal vasculature is unusually complex with rich arteriolar flow to the cortex in excess of metabolic requirements, consistent with its primary function as a filtering organ. After delivering blood to cortical glomeruli, the postglomerular circulation supplies deeper medullary segments that support energy-dependent solute transport at multiple levels of the renal tubule. These postglomerular vessels carry less blood, and high oxygen consumption leaves the deeper medullary regions at the margin of hypoxemia. Vascular disorders that commonly threaten the blood supply of the kidney include large vessel atherosclerosis, fibromuscular diseases, and embolic, inflammatory, and primary hematologic disorders that produce microvascular injury.

ATHEROSCLEROSIS AND KIDNEY CIRCULATION

MICROVASCULAR DISEASE

The glomerular capillary endothelium shares susceptibility to oxidative stress, pressure injury, and inflammation with other vascular territories. Rates of urinary albumin excretion (UAE) are predictive of systemic atherosclerotic disease events. Increased UAE may develop years before cardiovascular events. UAE and the risk of cardiovascular events are both reduced with pharmacologic therapy such as statins. Experimental studies demonstrate functional changes and rarefaction of renal microvessels under conditions of accelerated atherosclerosis and/or compromise of proximal perfusion pressures with large vessel disease **(Fig. 18-1)**.

MACROVASCULAR DISEASE

Large-vessel renal artery occlusive disease can result from extrinsic compression of the vessel, fibromuscular dysplasias, or, most commonly, from atherosclerotic disease. Any disorder that reduces perfusion pressure to the kidney can activate mechanisms that tend to restore renal pressures at the expense of developing systemic hypertension. Because restoration of perfusion pressures can reverse these pathways, renal artery stenosis is considered a specifically treatable "secondary" cause of hypertension.

Renal artery stenosis is common and often has only minor hemodynamic effects. Fibromuscular dysplasia (FMD) is reported in 3–5% of normal subjects presenting as potential kidney donors without hypertension. It may present clinically with hypertension in younger individuals (between age 15 and 50), most often women. FMD does not often threaten kidney function, but sometimes produces total occlusion and can be associated with renal artery aneurysms. Atherosclerotic renal artery stenosis (ARAS) is common in the general population (6.8% of a community-based sample above age 65), a prevalence that increases with age and for patients with other vascular conditions such as coronary artery disease (18–23%) and/or peripheral aortic or lower extremity disease (more than 30%). If untreated, ARAS progresses in nearly 50% of cases over a 5-year period, sometimes to total occlusion. Intensive treatment of arterial blood pressure and statin therapy appear to slow these rates and improve clinical outcomes.

Critical levels of stenosis lead to a reduction in perfusion pressure that activates the renin-angiotensin system, reduces sodium excretion, and activates sympathetic adrenergic pathways. These events lead to systemic hypertension characterized by angiotensin dependence in the early stages, widely varying pressures, loss of circadian blood pressure (BP) rhythms, and accelerated target organ injury, including left ventricular hypertrophy and renal fibrosis. Renovascular hypertension can be treated with agents that block the renin-angiotensin system and other drugs that modify these pressor pathways. It can also be treated with restoration of renal blood flow by either endovascular or surgical revascularization.

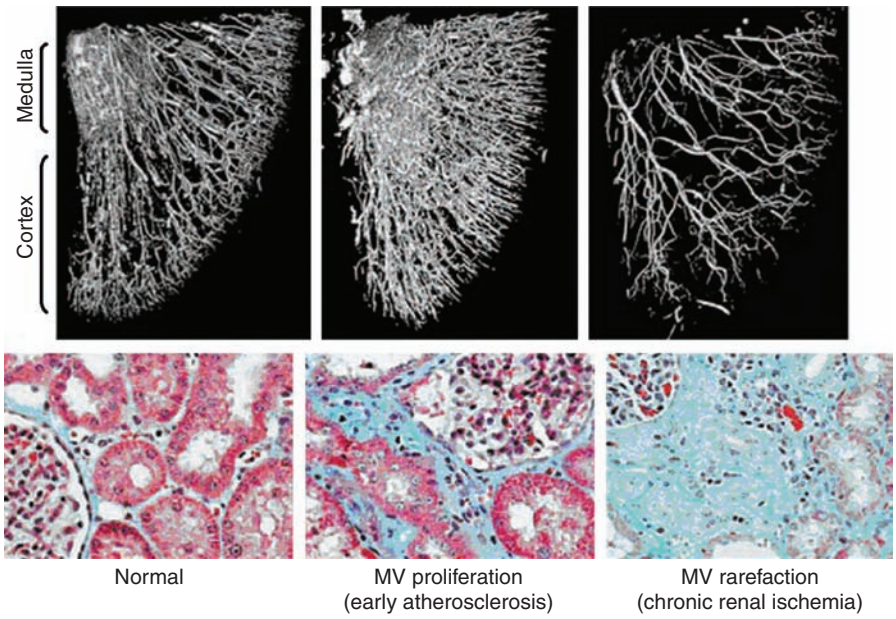


FIGURE 18-1
Examples of micro-CT images from vessels defined by radiopaque casts injected into the renal vasculature. These illustrate the complex, dense cortical capillary network supplying the kidney cortex that can either proliferate or succumb to rarefaction under the influence of atherosclerosis and/or occlusive disease. Changes in blood supply are followed by tubulointerstitial fibrosis and loss of kidney function. MV, microvascular (*From LO Lerman, AR Chade: Curr Opin Nephrol Hyper 18:160, 2009, with permission.*)

In most cases, patients require continued antihypertensive drug therapy because revascularization alone rarely lowers BP to normal.

ARAS and systemic hypertension tend to affect both the poststenotic and contralateral kidneys, reducing overall glomerular filtration rate (GFR) in ARAS. When kidney function is threatened by large vessel disease primarily, it has been labeled *ischemic nephropathy*. Unlike FMD, ARAS develops in patients with other risk factors for atherosclerosis and is commonly superimposed upon preexisting small vessel disease in the kidney resulting from hypertension, aging, and diabetes. Nearly 85% of patients considered for renal revascularization have stage 3–5 chronic kidney disease (CKD) with GFR below 60 mL/min per 1.73 m^2. The presence of ARAS is a strong predictor of morbidity- and mortality-related cardiovascular events, independent of whether renal revascularization is undertaken.

Diagnostic approaches to renal artery stenosis depend partly on the specific issues to be addressed. Noninvasive characterization of the renal vasculature may be achieved by several techniques summarized in **(Table 18-1)**. Although activation of the renin-angiotensin system is a key step in developing renovascular hypertension, it is transient. Levels of renin activity are therefore subject to timing, the effects of drugs and sodium intake, and do not reliably predict the response to vascular therapy. Renal artery velocities by Doppler ultrasound above 200 cm/s generally predict hemodynamically important lesions (above 60% vessel lumen occlusion), although treatment trials require velocity above 300 cm/s to avoid false positives. The renal resistive index has predictive value regarding the viability of the kidney. It remains operator and institution dependent, however. Captopril-enhanced renography has a strong negative predictive value when entirely normal. Magnetic resonance angiography (MRA) is now less often used, as gadolinium contrast has been associated with nephrogenic systemic fibrosis. Contrast-enhanced CT with vascular reconstruction provides excellent vascular images and functional assessment, but carries a small risk of contrast toxicity.

TREATMENT **Renal Artery Stenosis**

While restoring renal blood flow and perfusion seems intuitively beneficial for high-grade occlusive lesions, revascularization procedures also pose hazards and expense. Patients with FMD are commonly younger females with otherwise normal vessels and a long life expectancy. These patients often respond well to percutaneous renal artery angioplasty. If blood pressure can be controlled to goal levels and kidney function remains stable in patients with ARAS, it may be argued that medical therapy with follow-up for disease progression is equally effective. Prospective trials up to now fail to identify compelling benefits for interventional procedures regarding short-term results of blood pressure and renal function, although long-term studies regarding cardiovascular outcomes such as stroke,

TABLE 18-1

SUMMARY OF IMAGING MODALITIES FOR EVALUATING THE KIDNEY VASCULATURE

Perfusion Studies to Assess Differential Renal Blood Flow			
Captopril renography with technetium ^{99m} mertiatide (^{99m}Tc MAG3)	Captopril-mediated fall in filtration pressure amplifies differences in renal perfusion	Normal study excludes renovascular hypertension	Multiple limitations in patients with advanced atherosclerosis or creatinine >2.0 mg/dL (177 μmol/L)
Nuclear imaging with technetium mertiatide or technetium-labeled pentetic acid (DTPA) to estimate fractional flow to each kidney	Estimates fractional flow to each kidney	Allows calculation of single-kidney glomerular filtration rate	Results may be influenced by other conditions, e.g., obstructive uropathy
Vascular Studies to Evaluate the Renal Arteries			
Duplex ultrasonography	Shows the renal arteries and measures flow velocity as a means of assessing the severity of stenosis	Inexpensive; widely available	Heavily dependent on operator's experience; less useful than invasive angiography for the diagnosis of fibromuscular dysplasia and abnormalities in accessory renal arteries
Magnetic resonance angiography	Shows the renal arteries and perirenal aorta	Not nephrotoxic, but concerns for gadolinium toxicity exclude use in GFR <30 mL/min/1.73 m^2; provides excellent images	Expensive; gadolinium excluded in renal failure, unable to visualize stented vessels
Computed tomographic angiography	Shows the renal arteries and perirenal aorta	Provides excellent images; stents do not cause artifacts	Expensive, moderate volume of contrast required, potentially nephrotoxic
Intra-arterial angiography	Shows location and severity of vascular lesion	Considered "gold standard" for diagnosis of large vessel disease, usually performed simultaneously with planned intervention	Expensive, associated hazard of atheroemboli, contrast toxicity, procedure-related complications, e.g., dissection

Abbrevations: DTPA, diethylenetriamine pentaacetic acid (pentetic acid); GFR, glomerular filtration rate.

congestive heart failure, myocardial infarction, and end-stage renal failure are not yet complete. Medical therapy should include blockade of the renin-angiotensin system, attainment of goal blood pressures, cessation of tobacco, statins, and aspirin.

Techniques of renal revascularization are improving. With experienced operators, major complications develop in about 9% of cases, including renal artery dissection, capsular perforation, hemorrhage, and occasional atheroembolic disease. Although not common, atheroembolic disease can be catastrophic and accelerate both hypertension and kidney failure, exactly the events that revascularization is intended to prevent. Although renal blood flow usually can be restored by endovascular stenting, recovery of renal function is limited to about 25% of cases, with no change in 50%, and some deterioration evident in others. When hypertension is refractory to effective therapy, revascularization offers real benefits. Table 18-2 summarizes currently accepted guidelines for considering renal revascularization.

ATHEROEMBOLIC RENAL DISEASE

Emboli to the kidneys arise most frequently as a result of cholesterol crystals breaking free of atherosclerotic vascular plaque and lodging in downstream microvessels. Most clinical atheroembolic events follow angiographic procedures, often of the coronary vessels. It has been argued that nearly all vascular interventional procedures lead to plaque fracture and release of microemboli, but clinical manifestations develop only in a fraction of these. The incidence of clinical atheroemboli has been increasing with more vascular procedures and longer life spans. Atheroembolic renal disease is suspected in more than 3% of end-stage renal disease (ESRD) in elderly subjects and is likely underdiagnosed. It is more frequent in males with history of diabetes, hypertension, and ischemic cardiac disease. Atheroemboli in the kidney are strongly associated with aortic aneurysmal disease and renal artery stenosis. Most clinical cases can be associated with precipitating events, such as angiography, vascular surgery, anticoagulation with heparin, thrombolytic therapy,

TABLE 18-2

CLINICAL FACTORS FAVORING MEDICAL THERAPY AND REVASCULARIZATION OR SURVEILLANCE FOR RENAL ARTERY STENOSIS

Factors Favoring Medical Therapy and Revascularization for Renal Artery Stenosis
• Progressive decline in GFR during treatment of systemic hypertension
• Failure to achieve adequate blood pressure control with optimal medical therapy (medical failure)
• Rapid or recurrent decline in the GFR in association with a reduction in systemic pressure
• Decline in the GFR during therapy with ACE inhibitors or ARBs
• Recurrent congestive heart failure in a patient in whom the adequacy of left ventricular function does not explain a cause
Factors Favoring Medical Therapy and Surveillance of Renal Artery Disease
• Controlled blood pressure with stable renal function (e.g., stable renal insufficiency)
• Stable renal artery stenosis without progression on surveillance studies (e.g., serial duplex ultrasound)
• Very advanced age and/or limited life expectancy
• Extensive comorbidity that make revascularization too risky
• High risk for or previous experience with atheroembolic disease
• Other concomitant renal parenchymal diseases that cause progressive renal dysfunction (e.g., interstitial nephritis, diabetic nephropathy)

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; GFR, glomerular filtration rate.

or trauma. Clinical manifestations of this syndrome commonly develop between 1 and 14 days after an inciting event and may continue to develop for weeks thereafter. Systemic embolic disease manifestations, such as fever, abdominal pain, and weight loss are present in less than half of patients, although cutaneous manifestations including livedo reticularis, and localized toe gangrene may be more common. Worsening hypertension and deteriorating kidney function are common, sometimes reaching a malignant phase. Progressive renal failure can occur and require dialytic support. These cases often develop after a stuttering onset over many weeks and have an ominous prognosis. Mortality rate after 1 year reaches 38%, and although some may eventually recover sufficiently to no longer require dialysis, many do not.

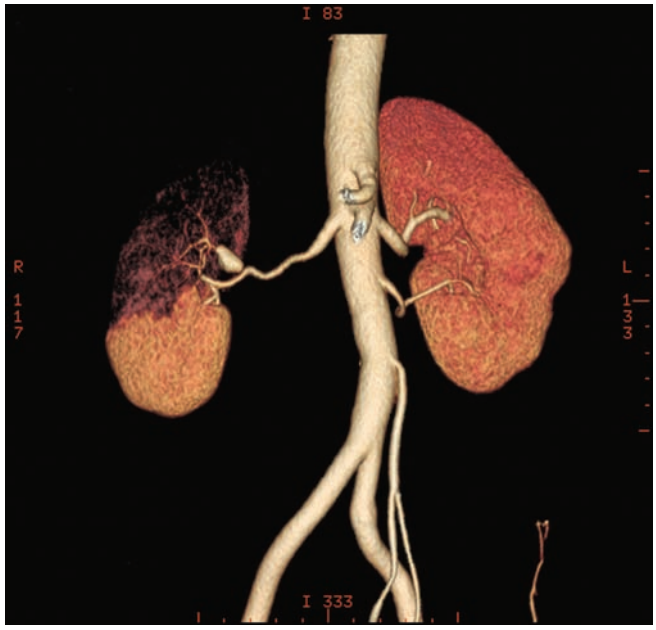
Beyond the clinical manifestations above, laboratory findings include rising creatinine, eosinophilia (60–80%), elevated sedimentation rate, and hypocomplementemia (15%). Establishing this diagnosis can be difficult and is often by exclusion. Definitive diagnosis depends upon kidney biopsy demonstrating microvessel occlusion with cholesterol crystals that leave a "cleft" in the vessel. Biopsies obtained from patients undergoing surgical revascularization of the kidney indicate that silent cholesterol emboli are frequently present before any further manipulation is performed.

No effective therapy is available for atheroembolic disease once it has developed. Withdrawal of anticoagulation is recommended. Late recovery of kidney function after supportive measures sometimes occurs, and statin therapy may improve outcome. The role of embolic protection devices in the renal circulation is unclear, but a few prospective trials have failed to demonstrate major benefits. These devices are limited to distal protection during the endovascular procedure and offer no protection from embolic debris after removal.

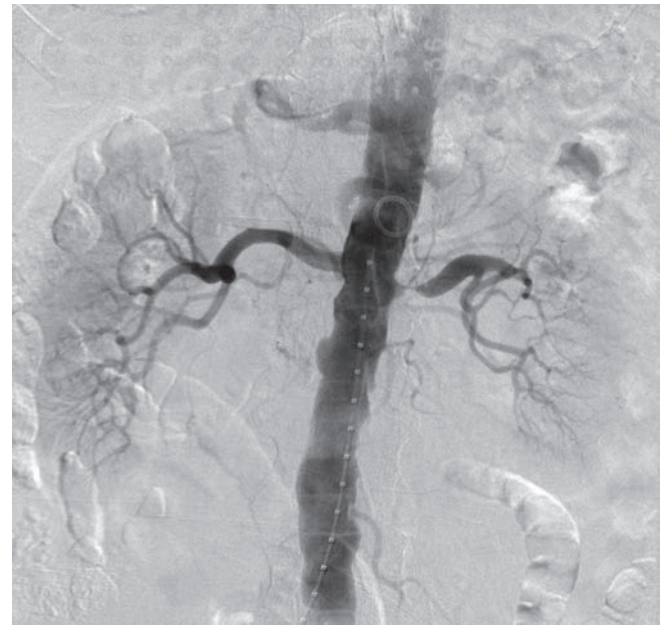
THROMBOEMBOLIC RENAL DISEASE

Thrombotic occlusion of renal vessels or branch arteries can lead to declining renal function and hypertension. It is difficult to diagnose and is often overlooked, especially in elderly patients. Thrombosis can develop as a result of local vessel abnormalities, such as local dissection, trauma, or inflammatory vasculitis. While hypercoagulability conditions sometimes present as renal artery thrombosis, this is rare. It can also derive from distant embolic events, e.g., the left atrium in patients with atrial fibrillation or from fat emboli originating from traumatized tissue, most commonly large bone fractures. Cardiac sources include vegetations from subacute bacterial endocarditis. Systemic emboli to the kidneys may also arise from the venous circulation if right-to-left shunting occurs, e.g., through a patent foramen ovale.

Clinical manifestations vary depending upon the rapidity of onset and extent of occlusion. Acute arterial thrombosis may produce flank pain, fever, leukocytosis, nausea, and vomiting. If kidney infarction results, enzymes such as lactate dehydrogenase (LDH) rise to extreme levels. If both kidneys are affected, renal function will decline precipitously with a drop in urine output. If a single kidney is involved, renal functional changes may be minor. Hypertension related to sudden release of renin from ischemic tissue can develop rapidly, so long as some viable tissue in the "peri-infarct" border zone remains. If the infarct zone demarcates precisely, the rise in blood pressure and renin activity may resolve. Diagnosis of renal infarction may be established by vascular imaging with MR, CT angiography, or arteriography **(Figs. 18-2*A* and *B*)**.



A



B

FIGURE 18-2

A.* CT angiogram illustrating loss of circulation to the upper pole of the right kidney in a patient with fibromuscular disease and a renal artery aneurysm.** Activation of the renin-angiotensin system produced rapidly developing hypertension. ***B. Angiogram illustrating high-grade renal artery stenosis affecting the left kidney. This lesion is often part of widespread atherosclerosis and sometimes is an extension of aortic plaque. This lesion develops in older individuals with preexisting atherosclerotic risk factors.

MANAGEMENT OF ARTERIAL THROMBOSIS OF THE KIDNEY

Options for interventions of newly detected arterial occlusion include surgical reconstruction, anticoagulation, thrombolytic therapy, endovascular procedures, and supportive care, particularly antihypertensive drug therapy. Application of these methods depends upon the patient's overall condition, the precipitating factors (e.g., local trauma or systemic illness), the magnitude of renal tissue and function at risk, and the likelihood of recurrent events in the future. For unilateral disease, e.g., arterial dissection with thrombosis, supportive care with anticoagulation may suffice. Acute, bilateral occlusion is potentially catastrophic, producing anuric renal failure. Depending upon the precipitating event, surgical or thrombolytic therapies can sometimes restore kidney viability.

MICROVASCULAR INJURY AND HYPERTENSION

ARTERIOLONEPHROSCLEROSIS

"Malignant" hypertension

Although BP rises with age, it has long been recognized that some individuals develop rapidly progressive BP elevations with target organ injury including retinal hemorrhages, encephalopathy, and declining kidney function. Placebo arms during the controlled trials of hypertension therapy identified progression to severe levels in 20% of subjects over 5 years. If untreated, patients with target organ injury including papilledema and declining kidney function suffered mortality rates in excess of 50% over 6–12 months, hence the designation "malignant." Postmortem studies of such patients identified vascular lesions, designated "fibrinoid necrosis," with breakdown of the vessel wall, deposition of eosinophilic material including fibrin, and a perivascular cellular infiltrate. A separate lesion was identified in the larger interlobular arteries in many patients with hyperplastic proliferation of the vascular wall cellular elements, deposition of collagen, and separation of layers, designated the "onionskin" lesion. For many of these patients, fibrinoid necrosis led to obliteration of glomeruli and loss of tubular structures. Progressive kidney failure ensued and without dialysis support led to early mortality in untreated malignant-phase hypertension. These vascular changes could develop with pressure-related injury from a variety of hypertensive pathways, including but not limited to activation of the renin-angiotensin system, and severe vasospasm associated with catecholamine release. Occasionally endothelial injury is sufficient to induce microangiopathic hemolysis as discussed below.

Antihypertensive therapy is the mainstay of therapy for malignant hypertension. With effective BP reduction, manifestations of vascular injury including

microangiopathic hemolysis and renal dysfunction can improve over time. Whereas mortality in series reported before the era of drug therapy suggested that 1-year mortality rates exceeded 90%, current survival over 5 years exceeds 50%.

Malignant hypertension is less common in Western countries, although it persists in parts of the world where medical care and antihypertensive drug therapy are less available. It most commonly develops in patients with treated hypertension who neglect to take medications, or who may use vasospastic drugs, such as cocaine. Renal abnormalities typically include rising serum creatinine, occasionally hematuria and proteinuria. Biochemical findings may include evidence of hemolysis (anemia, schistocytes, and reticulocytosis) and changes associated with kidney failure. African-American males are more likely to develop rapidly progressive hypertension and kidney failure than are whites in the United States. Genetic polymorphisms (MYH9) that are common in the African-American population and predispose to subtle focal sclerosing glomerular disease may be responsible, with hypertension developing secondary to renal disease in this instance.

"Hypertensive nephrosclerosis"

Based on experience with malignant hypertension and epidemiologic evidence linking BP with long-term risks of kidney failure, it has long been assumed that lesser degrees of hypertension induce less severe but prevalent changes in kidney vessels and loss of kidney function. As a result, a large portion of patients reaching ESRD without a specific etiologic diagnosis are assigned the designation "hypertensive nephrosclerosis." Pathologic examination commonly identifies afferent arteriolar thickening with deposition of homogeneous eosinophilic material (*hyaline arteriolosclerosis*) associated with narrowing of vascular lumina. Clinical manifestations include retinal vessel changes associated with hypertension (arteriolar narrowing, crossing changes), left ventricular hypertrophy, and elevated blood pressure. The role of these vascular changes in kidney function is unclear. Postmortem and biopsy samples from normotensive kidney donors demonstrate similar vessel changes associated with aging, dyslipidemia, and glucose intolerance. While BP reduction does slow progression of proteinuric kidney diseases and is warranted to reduce the excessive cardiovascular risks associated with CKD, antihypertensive therapy does not alter the course of kidney dysfunction identified specifically as hypertensive nephrosclerosis.

THROMBOTIC MICROANGIOPATHY

Thrombotic microangiopathy (TMA) refers to injured endothelial cells that are thickened, swollen, or detached mainly from arterioles and capillaries. Platelet and hyaline thrombi causing partial or complete occlusion are integral to the histopathology. TMA is the histologic result of microangiopathic hemolytic anemia (MAHA), which consumes platelets and erythrocytes and is characterized by thrombocytopenia and schistocytes. In the kidney, TMA is characterized by swelling of the endocapillary cells (endotheliosis), fibrin thrombi, platelet plugs, arterial intimal fibrosis, and membranoproliferative changes. In severe cases, the fibrin thrombi may extend into the arteriolar vascular pole producing glomerular collapse and sometimes cortical necrosis. Secondary focal segmental glomerulosclerosis may be seen in individuals who recover from acute TMA. Diseases that present with this lesion include thrombotic thrombocytopenia (TTP), hemolytic-uremia syndrome (HUS), malignant hypertension, scleroderma renal crisis, antiphospholipid syndrome, preeclampsia/HELLP (hemolysis, elevated liver enzymes, *low platelet* count) syndrome, HIV infection, and radiation nephropathy.

HEMOLYTIC-UREMIC SYNDROME (HUS)/ THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

HUS and TTP are the prototypes of MAHA. Whether they represent a spectrum of the same disease or two distinct entities continues to be debated. Histologically, the diseases are inseparable, but they differ regarding epidemiology and pathophysiology. Typical HUS usually affects children (most under the age of 5) and is preceded by hemorrhagic diarrhea. Typical TTP affects individuals in their thirties and forties. Neurologic symptoms are more common in TTP and have significant morbidity and mortality rates if not treated with plasma exchange, while plasma exchange is ineffective in most HUS. The argument is strengthened with the discovery of a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13 (ADAMTS13), a von Willebrand factor (vWF) cleaving protease that is either absent or inactive in TTP but not in HUS. However, neurologic symptoms can occur in HUS, and low ADAMTS13 activity has been identified in HUS cases. Furthermore, plasma infusion/exchange is effective in some HUS. As a result, the distinction between the two is blurred, and they are often identified simply as HUS/TTP.

HEMOLYTIC-UREMIC SYNDROME

There are at least four variants of HUS. The most common is D+ HUS referring to its association with bacterial gastroenteritis. This typically affects young children (<5 years), but adults are also susceptible. More than 80% of cases are preceded within a week by diarrhea, often bloody. Gastrointestinal symptoms include abdominal pain, cramping, and vomiting. Fever is typically absent.

Neurologic symptoms are common and may include lethargy, encephalopathy, seizures, and even cerebral infarction. The pathogenic agent linked to D+ HUS is the shiga toxin, also referred to as *verotoxin*. This toxin is produced by certain strains of *Escherichia coli* and *Shigella dysenteriae*. In the United States and Europe, the most common shiga-toxigenic *E. coli* (STEC) strain is the 0157:H7. Other strains such as 0157/H^-, 0111:H^-, 026:H11/H^-, and 0145:H28 can also produce shiga toxin. Once shiga toxin enters the circulation, it binds to neutrophils and preferentially localizes in the kidney, where it causes damage to the endothelial cells. This results in platelet aggregation, which initiates the microangiopathic process. Another bacterium associated with HUS is *Streptococcus pneumoniae*. This bacterium produces a neuraminidase that cleaves the *N*-acetyl neuraminic acid moieties that cover the Thomsen-Friedenreich antigen on platelets and endothelial cells. Exposure of this normally cryptic antigen to preformed IgM results in severe MAHA.

Another variant produces atypical HUS (aHUS), caused by congenital complement dysregulation rather than a toxin. These patients have low C3 levels, a characteristic of alternative pathway activation. The most common cause is a deficiency of factor H, which has been linked to families with aHUS. Factor H competes with factor B to prevent the formation of C3b,Bb and acts as a cofactor for factor I, which proteolytically degrades C3b. More than 70 mutations of the factor H gene have been identified. Most are missense mutations that produce normal levels of factor H with abnormalities mainly in the C-terminus region, which affect its binding to C3b. Other mutations result in low or complete absence of the protein. Deficiencies in other complement regulatory proteins such as factor I, factor B, membrane cofactor protein or MCP (CD46), C3, complement factor H–related protein 1 (CFHR1), CFHR3, and CFHR5 have also been described. Finally, an autoimmune variant of HUS has been discovered. Deficient for CFHR protein and factor H autoantibody–positive (DEAP), HUS occurs when an autoantibody is formed against factor H. DEAP-HUS is often associated with a deletion of an 84-kb fragment of the chromosome that encodes for CFHR1 and CFHR3. The autoantibody blocks the binding of factor H to C3b and surface-bound C3 convertase.

THROMBOTIC THROMBOCYTOPENIC PURPURA

Traditionally TTP is characterized by the pentad (hemolytic anemia, thrombocytopenia, neurologic symptoms, fever, and renal failure). Classic TTP is differentiated from HUS by neurologic involvement. However, in practice, differentiation between TTP and HUS is unreliable due to overlap in clinical manifestations. TTP has been linked with the absence of or marked decreased activity in the metalloprotease ADAMTS13 specific for vWF, although this is not universally present. Even complete absence of ADAMTS13 alone does not produce TTP. Most often, an additional trigger (such as infection, surgery, pancreatitis, or pregnancy) initiates clinical TTP.

Data from the Oklahoma TTP/HUS Registry reveal an incidence rate of 11.3 per 10^6 patients. The median age of the patients was 40 years. Higher frequency was noted among blacks, with an incidence more than nine times higher than non-blacks. Women have nearly three times the incidence, similar to the demographics for systemic lupus erythematosus. If untreated, TTP has a mortality rate exceeding 90%. Even with modern therapy, 20% of the patients die within the first month from complications of microvascular thrombosis.

Several subtypes of TTP have been described. The classic form is acquired or idiopathic TTP, which usually follows an infection or malignancy, or an intense inflammatory reaction such as pancreatitis. This variant typically occurs with deficiency of ADAMTS13 or its activity and is the result of an autoantibody. The autoantibody (IgG or IgM) can either increase clearance of ADAMTS13 or inhibit its activity. A hereditary form with congenital deficiency of ADAMTS13 is seen in patients with Upshaw-Schulman syndrome characterized by MAHA and thrombocytopenia. TTP in these patients can start within the first weeks of life, but in others, may not start until several years of age. Environmental and genetic factors are thought to influence the development of TTP. Plasma transfusion is effective as a prevention and treatment during the TTP episodes.

Drug-induced TTP/TMA is a recognized complication of chemotherapeutic agents, immunosuppressive agents, antiplatelet agents, and quinine. Two mechanisms are responsible for drug-induced TMA. With chemotherapeutic agents (mitomycin C, gemcitabine, etc.) and immunosuppressive agents (cyclosporine, tacrolimus, and sirolimus), endothelial damage is the main cause of the MAHA. This process is usually dose dependent. Alternatively, drugs can induce autoantibodies that produce TMA. Suppression of ADAMTS13 activity and formation of an autoantibody has been detected in patients exposed to ticlopidine. Quinine appears to induce autoantibodies against granulocytes, lymphocytes, endothelial cells, and platelet glycoprotein IbB/IX or IIb/IIIa complexes but not to ADAMTS13. Quinine-associated TTP is more common in women. Autoantibody-associated TTP can occur after a single dose in patients who had previous exposure to the drug. Most patients developing TTP from clopidogrel do not have either autoantibodies or decreased ADAMTS13 activity. Drugs that inhibit vascular endothelial growth factor (VEGF) sometimes produce TMA. The mechanism is not fully understood.

Treatment of HUS/TTP should be based on the pathophysiologic pathways that are identified. Autoantibody-mediated TTP and DEAP HUS should be treated with plasma exchange or plasmapheresis. In addition to removing the autoantibodies, plasma exchange replaces ADAMTS13. Twice-daily plasma exchanges, vincristine, and rituximab occasionally have been found to be effective in refractory cases. Plasma infusion is usually sufficient for congenital TTP such as Upshaw-Schulman syndrome. Plasma exchange should be considered if larger volumes of plasma are necessary. TTP secondary to drug-induced autoantibodies responds well to plasma exchange, while drugs that cause endothelial damage may not. D+ HUS should be treated with supportive measures. Plasma exchange has not been found to be effective. Antimotility agents and antibiotics increase the incidence of HUS and should be avoided. Conversely, plasma infusion/exchange may be beneficial in aHUS by repleting complement regulatory proteins. Antibiotics and washed red cells should be given in neuraminidase-associated HUS. Plasma and whole blood should be avoided since they contain IgM, which would exacerbate the MAHA. The coexistence of factor H and ADAMTS13 deficiency can exacerbate TTP and make it less responsive to plasma infusion, illustrating the complexity of managing these disorders.

TRANSPLANTATION-ASSOCIATED THROMBOTIC MICROANGIOPATHY (TA-TMA)

TA-TMA can develop after hematopoietic stem cell transplantation (HSCT) with an incidence of 8.2%. Etiologic factors include conditioning regimens, immunosuppression, infections, and graft-versus-host disease. Other risk factors include female sex, age, and human leukocyte antigen (HLA)-mismatched donor grafts. TA-TMA usually occurs within the first 100 days after HSCT. **Table 18-3** lists definitions of TA-TMA currently used for clinical trials. A firm diagnosis may be difficult because thrombocytopenia, anemia, and renal insufficiency are common in the posttransplant period. TA-TMA carries a high mortality rate (75% within 3 months). Plasma exchange is beneficial in less than 50% of patients, most of whom have more than 5% ADAMTS13 activity. Calciuria inhibitors should be discontinued, and substitution with daclizumab [antibody to the interleukin 2 (IL-2) receptor] is recommended. Treatment with rituximab and defibrotide may also be helpful.

HIV-RELATED TMA

TMA is mainly a complication encountered before widespread use of highly active retroviral therapy for HIV. It is seen in patients with advanced AIDS and low CD4 count, although it occasionally can be the first manifestation of HIV infection. The presence of MAHA thrombocytopenia and renal failure are suggestive, but renal biopsy is required to establish the diagnosis since HIV is associated with several other renal diseases. The median platelet count is 77,000/μL with a range of 10,000 to 160,000/μL, which may prohibit a renal biopsy in some patients. Cytomegalovirus (CMV) coinfection may also be a risk factor. The mechanism of injury is unclear, but HIV may induce apoptosis in endothelial cells. Plasma exchange is effective and is recommended in conjunction with antiviral therapy.

TABLE 18-3
CRITERIA FOR ESTABLISHING MICROANGIOPATHIC KIDNEY INJURY ASSOCIATED WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION

INTERNATIONAL WORKING GROUP	BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK TOXICITY COMMITTEE
>4% schistocytes in the blood	RBC fragmentation and at least 2 schistocytes per high-power field
De novo, prolonged, or progressive thrombocytopenia	Concurrent increase in LDH above baseline
A sudden and persistent increase in LDH	Negative direct and indirect Coombs test
Decrease in hemoglobin or increased RBC transfusion requirement	Concurrent renal and/or neurologic dysfunction without other explanations
Decrease in haptoglobin concentration	

Note: These features underscore the need to identify pathways of hemolysis and thrombocytopenia that accompany deterioration of kidney function.
Abbreviations: LDH, lactate dehydrogenase; RBC, red blood cell.

RADIATION NEPHROPATHY

Radiation can produce microangiopathic injury after either local or total body irradiation. The kidney is one of the most radiosensitive organs, and injury can result with as little as 4–5 Gy exposure. It is characterized by renal insufficiency, proteinuria, and hypertension usually presenting 6 months or longer after radiation exposure. Renal biopsy reveals classic TMA in the kidney with damage to glomerular, tubular, and vascular cells. Systemic evidence for MAHA is rare. Because of its high incidence after allogeneic HSCT, it is often referred to as bone marrow transplant (BMT) nephropathy. No specific therapy is available, although some evidence supports treatment with renin-angiotensin system blockade.

SCLERODERMA (PROGRESSIVE SYSTEMIC SCLEROSIS)

Scleroderma commonly affects the kidney, with 52% of subjects with widespread scleroderma having renal involvement sometime during the follow-up period. Of these, 19% were due to scleroderma renal crisis (SRC). Other renal manifestations in scleroderma include transient (prerenal) or medication-related forms of acute kidney injury [e.g., d-penicillamine, nonsteroidal anti-inflammatory drugs (NSAIDs), or cyclosporine]. SRC occurs in patients with diffuse systemic sclerosis (12 vs. 2% in limited systemic sclerosis). SRC is the most severe manifestation, characterized by accelerated hypertension, a rapid decline in renal function, nephrotic proteinuria, and hematuria. Retinopathy and encephalopathy may accompany the hypertension. Salt and water retention with microvascular injury can lead to pulmonary edema. Other manifestations include myocarditis, pericarditis, and arrhythmias, which denote an especially poor prognosis. Although MAHA is present in over half of the patients, coagulopathy is rare.

The renal lesion in SRC is characterized by arcuate artery intimal and medial proliferation with luminal narrowing. This lesion is described as *onionskinning* and can be accompanied by glomerular collapse due to reduced blood flow. Histologically it is indistinguishable from malignant hypertension. Fibrinoid necrosis and thrombosis are common. Before the availability of angiotensin-converting enzyme (ACE) inhibitors, the mortality rate for SRC at 1 month was greater than 90%. Introduction of renin-angiotensin system blockade has lowered the mortality rate to 30% at 3 years. Nearly two-thirds of patients with SRC require dialysis support. Half of those needing dialysis as a result of SRC will recover renal function (median time = 1 year). Glomerulonephritis and vasculitis associated with antineutrophil cytoplasmic antibodies (ANCAs) and systemic lupus erythematosus have been described in patients with scleroderma. An association has been found with antinuclear antibodies' (ANAs) speckled pattern and anti-RNA polymerase antibodies (I and III). Anti-U3-RNP may identify young patients at risk for SRC. Anticentromere antibody (ACA), however, is a negative predictor of SRC. Because of the overlap between SRC and other autoimmune disorders, a renal biopsy is recommended for patients with atypical renal involvement, especially if hypertension is absent.

Treatment with ACE inhibition is the first-line therapy unless contraindicated. The goal of therapy is to reduce systolic blood pressure by 20 mmHg and diastolic by 10 mmHg every 24 hours until blood pressure is normalized. Additional antihypertensive therapy may be added once the ACE inhibition is maximized. Both ACE inhibitors and angiotensin II receptor antagonists are effective, although published data show that treatment is superior with ACE inhibitors. ACE inhibition alone does not prevent SRC, although it reduces the role of hypertension. Intravenous iloprost has been used in Europe for blood pressure management and improvement of renal perfusion. Kidney transplantation is not recommended for 2 years after the start of dialysis, since delayed recovery may occur.

ANTIPHOSPHOLIPID SYNDROME (APS)

Antiphospholipid syndrome can be either primary or secondary to systemic lupus erythematosus. It is characterized by systemic thrombosis (arterial and venous) and fetal morbidity mediated by antiphospholipid antibodies (aPLs). The aPLs are mainly anticardiolipin (aCL) antibodies, which can be IgG, IgM, or IgA, lupus anticoagulant (LA), and anti-β-2 glycoprotein I antibodies (antiβ2GPI). Patients with both aCL and antiβ2GPI appear to have the highest risk of thrombosis. The vascular compartment within the kidney is the main site of renal involvement. Arteriosclerosis is commonly present in the arcuate and intralobular arteries. In the intralobular arteries, fibrous intimal hyperplasia characterized by intimal thickening secondary to intense myofibroblastic intimal cellular proliferation with extracellular matrix deposition is frequently seen along with onionskinning. Arterial and arteriolar fibrous and fibrocellular occlusions are present in over two-thirds of the biopsies. Cortical necrosis and focal cortical atrophy may result from vascular occlusion. TMA is commonly present in the renal biopsies, although signs of MAHA and platelet consumption are usually absent. TMA is especially common in the catastrophic variant of APS. In patients with secondary antiphospholipid syndrome (APS), other glomerulopathies may be present including membranous nephropathy, minimal change disease, focal segmental glomerulosclerosis, and pauci-immune crescentic glomerulonephritis.

Large vessels can be involved in APS and may form the proximal nidus near the ostium for thrombosis of the renal artery. Renal vein thrombosis can occur and should be suspected in patients with lupus anticoagulant LA who develop nephrotic range proteinuria. Progression to end-stage renal disease can occur, and thrombosis may form in the vascular access and the renal allografts. Hypertension is common. Treatment entails lifelong anticoagulation. Glucocorticoids may be beneficial in accelerated hypertension. Immunosuppression and plasma exchange may be helpful for catastrophic episodes of APS, but themselves do not reduce recurrent thrombosis.

HELLP SYNDROME

HELLP (*h*emolysis, *e*levated *l*iver *e*nzymes, *l*ow *p*latelets) syndrome is a dangerous complication of pregnancy. Occurring in 0.5–0.9% of all pregnancies and 10–20% of cases with severe preeclampsia, it has a mortality rate that

ranges between 7.4 and 34%. Most commonly occurring in the third trimester, 10% of cases occur before week 27 and 30% postpartum. Although most consider HELLP to be a severe form of preeclampsia, nearly 20% are not preceded by preeclampsia. HELLP patients have increased inflammatory markers [C-reactive protein (CRP), IL-1Ra, and IL-6] as compared to preeclampsia alone.

Renal failure occurs in half of patients with HELLP, although the etiology is not well understood. Limited data suggest renal failure is the result of a combination of preeclampsia and acute tubular necrosis from HELLP. Renal histologic findings are those of TMA with endothelial cell swelling and occlusion of the capillary lumens, but luminal thrombi are typically absent. However, thrombi become more common in severe eclampsia and HELLP. Although renal failure is common, the organ that defines this syndrome is the liver. Subcapsular hepatic hematomas sometimes produce spontaneous rupture of the liver and can be a life-threatening complication. Neurologic complications such as strokes, cerebral infarcts, cerebral and brainstem hemorrhage, and cerebral edema are other major potentially life-threatening complications. Nonfatal complications include placental abruption, permanent vision loss due to Purtscher-like (hemorrhagic and vasoocclusive vasculopathy) retinopathy, pulmonary edema, bleeding, and fetal demise.

The HELLP syndrome shares many features with other forms of MAHA. Distinguishing the specific disorders is complicated by the fact that both aHUS and TTP flares can be triggered by pregnancy. Patients with antiphospholipid syndrome have a higher risk of HELLP. A history of episodes of MAHA before pregnancy is helpful. Serum levels of ADAMTS13 activity is reduced (30–60%) in HELLP but not to the levels seen in TTP (<5%). Some authors suggest using the LDH-to-AST ratio for diagnosis. Patients with HELLP and preeclampsia have an LDH-to-AST ratio of 13 to 1 versus 29 to 1 in patients without preeclampsia. Other markers such as antithrombin III (decreased in HELLP but not in TTP) and d-dimer (elevated in HELLP but not in TTP) may aid in the diagnosis. HELLP syndrome resolves spontaneously in most cases after delivery, although a portion of HELLP occurs postpartum. Glucocorticoids may decrease inflammatory markers, although two randomized, controlled trials failed to confirm beneficial effects. Plasma exchange should be considered if the hemolysis is refractory to glucocorticoids and/or delivery, especially if TTP had not been ruled out.

SICKLE CELL NEPHROPATHY

Renal complications in sickle cell disease (SCD) result from occlusion of the vasa recta in the renal medulla. The low partial pressure of oxygen and high osmolarity predispose to hemoglobin S polymerization and erythrocyte sickling. Sequelae include hyposthenuria, hematuria, and papillary necrosis. The kidney responds by increasing blood flow and GFR mediated by prostaglandins. This dependence on prostaglandins may explain why patients with SCD experience greater reduction of GFR by NSAIDs than others. The glomeruli are typically enlarged. Intracapillary fragmentation and phagocytosis of sickled erythrocytes are thought to be responsible for the membranoproliferative glomerulonephritis-like lesion, and focal segmental glomerulosclerosis is sometimes seen. Proteinuria is present in 20–30% of the patients, and nephrotic range proteinuria is associated with renal failure. ACE inhibitors reduce proteinuria, although data are lacking on prevention of renal failure. Patients with SCD are also more prone to acute renal failure. The cause is thought to reflect microvascular occlusion associated with nontraumatic rhabdomyolysis, high fever, infection, and generalized sickling. Chronic kidney disease is present in 12–20% of patients. Despite the frequency of renal disease, hypertension is uncommon in patients with SCD.

RENAL VEIN THROMBOSIS

Renal vein thrombosis (RVT) can either present with flank pain, tenderness, hematuria, rapid decline in renal function, and proteinuria or it can be silent. Occasionally, RVT is identified during workup for pulmonary embolism. The left renal vein is more commonly involved and two-thirds of cases are bilateral. Etiologies can be divided into three broad categories: endothelial damage, venous stasis, and hypercoagulable states. Homocystinuria, endovascular intervention, and surgery can produce vascular endothelial damage. Dehydration, which is more common in males, is a common cause of stasis in the pediatric population. Stasis also can result from compression and kinking of the renal veins from retroperitoneal processes such as retroperitoneal fibrosis and abdominal neoplasms. Thrombosis can occur throughout the renal circulation with antiphospholipid antibody syndrome. RVT can also be secondary to nephrotic syndrome, particularly membranous nephropathy. Other hypercoagulable states associated with RVT include proteins C and S, antithrombin deficiency, factor V Leiden, disseminated malignancy, and oral contraceptives.

Diagnostic screening can be performed with Doppler ultrasound, which is more sensitive than ultrasound alone. The most sensitive test is CT angiography, which is nearly 100% sensitive. MR angiography is another option but is more expensive and requires sedation in pediatric patients. Treatment for RVT is anticoagulation and therapy for the underlying cause. Endovascular thrombolysis may be considered in severe cases. Occasionally nephrectomy may be undertaken for life-threatening complications. Vena caval filters are often used to prevent migration of the thrombi.

CHAPTER 19

HYPERTENSIVE VASCULAR DISEASE

Theodore A. Kotchen

Hypertension is one of the leading causes of the global burden of disease. Approximately 7.6 million deaths (13–15% of the total) and 92 million disability-adjusted life years worldwide were attributable to high blood pressure in 2001. Hypertension doubles the risk of cardiovascular diseases, including coronary heart disease (CHD), congestive heart failure (CHF), ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease. It often is associated with additional cardiovascular disease risk factors, and the risk of cardiovascular disease increases with the total burden of risk factors. Although antihypertensive therapy clearly reduces the risks of cardiovascular and renal disease, large segments of the hypertensive population are either untreated or inadequately treated.

EPIDEMIOLOGY

Blood pressure levels, the rate of age-related increases in blood pressure, and the prevalence of hypertension vary among countries and among subpopulations within a country. Hypertension is present in all populations except for a small number of individuals living in primitive, culturally isolated societies. In industrialized societies, blood pressure increases steadily during the first two decades of life. In children and adolescents, blood pressure is associated with growth and maturation. Blood pressure "tracks" over time in children and between adolescence and young adulthood. In the United States, average systolic blood pressure is higher for men than for women during early adulthood, although among older individuals the age-related rate of rise is steeper for women. Consequently, among individuals aged 60 and older, systolic blood pressures of women are higher than those of men. Among adults, diastolic blood pressure also increases progressively with age until ~55 years, after which it tends to decrease. The consequence is a widening of pulse pressure (the difference between systolic and diastolic blood pressure) beyond age 60. The probability that a middle-aged or elderly individual will develop hypertension in his or her lifetime is 90%.

In the United States, based on results of the National Health and Nutrition Examination Survey (NHANES), approximately 30% (age-adjusted prevalence) of adults, or at least 65 million individuals, have hypertension (defined as any one of the following: systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, taking antihypertensive medications). Hypertension prevalence is 33.5% in non-Hispanic blacks, 28.9% in non-Hispanic whites, and 20.7% in Mexican Americans. The likelihood of hypertension increases with age, and among individuals age ≥60, the prevalence is 65.4%. Recent evidence suggests that the prevalence of hypertension in the United States may be increasing, possibly as a consequence of increasing obesity. The prevalence of hypertension and stroke mortality rates are higher in the southeastern United States than in other regions. In African Americans, hypertension appears earlier, is generally more severe, and results in higher rates of morbidity and mortality from stroke, left ventricular hypertrophy, CHF, and end-stage renal disease (ESRD) than in white Americans.

Both environmental and genetic factors may contribute to regional and racial variations in blood pressure and hypertension prevalence. Studies of societies undergoing "acculturation" and studies of migrants from a less to a more urbanized setting indicate a profound environmental contribution to blood pressure. Obesity and weight gain are strong independent risk factors for hypertension. It has been estimated that 60% of hypertensives are >20% overweight. Among populations, hypertension prevalence is related to dietary NaCl intake, and the age-related increase in blood pressure may be augmented by a high NaCl intake. Low dietary intakes of calcium and potassium also may contribute to the risk of hypertension. The urine sodium-to-potassium ratio is a stronger correlate of blood pressure than is either sodium or potassium alone. Alcohol consumption, psychosocial

stress, and low levels of physical activity also may contribute to hypertension.

Adoption, twin, and family studies document a significant heritable component to blood pressure levels and hypertension. Family studies controlling for a common environment indicate that blood pressure heritabilities are in the range of 15–35%. In twin studies, heritability estimates of blood pressure are ~60% for males and 30–40% for females. High blood pressure before age 55 occurs 3.8 times more frequently among persons with a positive family history of hypertension.

GENETIC CONSIDERATIONS

Although specific genetic variants have been identified in rare Mendelian forms of hypertension (Table 19-5), these variants are not applicable to the vast majority (>98%) of patients with essential hypertension. For most individuals, it is likely that hypertension represents a polygenic disorder in which a combination of genes acts in concert with environmental exposures to make only a modest contribution to blood pressure. Further, different subsets of genes may lead to different phenotypes associated with hypertension, e.g., obesity, dyslipidemia, insulin resistance.

Several strategies are being utilized in the search for specific hypertension-related genes. Animal models (including selectively bred rats and congenic rat strains) provide a powerful approach for evaluating genetic loci and genes associated with hypertension. Comparative mapping strategies allow for the identification of syntenic genomic regions between the rat and human genomes that may be involved in blood pressure regulation. In association studies, different alleles (or combinations of alleles at different loci) of specific candidate genes or chromosomal regions are compared in hypertensive patients and normotensive control subjects. Current evidence suggests that genes that encode components of the renin-angiotensin-aldosterone system, along with angiotensinogen and angiotensin-converting enzyme (ACE) polymorphisms, may be related to hypertension and to blood pressure sensitivity to dietary NaCl. The alpha-adducin gene is thought to be associated with increased renal tubular absorption of sodium, and variants of this gene may be associated with hypertension and salt sensitivity of blood pressure. Other genes possibly related to hypertension include genes encoding the AT_1 receptor, aldosterone synthase, and the β_2 adrenoreceptor. Genomewide association studies involve rapidly scanning markers across the entire genome to identify loci (not specific genes) associated with an observable trait (e.g., blood pressure) or a particular disease. This strategy has been facilitated by the availability of dense genotyping chips and the International HapMap. To date, the results of candidate gene studies often have not been replicated, and in contrast to several other polygenic disorders, genomewide association studies have had limited success in identifying genetic determinants of hypertension.

Preliminary evidence suggests that there may also be genetic determinants of target organ damage attributed to hypertension. Family studies indicate significant heritability of left ventricular mass, and there is considerable individual variation in the responses of the heart to hypertension. Family studies and variations in candidate genes associated with renal damage suggest that genetic factors also may contribute to hypertensive nephropathy. Specific genetic variants have been linked to CHD and stroke.

In the future, it is possible that DNA analysis will predict individual risk for hypertension and target organ damage and will identify responders to specific classes of antihypertensive agents. However, with the exception of the rare, monogenic hypertensive diseases, the genetic variants associated with hypertension remain to be confirmed, and the intermediate steps by which these variants affect blood pressure remain to be determined.

MECHANISMS OF HYPERTENSION

To provide a framework for understanding the pathogenesis of and treatment options for hypertensive disorders, it is useful to understand factors involved in the regulation of both normal and elevated arterial pressure. Cardiac output and peripheral resistance are the two determinants of arterial pressure **(Fig. 19-1)**. Cardiac output is determined by stroke volume and heart rate; stroke volume is related to myocardial contractility and to the size of the vascular compartment. Peripheral resistance is determined by functional and anatomic changes in small arteries (lumen diameter 100–400 μm) and arterioles.

INTRAVASCULAR VOLUME

Vascular volume is a primary determinant of arterial pressure over the long term. Sodium is predominantly an extracellular ion and is a primary determinant of the extracellular fluid volume. When NaCl intake exceeds

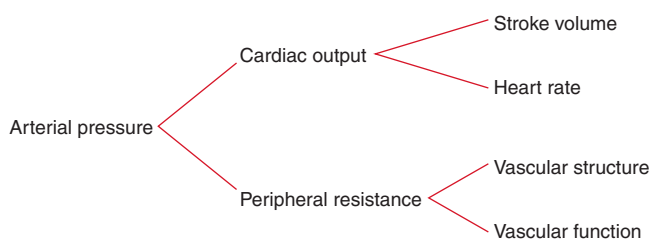


FIGURE 19-1
Determinants of arterial pressure.

the capacity of the kidney to excrete sodium, vascular volume initially expands and cardiac output increases. However, many vascular beds (including kidney and brain) have the capacity to autoregulate blood flow, and if constant blood flow is to be maintained in the face of increased arterial pressure, resistance within that bed must increase, since

$$\text{Blood flow} = \frac{\text{pressure across the vascular bed}}{\text{vascular resistance}}$$

The initial elevation of blood pressure in response to vascular volume expansion may be related to an increase of cardiac output; however, over time, peripheral resistance increases and cardiac output reverts toward normal. The effect of sodium on blood pressure is related to the provision of sodium with chloride; nonchloride salts of sodium have little or no effect on blood pressure. As arterial pressure increases in response to a high NaCl intake, urinary sodium excretion increases and sodium balance is maintained at the expense of an increase in arterial pressure. The mechanism for this "pressure-natriuresis" phenomenon may involve a subtle increase in the glomerular filtration rate, decreased absorbing capacity of the renal tubules, and possibly hormonal factors such as atrial natriuretic factor. In individuals with an impaired capacity to excrete sodium, greater increases in arterial pressure are required to achieve natriuresis and sodium balance.

NaCl-dependent hypertension may be a consequence of a decreased capacity of the kidney to excrete sodium, due either to intrinsic renal disease or to increased production of a salt-retaining hormone (mineralocorticoid) resulting in increased renal tubular reabsorption of sodium. Renal tubular sodium reabsorption also may be augmented by increased neural activity to the kidney. In each of these situations, a higher arterial pressure may be required to achieve sodium balance. Conversely, salt-wasting disorders are associated with low blood pressure levels. ESRD is an extreme example of volume-dependent hypertension. In ~80% of these patients, vascular volume and hypertension can be controlled with adequate dialysis; in the other 20%, the mechanism of hypertension is related to increased activity of the renin-angiotensin system and is likely to be responsive to pharmacologic blockade of renin-angiotensin.

AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system maintains cardiovascular homeostasis via pressure, volume, and chemoreceptor signals. Adrenergic reflexes modulate blood pressure over the short term, and adrenergic function, in concert with hormonal and volume-related factors, contributes to the long-term regulation of arterial pressure. The three endogenous catecholamines are norepinephrine, epinephrine, and dopamine. All three play important roles in tonic and phasic cardiovascular regulation.

The activities of the adrenergic receptors are mediated by guanosine nucleotide-binding regulatory proteins (G proteins) and by intracellular concentrations of downstream second messengers. In addition to receptor affinity and density, physiologic responsiveness to catecholamines may be altered by the efficiency of receptor-effector coupling at a site "distal" to receptor binding. The receptor sites are relatively specific both for the transmitter substance and for the response that occupancy of the receptor site elicits. Norepinephrine and epinephrine are agonists for all adrenergic receptor subtypes, although with varying affinities. Based on their physiology and pharmacology, adrenergic receptors have been divided into two principal types: α and β. These types have been differentiated further into α_1, α_2, β_1, and β_2 receptors. Recent molecular cloning studies have identified several additional subtypes. α Receptors are occupied and activated more avidly by norepinephrine than by epinephrine, and the reverse is true for β receptors. α_1 Receptors are located on postsynaptic cells in smooth muscle and elicit vasoconstriction. α_2 Receptors are localized on presynaptic membranes of postganglionic nerve terminals that synthesize norepinephrine. When activated by catecholamines, α_2 receptors act as negative feedback controllers, inhibiting further norepinephrine release. In the kidney, activation of α_1-adrenergic receptors increases renal tubular reabsorption of sodium. Different classes of antihypertensive agents either inhibit α_1 receptors or act as agonists of α_2 receptors and reduce systemic sympathetic outflow. Activation of myocardial β_1 receptors stimulates the rate and strength of cardiac contraction and consequently increases cardiac output. β_1 Receptor activation also stimulates renin release from the kidney. Another class of antihypertensive agents acts by inhibiting β_1 receptors. Activation of β_2 receptors by epinephrine relaxes vascular smooth muscle and results in vasodilation.

Circulating catecholamine concentrations may affect the number of adrenoreceptors in various tissues. Downregulation of receptors may be a consequence of sustained high levels of catecholamines and provides an explanation for decreasing responsiveness, or tachyphylaxis, to catecholamines. For example, orthostatic hypotension frequently is observed in patients with pheochromocytoma, possibly due to the lack of norepinephrine-induced vasoconstriction with assumption of the upright posture. Conversely, with chronic reduction of neurotransmitter substances, adrenoreceptors may increase in number or be upregulated, resulting in increased responsiveness to the neurotransmitter. Chronic administration of agents that block adrenergic receptors may result in upregulation, and withdrawal of those agents may produce a condition of temporary

hypersensitivity to sympathetic stimuli. For example, clonidine is an antihypertensive agent that is a centrally acting α_2 agonist that inhibits sympathetic outflow. Rebound hypertension may occur with the abrupt cessation of clonidine therapy, probably as a consequence of upregulation of α_1 receptors.

Several reflexes modulate blood pressure on a minute-to-minute basis. One arterial baroreflex is mediated by stretch-sensitive sensory nerve endings in the carotid sinuses and the aortic arch. The rate of firing of these baroreceptors increases with arterial pressure, and the net effect is a decrease in sympathetic outflow, resulting in decreases in arterial pressure and heart rate. This is a primary mechanism for rapid buffering of acute fluctuations of arterial pressure that may occur during postural changes, behavioral or physiologic stress, and changes in blood volume. However, the activity of the baroreflex declines or adapts to sustained increases in arterial pressure such that the baroreceptors are reset to higher pressures. Patients with autonomic neuropathy and impaired baroreflex function may have extremely labile blood pressures with difficult-to-control episodic blood pressure spikes associated with tachycardia.

In both normal-weight and obese individuals, hypertension often is associated with increased sympathetic outflow. Based on recordings of postganglionic muscle nerve activity (detected by a microelectrode inserted in a peroneal nerve in the leg), sympathetic outflow tends to be higher in hypertensive than in normotensive individuals. Sympathetic outflow is increased in obesity-related hypertension and in hypertension associated with obstructive sleep apnea. Baroreceptor activation via electrical stimulation of carotid sinus afferent nerves has been shown to lower blood pressure in patients with "resistant" hypertension. Drugs that block the sympathetic nervous system are potent antihypertensive agents, indicating that the sympathetic nervous system plays a permissive, although not necessarily a causative, role in the maintenance of increased arterial pressure.

Pheochromocytoma is the most blatant example of hypertension related to increased catecholamine production, in this instance by a tumor. Blood pressure can be reduced by surgical excision of the tumor or by pharmacologic treatment with an α_1 receptor antagonist or with an inhibitor of tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis.

RENIN-ANGIOTENSIN-ALDOSTERONE

The renin-angiotensin-aldosterone system contributes to the regulation of arterial pressure primarily via the vasoconstrictor properties of angiotensin II and the sodium-retaining properties of aldosterone. Renin is an aspartyl protease that is synthesized as an enzymatically inactive precursor, prorenin. Most renin in the circulation is synthesized in the renal afferent renal arteriole. Prorenin may be secreted directly into the circulation or may be activated within secretory cells and released as active renin. Although human plasma contains two to five times more prorenin than renin, there is no evidence that prorenin contributes to the physiologic activity of this system. There are three primary stimuli for renin secretion: (1) decreased NaCl transport in the distal portion of the thick ascending limb of the loop of Henle that abuts the corresponding afferent arteriole (macula densa), (2) decreased pressure or stretch within the renal afferent arteriole (baroreceptor mechanism), and (3) sympathetic nervous system stimulation of renin-secreting cells via β_1 adrenoreceptors. Conversely, renin secretion is inhibited by increased NaCl transport in the thick ascending limb of the loop of Henle, by increased stretch within the renal afferent arteriole, and by β_1 receptor blockade. In addition, angiotensin II directly inhibits renin secretion due to angiotensin II type 1 receptors on juxtaglomerular cells, and renin secretion increases in response to pharmacologic blockade of either ACE or angiotensin II receptors.

Once released into the circulation, active renin cleaves a substrate, angiotensinogen, to form an inactive decapeptide, angiotensin I **(Fig. 19-2)**. A converting enzyme, located primarily but not exclusively in the pulmonary circulation, converts angiotensin I to the active octapeptide, angiotensin II, by releasing the C-terminal histidyl-leucine dipeptide. The same converting enzyme cleaves a number of other peptides, including and thereby inactivating the vasodilator bradykinin. Acting primarily through angiotensin II type 1

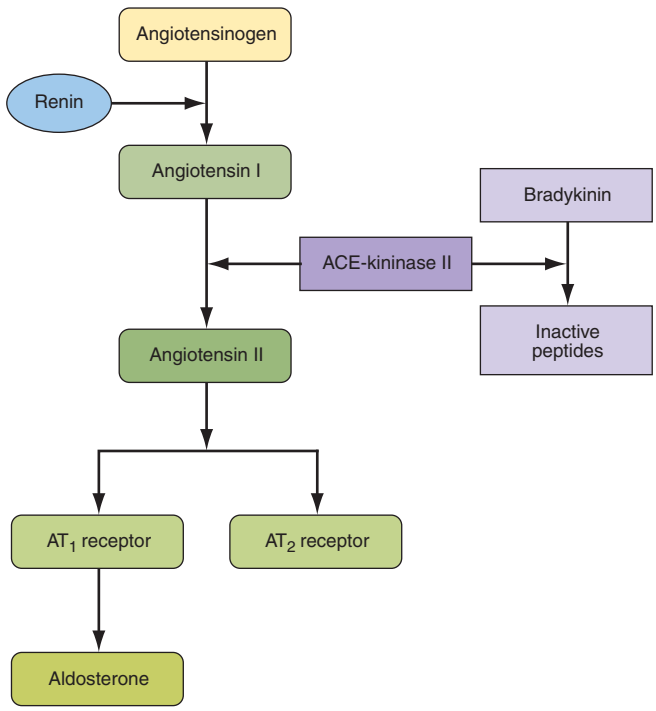


FIGURE 19-2
Renin-angiotensin-aldosterone axis.

(AT_1) receptors on cell membranes, angiotensin II is a potent pressor substance, the primary tropic factor for the secretion of aldosterone by the adrenal zona glomerulosa, and a potent mitogen that stimulates vascular smooth muscle cell and myocyte growth. Independent of its hemodynamic effects, angiotensin II may play a role in the pathogenesis of atherosclerosis through a direct cellular action on the vessel wall. An angiotensin II type 2 (AT_2) receptor has been characterized. It is widely distributed in the kidney and has the opposite functional effects of the AT_1 receptor. The AT_2 receptor induces vasodilation, sodium excretion, and inhibition of cell growth and matrix formation. Experimental evidence suggests that the AT_2 receptor improves vascular remodeling by stimulating smooth muscle cell apoptosis and contributes to the regulation of glomerular filtration rate. AT_1 receptor blockade induces an increase in AT_2 receptor activity.

Renin-secreting tumors are clear examples of renin-dependent hypertension. In the kidney, these tumors include benign hemangiopericytomas of the juxtaglomerular apparatus and, infrequently, renal carcinomas, including Wilms' tumors. Renin-producing carcinomas also have been described in lung, liver, pancreas, colon, and adrenals. In these instances, in addition to excision and/or ablation of the tumor, treatment of hypertension includes pharmacologic therapies targeted to inhibit angiotensin II production or action. Renovascular hypertension is another renin-mediated form of hypertension. Obstruction of the renal artery leads to decreased renal perfusion pressure, thereby stimulating renin secretion. Over time, as a consequence of secondary renal damage, this form of hypertension may become less renin dependent.

Angiotensinogen, renin, and angiotensin II are also synthesized locally in many tissues, including the brain, pituitary, aorta, arteries, heart, adrenal glands, kidneys, adipocytes, leukocytes, ovaries, testes, uterus, spleen, and skin. Angiotensin II in tissues may be formed by the enzymatic activity of renin or by other proteases, e.g., tonin, chymase, and cathepsins. In addition to regulating local blood flow, tissue angiotensin II is a mitogen that stimulates growth and contributes to modeling and repair. Excess tissue angiotensin II may contribute to atherosclerosis, cardiac hypertrophy, and renal failure, and consequently may be a target for pharmacologic therapy to prevent target organ damage.

Angiotensin II is the primary tropic factor regulating the synthesis and secretion of aldosterone by the zona glomerulosa of the adrenal cortex. Aldosterone synthesis is also dependent on potassium, and aldosterone secretion may be decreased in potassium-depleted individuals. Although acute elevations of adrenocorticotropic hormone (ACTH) levels also increase aldosterone secretion, ACTH is not an important tropic factor for the chronic regulation of aldosterone.

Aldosterone is a potent mineralocorticoid that increases sodium reabsorption by amiloride-sensitive epithelial sodium channels (ENaC) on the apical surface of the principal cells of the renal cortical collecting duct (Chap. 1). Electric neutrality is maintained by exchanging sodium for potassium and hydrogen ions. Consequently, increased aldosterone secretion may result in hypokalemia and alkalosis. Because potassium depletion may inhibit aldosterone synthesis, clinically, hypokalemia should be corrected before a patient is evaluated for hyperaldosteronism.

Mineralocorticoid receptors also are expressed in the colon, salivary glands, and sweat glands. Cortisol also binds to these receptors but normally functions as a less potent mineralocorticoid than aldosterone because cortisol is converted to cortisone by the enzyme 11 β-hydroxysteroid dehydrogenase type 2. Cortisone has no affinity for the mineralocorticoid receptor. Primary aldosteronism is a compelling example of mineralocorticoid-mediated hypertension. In this disorder, adrenal aldosterone synthesis and release are independent of renin-angiotensin, and renin release is suppressed by the resulting volume expansion.

Aldosterone also has effects on nonepithelial targets. Aldosterone and/or mineralocorticoid receptor activation induces structural and functional alterations in the heart, kidney, and blood vessels, leading to myocardial fibrosis, nephrosclerosis, and vascular inflammation and remodeling, perhaps as a consequence of oxidative stress. These effects are amplified by a high salt intake. In animal models, high circulating aldosterone levels stimulate cardiac fibrosis and left ventricular hypertrophy, and spironolactone (an aldosterone antagonist) prevents aldosterone-induced myocardial fibrosis. Pathologic patterns of left ventricular geometry also have been associated with elevations of plasma aldosterone concentration in patients with essential hypertension as well as in patients with primary aldosteronism. In patients with CHF, low-dose spironolactone reduces the risk of progressive heart failure and sudden death from cardiac causes by 30%. Owing to a renal hemodynamic effect, in patients with primary aldosteronism, high circulating levels of aldosterone also may cause glomerular hyperfiltration and albuminuria. These renal effects are reversible after removal of the effects of excess aldosterone by adrenalectomy or spironolactone.

Increased activity of the renin-angiotensin-aldosterone axis is not invariably associated with hypertension. In response to a low-NaCl diet or to volume contraction, arterial pressure and volume homeostasis may be maintained by increased activity of the renin-angiotensin-aldosterone axis. Secondary aldosteronism (i.e., increased aldosterone secondary to increased renin-angiotensin), but not hypertension, also is observed in edematous states such as CHF and liver disease.

VASCULAR MECHANISMS

Vascular radius and compliance of resistance arteries are also important determinants of arterial pressure. Resistance to flow varies inversely with the fourth power of the radius, and, consequently, small decreases in lumen size significantly increase resistance. In hypertensive patients, structural, mechanical, or functional changes may reduce the lumen diameter of small arteries and arterioles. Remodeling refers to geometric alterations in the vessel wall without a change in vessel volume. Hypertrophic (increased cell size and increased deposition of intercellular matrix) or eutrophic vascular remodeling results in decreased lumen size and hence contributes to increased peripheral resistance. Apoptosis, low-grade inflammation, and vascular fibrosis also contribute to remodeling. Lumen diameter also is related to elasticity of the vessel. Vessels with a high degree of elasticity can accommodate an increase of volume with relatively little change in pressure, whereas in a semirigid vascular system, a small increment in volume induces a relatively large increment of pressure.

Hypertensive patients have stiffer arteries, and arteriosclerotic patients may have particularly high systolic blood pressures and wide pulse pressures as a consequence of decreased vascular compliance due to structural changes in the vascular wall. Recent evidence suggests that arterial stiffness has independent predictive value for cardiovascular events. Clinically, a number of devices are available to evaluate arterial stiffness or compliance, including ultrasound and magnetic resonance imaging (MRI).

Ion transport by vascular smooth muscle cells may contribute to hypertension-associated abnormalities of vascular tone and vascular growth, both of which are modulated by intracellular pH (pH_i). Three ion transport mechanisms participate in the regulation of pH_i: (1) Na^+-H^+ exchange, (2) Na^+-dependent HCO_3^--Cl^- exchange, and (3) cation-independent HCO_3^--Cl^- exchange. Based on measurements in cell types that are more accessible than vascular smooth muscle (e.g., leukocytes, erythrocytes, platelets, skeletal muscle), activity of the Na^+-H^+ exchanger is increased in hypertension, and this may result in increased vascular tone by two mechanisms. First, increased sodium entry may lead to increased vascular tone by activating Na^+-Ca^{2+} exchange and thereby increasing intracellular calcium. Second, increased pH_i enhances calcium sensitivity of the contractile apparatus, leading to an increase in contractility for a given intracellular calcium concentration. Additionally, increased Na^+-H^+ exchange may stimulate growth of vascular smooth muscle cells by enhancing sensitivity to mitogens.

Vascular endothelial function also modulates vascular tone. The vascular endothelium synthesizes and releases a spectrum of vasoactive substances, including nitric oxide, a potent vasodilator. Endothelium-dependent vasodilation is impaired in hypertensive patients. This impairment often is assessed with high-resolution ultrasonography before and after the hyperemic phase of reperfusion that follows 5 minutes of forearm ischemia. Alternatively, endothelium-dependent vasodilation may be assessed in response to an intra-arterially infused endothelium-dependent vasodilator, e.g., acetylcholine. Endothelin is a vasoconstrictor peptide produced by the endothelium, and orally active endothelin antagonists may lower blood pressure in patients with resistant hypertension.

Currently, it is not known if the hypertension-related vascular abnormalities of ion transport and endothelial function are primary alterations or secondary consequences of elevated arterial pressure. Limited evidence suggests that vascular compliance and endothelium-dependent vasodilation may be improved by aerobic exercise, weight loss, and antihypertensive agents. It remains to be determined whether these interventions affect arterial structure and stiffness via a blood pressure–independent mechanism and whether different classes of antihypertensive agents preferentially affect vascular structure and function.

PATHOLOGIC CONSEQUENCES OF HYPERTENSION

Hypertension is an independent predisposing factor for heart failure, coronary artery disease, stroke, renal disease, and peripheral arterial disease (PAD).

HEART

Heart disease is the most common cause of death in hypertensive patients. Hypertensive heart disease is the result of structural and functional adaptations leading to left ventricular hypertrophy, CHF, abnormalities of blood flow due to atherosclerotic coronary artery disease and microvascular disease, and cardiac arrhythmias.

Both genetic and hemodynamic factors contribute to left ventricular hypertrophy. Clinically, left ventricular hypertrophy can be diagnosed by electrocardiography, although echocardiography provides a more sensitive measure of left ventricular wall thickness. Individuals with left ventricular hypertrophy are at increased risk for CHD, stroke, CHF, and sudden death. Aggressive control of hypertension can regress or reverse left ventricular hypertrophy and reduce the risk of cardiovascular disease. It is not clear whether different classes of antihypertensive agents have an added impact on reducing left ventricular mass, independent of their blood pressure–lowering effect.

CHF may be related to systolic dysfunction, diastolic dysfunction, or a combination of the two. Abnormalities of diastolic function that range from asymptomatic heart disease to overt heart failure are common in

hypertensive patients. Patients with diastolic heart failure have a preserved ejection fraction, which is a measure of systolic function. Approximately one-third of patients with CHF have normal systolic function but abnormal diastolic function. Diastolic dysfunction is an early consequence of hypertension-related heart disease and is exacerbated by left ventricular hypertrophy and ischemia. Cardiac catheterization provides the most accurate assessment of diastolic function. Alternatively, diastolic function can be evaluated by several noninvasive methods, including echocardiography and radionuclide angiography.

BRAIN

Stroke is the second most frequent cause of death in the world; it accounts for 5 million deaths each year, with an additional 15 million persons having nonfatal strokes. Elevated blood pressure is the strongest risk factor for stroke. Approximately 85% of strokes are due to infarction, and the remainder are due to either intracerebral or subarachnoid hemorrhage. The incidence of stroke rises progressively with increasing blood pressure levels, particularly systolic blood pressure in individuals >65 years. Treatment of hypertension convincingly decreases the incidence of both ischemic and hemorrhagic strokes.

Hypertension also is associated with impaired cognition in an aging population, and longitudinal studies support an association between midlife hypertension and late-life cognitive decline. Hypertension-related cognitive impairment and dementia may be a consequence of a single infarct due to occlusion of a "strategic" larger vessel or multiple lacunar infarcts due to occlusive small vessel disease resulting in subcortical white matter ischemia. Several clinical trials suggest that antihypertensive therapy has a beneficial effect on cognitive function, although this remains an active area of investigation.

Cerebral blood flow remains unchanged over a wide range of arterial pressures (mean arterial pressure of 50–150 mmHg) through a process termed *autoregulation* of blood flow. In patients with the clinical syndrome of malignant hypertension, encephalopathy is related to failure of autoregulation of cerebral blood flow at the upper pressure limit, resulting in vasodilation and hyperperfusion. Signs and symptoms of hypertensive encephalopathy may include severe headache, nausea and vomiting (often of a projectile nature), focal neurologic signs, and alterations in mental status. Untreated, hypertensive encephalopathy may progress to stupor, coma, seizures, and death within hours. It is important to distinguish hypertensive encephalopathy from other neurologic syndromes that may be associated with hypertension, e.g., cerebral ischemia, hemorrhagic or thrombotic stroke, seizure disorder, mass lesions, pseudotumor cerebri, delirium tremens, meningitis, acute intermittent porphyria, traumatic or chemical injury to the brain, and uremic encephalopathy.

KIDNEY

The kidney is both a target and a cause of hypertension. Primary renal disease is the most common etiology of secondary hypertension. Mechanisms of kidney-related hypertension include a diminished capacity to excrete sodium, excessive renin secretion in relation to volume status, and sympathetic nervous system overactivity. Conversely, hypertension is a risk factor for renal injury and end-stage renal disease. The increased risk associated with high blood pressure is graded, continuous, and present throughout the distribution of blood pressure above optimal pressure. Renal risk appears to be more closely related to systolic than to diastolic blood pressure, and black men are at greater risk than white men for developing ESRD at every level of blood pressure. Proteinuria is a reliable marker of the severity of chronic kidney disease and is a predictor of its progression. Patients with high urine protein excretion (>3 g/24 h) have a more rapid rate of progression than do those with lower protein excretion rates.

Atherosclerotic, hypertension-related vascular lesions in the kidney primarily affect preglomerular arterioles, resulting in ischemic changes in the glomeruli and postglomerular structures. Glomerular injury also may be a consequence of direct damage to the glomerular capillaries due to glomerular hyperperfusion. Studies of hypertension-related renal damage, primarily in experimental animals, suggest that loss of autoregulation of renal blood flow at the afferent arteriole results in transmission of elevated pressures to an unprotected glomerulus with ensuing hyperfiltration, hypertrophy, and eventual focal segmental glomerular sclerosis. With progressive renal injury there is a loss of autoregulation of renal blood flow and glomerular filtration rate, resulting in a lower blood pressure threshold for renal damage and a steeper slope between blood pressure and renal damage. The result may be a vicious cycle of renal damage and nephron loss leading to more severe hypertension, glomerular hyperfiltration, and further renal damage. Glomerular pathology progresses to glomerulosclerosis, and eventually the renal tubules may also become ischemic and gradually atrophic. The renal lesion associated with malignant hypertension consists of fibrinoid necrosis of the afferent arterioles, sometimes extending into the glomerulus, and may result in focal necrosis of the glomerular tuft.

Clinically, macroalbuminuria (a random urine albumin/creatinine ratio >300 mg/g) or microalbuminuria (a random urine albumin/creatinine ratio 30–300 mg/g) are early markers of renal injury. These are also risk factors for renal disease progression and cardiovascular disease.

PERIPHERAL ARTERIES

In addition to contributing to the pathogenesis of hypertension, blood vessels may be a target organ for

atherosclerotic disease secondary to long-standing elevated blood pressure. Hypertensive patients with arterial disease of the lower extremities are at increased risk for future cardiovascular disease. Although patients with stenotic lesions of the lower extremities may be asymptomatic, intermittent claudication is the classic symptom of PAD. This is characterized by aching pain in the calves or buttocks while walking that is relieved by rest. The ankle-brachial index is a useful approach for evaluating PAD and is defined as the ratio of noninvasively assessed ankle to brachial (arm) systolic blood pressure. An ankle-brachial index <0.90 is considered diagnostic of PAD and is associated with >50% stenosis in at least one major lower limb vessel. Several studies suggest that an ankle-brachial index <0.80 is associated with elevated blood pressure, particularly systolic blood pressure.

DEFINING HYPERTENSION

From an epidemiologic perspective, there is no obvious level of blood pressure that defines hypertension. In adults, there is a continuous, incremental risk of cardiovascular disease, stroke, and renal disease across levels of both systolic and diastolic blood pressure. The Multiple Risk Factor Intervention Trial (MRFIT), which included >350,000 male participants, demonstrated a continuous and graded influence of both systolic and diastolic blood pressure on CHD mortality, extending down to systolic blood pressures of 120 mmHg. Similarly, results of a meta-analysis involving almost 1 million participants indicate that ischemic heart disease mortality, stroke mortality, and mortality from other vascular causes are directly related to the height of the blood pressure, beginning at 115/75 mmHg, without evidence of a threshold. Cardiovascular disease risk doubles for every 20-mmHg increase in systolic and 10-mmHg increase in diastolic pressure. Among older individuals, systolic blood pressure and pulse pressure are more powerful predictors of cardiovascular disease than is diastolic blood pressure.

Clinically, hypertension may be defined as that level of blood pressure at which the institution of therapy reduces blood pressure–related morbidity and mortality. Current clinical criteria for defining hypertension generally are based on the average of two or more seated blood pressure readings during each of two or more outpatient visits. A recent classification recommends blood pressure criteria for defining normal blood pressure, prehypertension, hypertension (stages I and II), and isolated systolic hypertension, which is a common occurrence among the elderly (Table 19-1). In children and adolescents, hypertension generally is defined as systolic and/or diastolic blood pressure consistently >95th percentile for age, sex, and height. Blood pressures between the 90th and 95th percentiles are considered prehypertensive and are an indication for lifestyle interventions.

TABLE 19-1
BLOOD PRESSURE CLASSIFICATION

BLOOD PRESSURE CLASSIFICATION	SYSTOLIC, mmHg	DIASTOLIC, mmHg
Normal	<120	*and* <80
Prehypertension	120–139	*or* 80–89
Stage 1 hypertension	140–159	*or* 90–99
Stage 2 hypertension	≥160	*or* ≥100
Isolated systolic hypertension	≥140	*and* <90

Source: Adapted from AV Chobanian et al: JAMA 289:2560, 2003.

Home blood pressure and average 24-h ambulatory blood pressure measurements are generally lower than clinic blood pressures. Because ambulatory blood pressure recordings yield multiple readings throughout the day and night, they provide a more comprehensive assessment of the vascular burden of hypertension than do a limited number of office readings. Increasing evidence suggests that home blood pressures, including 24-h blood pressure recordings, more reliably predict target organ damage than do office blood pressures. Blood pressure tends to be higher in the early morning hours, soon after waking, than at other times of day. Myocardial infarction and stroke are more common in the early morning hours. Nighttime blood pressures are generally 10–20% lower than daytime blood pressures, and an attenuated nighttime blood pressure "dip" is associated with increased cardiovascular disease risk. Recommended criteria for a diagnosis of hypertension are average awake blood pressure ≥135/85 mmHg and asleep blood pressure ≥120/75 mmHg. These levels approximate a clinic blood pressure of 140/90 mmHg.

Approximately 15–20% of patients with stage 1 hypertension (as defined in Table 19-1) based on office blood pressures have average ambulatory readings <135/85 mmHg. This phenomenon, so-called white coat hypertension, also may be associated with an increased risk of target organ damage (e.g., left ventricular hypertrophy, carotid atherosclerosis, overall cardiovascular morbidity), although to a lesser extent than in individuals with elevated office and ambulatory readings. Individuals with white coat hypertension are also at increased risk for developing sustained hypertension.

CLINICAL DISORDERS OF HYPERTENSION

Depending on methods of patient ascertainment, ~80–95% of hypertensive patients are diagnosed as having "essential" hypertension (also referred to as primary or idiopathic hypertension). In the remaining 5–20%

TABLE 19-2

SYSTOLIC HYPERTENSION WITH WIDE PULSE PRESSURE
1. Decreased vascular compliance (arteriosclerosis)
2. Increased cardiac output
a. Aortic regurgitation
b. Thyrotoxicosis
c. Hyperkinetic heart syndrome
d. Fever
e. Arteriovenous fistula
f. Patent ductus arteriosus

of hypertensive patients, a specific underlying disorder causing the elevation of blood pressure can be identified (Tables 19-2 and 19-3). In individuals with "secondary" hypertension, a specific mechanism for the blood pressure elevation is often more apparent.

ESSENTIAL HYPERTENSION

Essential hypertension tends to be familial and is likely to be the consequence of an interaction between environmental and genetic factors. The prevalence of essential hypertension increases with age, and individuals with relatively high blood pressures at younger ages are at increased risk for the subsequent development of hypertension. It is likely that essential hypertension represents a spectrum of disorders with different underlying pathophysiologies. In the majority of patients with established hypertension, peripheral resistance is increased and cardiac output is normal or decreased; however, in younger patients with mild or labile hypertension, cardiac output may be increased and peripheral resistance may be normal.

When plasma renin activity (PRA) is plotted against 24-h sodium excretion, ~10–15% of hypertensive patients have high PRA and 25% have low PRA. High-renin patients may have a vasoconstrictor form of hypertension, whereas low-renin patients may have volume-dependent hypertension. Inconsistent associations between plasma aldosterone and blood pressure have been described in patients with essential hypertension. The association between aldosterone and blood pressure is more striking in African Americans, and PRA tends to be low in hypertensive African Americans. This raises the possibility that subtle increases in aldosterone may contribute to hypertension in at least some groups of patients who do not have overt primary aldosteronism. Furthermore, spironolactone, an aldosterone antagonist, may be a particularly effective antihypertensive agent for some patients with essential hypertension, including some patients with "drug-resistant" hypertension.

OBESITY AND THE METABOLIC SYNDROME

There is a well-documented association between obesity (body mass index >30 kg/m^2) and hypertension. Further, cross-sectional studies indicate a direct linear correlation between body weight (or body mass index) and blood pressure. Centrally located body fat is a more important determinant of blood pressure elevation than is peripheral body fat. In longitudinal studies, a direct correlation exists between change in weight and change in blood pressure over time. Sixty percent of hypertensive adults are more than 20% overweight. It has been established that 60–70% of hypertension in adults may be directly attributable to adiposity.

TABLE 19-3

SECONDARY CAUSES OF SYSTOLIC AND DIASTOLIC HYPERTENSION	
Renal	Parenchymal diseases, renal cysts (including polycystic kidney disease), renal tumors (including renin-secreting tumors), obstructive uropathy
Renovascular	Arteriosclerotic, fibromuscular dysplasia
Adrenal	Primary aldosteronism, Cushing's syndrome, 17α-hydroxylase deficiency, 11β-hydroxylase deficiency, 11-hydroxysteroid dehydrogenase deficiency (licorice), pheochromocytoma
Aortic coarctation	
Obstructive sleep apnea	
Preeclampsia/eclampsia	
Neurogenic	Psychogenic, diencephalic syndrome, familial dysautonomia, polyneuritis (acute porphyria, lead poisoning), acute increased intracranial pressure, acute spinal cord section
Miscellaneous endocrine	Hypothyroidism, hyperthyroidism, hypercalcemia, acromegaly
Medications	High-dose estrogens, adrenal steroids, decongestants, appetite suppressants, cyclosporine, tricyclic antidepressants, monamine oxidase inhibitors, erythropoietin, nonsteroidal anti-inflammatory agents, cocaine
Mendelian forms of hypertension	See Table 19-4

Hypertension and dyslipidemia frequently occur together and in association with resistance to insulin-stimulated glucose uptake. This clustering of risk factors is often, but not invariably, associated with obesity, particularly abdominal obesity. Insulin resistance also is associated with an unfavorable imbalance in the endothelial production of mediators that regulate platelet aggregation, coagulation, fibrinolysis, and vessel tone. When these risk factors cluster, the risks for CHD, stroke, diabetes, and cardiovascular disease mortality are increased further.

Depending on the populations studied and the methodologies for defining insulin resistance, ~25–50% of nonobese, nondiabetic hypertensive persons are insulin resistant. The constellation of insulin resistance, abdominal obesity, hypertension, and dyslipidemia has been designated as the *metabolic syndrome*. As a group, first-degree relatives of patients with essential hypertension are also insulin resistant, and hyperinsulinemia (a surrogate marker of insulin resistance) may predict the eventual development of hypertension and cardiovascular disease. Although the metabolic syndrome may in part be heritable as a polygenic condition, the expression of the syndrome is modified by environmental factors, such as degree of physical activity and diet. Insulin sensitivity increases and blood pressure decreases in response to weight loss. The recognition that cardiovascular disease risk factors tend to cluster within individuals has important implications for the evaluation and treatment of hypertension. Evaluation of both hypertensive patients and individuals at risk for developing hypertension should include assessment of overall cardiovascular disease risk. Similarly, introduction of lifestyle modification strategies and drug therapies should address overall risk and not simply focus on hypertension.

RENAL PARENCHYMAL DISEASES

Virtually all disorders of the kidney may cause hypertension (Table 19-3), and renal disease is the most common cause of secondary hypertension. Hypertension is present in >80% of patients with chronic renal failure. In general, hypertension is more severe in glomerular diseases than in interstitial diseases such as chronic pyelonephritis. Conversely, hypertension may cause nephrosclerosis, and in some instances it may be difficult to determine whether hypertension or renal disease was the initial disorder. Proteinuria >1000 mg/d and an active urine sediment are indicative of primary renal disease. In either instance, the goals are to control blood pressure and retard the rate of progression of renal dysfunction.

RENOVASCULAR HYPERTENSION

Hypertension due to an occlusive lesion of a renal artery, renovascular hypertension, is a potentially curable form of hypertension. In the initial stages, the mechanism of hypertension generally is related to activation of the renin-angiotensin system. However, renin activity and other components of the renin-angiotensin system may be elevated only transiently; over time, sodium retention and recruitment of other pressure mechanisms may contribute to elevated arterial pressure. Two groups of patients are at risk for this disorder: older arteriosclerotic patients who have a plaque obstructing the renal artery, frequently at its origin, and patients with fibromuscular dysplasia. Atherosclerosis accounts for the large majority of patients with renovascular hypertension. Although fibromuscular dysplasia may occur at any age, it has a strong predilection for young white women. The prevalence in females is eightfold that in males. There are several histologic variants of fibromuscular dysplasia, including medial fibroplasia, perimedial fibroplasia, medial hyperplasia, and intimal fibroplasia. Medial fibroplasia is the most common variant and accounts for approximately two-thirds of patients. The lesions of fibromuscular dysplasia are frequently bilateral and, in contrast to atherosclerotic renovascular disease, tend to affect more distal portions of the renal artery.

In addition to the age and sex of the patient, several clues from the history and physical examination suggest a diagnosis of renovascular hypertension. The diagnosis should be considered in patients with other evidence of atherosclerotic vascular disease. Although response to antihypertensive therapy does not exclude the diagnosis, severe or refractory hypertension, recent loss of hypertension control or recent onset of moderately severe hypertension, and unexplained deterioration of renal function or deterioration of renal function associated with an ACE inhibitor should raise the possibility of renovascular hypertension. Approximately 50% of patients with renovascular hypertension have an abdominal or flank bruit, and the bruit is more likely to be hemodynamically significant if it lateralizes or extends throughout systole into diastole.

If blood pressure is adequately controlled with a simple antihypertensive regimen and renal function remains stable, there may be little impetus to pursue an evaluation for renal artery stenosis, particularly in an older patient with atherosclerotic disease and comorbid conditions. Patients with long-standing hypertension, advanced renal insufficiency, or diabetes mellitus are less likely to benefit from renal vascular repair. The most effective medical therapies include an ACE inhibitor or an angiotensin II receptor blocker; however, these agents decrease glomerular filtration rate in a stenotic kidney owing to efferent renal arteriolar dilation. In the presence of bilateral renal artery stenosis or renal artery stenosis to a solitary kidney, progressive renal insufficiency may result from the use of these agents. Importantly, the renal insufficiency is generally reversible after discontinuation of the offending drug.

If renal artery stenosis is suspected and if the clinical condition warrants an intervention such as percutaneous transluminal renal angioplasty (PTRA), placement of a vascular endoprosthesis (stent), or surgical renal revascularization, imaging studies should be the next step in the evaluation. As a screening test, renal blood flow may be evaluated with a radionuclide [^{131}I]-orthoiodohippurate (OIH) scan or glomerular filtration rate may be evaluated with a [^{99m}Tc]-diethylenetriamine pentaacetic acid (DTPA) scan before and after a single dose of captopril (or another ACE inhibitor). The following are consistent with a positive study: (1) decreased relative uptake by the involved kidney, which contributes <40% of total renal function, (2) delayed uptake on the affected side, and (3) delayed washout on the affected side. In patients with normal, or nearly normal, renal function, a normal captopril renogram essentially excludes functionally significant renal artery stenosis; however, its usefulness is limited in patients with renal insufficiency (creatinine clearance <20 mL/min) or bilateral renal artery stenosis. Additional imaging studies are indicated if the scan is positive. Doppler ultrasound of the renal arteries produces reliable estimates of renal blood flow velocity and offers the opportunity to track a lesion over time. Positive studies usually are confirmed at angiography, whereas false-negative results occur frequently, particularly in obese patients. Gadolinium-contrast magnetic resonance angiography offers clear images of the proximal renal artery but may miss distal lesions. An advantage is the opportunity to image the renal arteries with an agent that is not nephrotoxic. Contrast arteriography remains the "gold standard" for evaluation and identification of renal artery lesions. Potential risks include nephrotoxicity, particularly in patients with diabetes mellitus or preexisting renal insufficiency.

Some degree of renal artery obstruction may be observed in almost 50% of patients with atherosclerotic disease, and there are several approaches for evaluating the functional significance of such a lesion to predict the effect of vascular repair on blood pressure control and renal function. Each approach has varying degrees of sensitivity and specificity, and no single test is sufficiently reliable to determine a causal relationship between a renal artery lesion and hypertension. Functionally significant lesions generally occlude more than 70% of the lumen of the affected renal artery. On angiography, the presence of collateral vessels to the ischemic kidney suggests a functionally significant lesion. A lateralizing renal vein renin ratio (ratio >1.5 of affected side/contralateral side) has a 90% predictive value for a lesion that would respond to vascular repair; however, the false-negative rate for blood pressure control is 50–60%. Measurement of the pressure gradient across a renal artery lesion does not reliably predict the response to vascular repair.

In the final analysis, a decision concerning vascular repair versus medical therapy and the type of repair procedure should be individualized for each patient. Patients with fibromuscular disease have more favorable outcomes than do patients with atherosclerotic lesions, presumably owing to their younger age, shorter duration of hypertension, and less systemic disease. Because of its low risk-versus-benefit ratio and high success rate (improvement or cure of hypertension in 90% of patients and restenosis rate of 10%), PTRA is the initial treatment of choice for these patients. Surgical revascularization may be undertaken if PTRA is unsuccessful or if a branch lesion is present. In atherosclerotic patients, vascular repair should be considered if blood pressure cannot be controlled adequately despite optimal medical therapy or if renal function deteriorates. Surgery may be the preferred initial approach for younger atherosclerotic patients without comorbid conditions; however, for most atherosclerotic patients, depending on the location of the lesion, the initial approach may be PTRA and/or stenting. Surgical revascularization may be indicated if these approaches are unsuccessful, the vascular lesion is not amenable to PTRA or stenting, or concomitant aortic surgery is required, e.g., to repair an aneurysm. A National Institutes of Health–sponsored prospective, randomized clinical trial is in progress comparing medical therapy alone with medical therapy plus renal revascularization regarding Cardiovascular Outcomes for Renal Atherosclerotic Lesions (CORAL).

PRIMARY ALDOSTERONISM

Excess aldosterone production due to primary aldosteronism is a potentially curable form of hypertension. In patients with primary aldosteronism, increased aldosterone production is independent of the renin-angiotensin system, and the consequences are sodium retention, hypertension, hypokalemia, and low PRA. The reported prevalence of this disorder varies from <2% to ~15% of hypertensive individuals. In part, this variation is related to the intensity of screening and the criteria for establishing the diagnosis.

History and physical examination provide little information about the diagnosis. The age at the time of diagnosis is generally the third through fifth decade. Hypertension is usually mild to moderate but occasionally may be severe; primary aldosteronism should be considered in all patients with refractory hypertension. Hypertension in these patients may be associated with glucose intolerance. Most patients are asymptomatic, although, infrequently, polyuria, polydipsia, paresthesias, or muscle weakness may be present as a consequence of hypokalemic alkalosis. In a hypertensive patient with unprovoked hypokalemia (i.e., unrelated to diuretics, vomiting, or diarrhea), the prevalence of primary aldosteronism approaches 40–50%. In patients on diuretics, serum potassium <3.1 mmol/L (<3.1 meq/L) also raises the possibility of primary aldosteronism; however,

serum potassium is an insensitive and nonspecific screening test. However, serum potassium is normal in ~25% of patients subsequently found to have an aldosterone-producing adenoma, and higher percentages of patients with other etiologies of primary aldosteronism are not hypokalemic. Additionally, hypokalemic hypertension may be a consequence of secondary aldosteronism, other mineralocorticoid- and glucocorticoid-induced hypertensive disorders, and pheochromocytoma.

The ratio of plasma aldosterone to plasma renin activity (PA/PRA) is a useful screening test. These measurements preferably are obtained in ambulatory patients in the morning. A ratio >30:1 in conjunction with a plasma aldosterone concentration >555 pmol/L (>20 ng/dL) reportedly has a sensitivity of 90% and a specificity of 91% for an aldosterone-producing adenoma. In a Mayo Clinic series, an aldosterone-producing adenoma subsequently was confirmed surgically in >90% of hypertensive patients with a PA/PRA ratio ≥20 and a plasma aldosterone concentration ≥415 pmol/L (≥15 ng/dL). There are, however, several caveats to interpreting the ratio. The cutoff for a "high" ratio is laboratory and assay dependent. Some antihypertensive agents may affect the ratio (e.g., aldosterone antagonists, angiotensin receptor antagonists, and ACE inhibitors may increase renin; aldosterone antagonists may increase aldosterone). Current recommendations are to withdraw aldosterone antagonists for at least 4 weeks before obtaining these measurements, with this caveat. The ratio has been reported to be useful as a screening test in measurements obtained with patients taking their usual antihypertensive medications. A high ratio in the absence of an elevated plasma aldosterone level is considerably less specific for primary aldosteronism since many patients with essential hypertension have low renin levels in this setting, particularly African Americans and elderly patients. In patients with renal insufficiency, the ratio may also be elevated because of decreased aldosterone clearance. In patients with an elevated PA/PRA ratio, the diagnosis of primary aldosteronism can be confirmed by demonstrating failure to suppress plasma aldosterone to <277 pmol/L (<10 ng/dL) after IV infusion of 2 L of isotonic saline over 4 h; post-saline infusion plasma aldosterone values between 138 and 277 pmol/L (5–10 ng/dL) are not determinant. Alternative confirmatory tests include failure to suppress aldosterone (based on test-specific criteria) in response to an oral NaCl load, fludrocortisone, or captopril.

Several adrenal abnormalities may culminate in the syndrome of primary aldosteronism, and appropriate therapy depends on the specific etiology. Some 60–70% of patients have an aldosterone-producing adrenal adenoma. The tumor is almost always unilateral, and most often measures <3 cm in diameter. Most of the remainder of these patients have bilateral adrenocortical hyperplasia (idiopathic hyperaldosteronism). Rarely, primary aldosteronism may be caused by an adrenal carcinoma or an ectopic malignancy, e.g., ovarian arrhenoblastoma. Most aldosterone-producing carcinomas, in contrast to adrenal adenomas and hyperplasia, produce excessive amounts of other adrenal steroids in addition to aldosterone. Functional differences in hormone secretion may assist in the differential diagnosis. Aldosterone biosynthesis is more responsive to adrenocorticotropic hormone (ACTH) in patients with adenoma and more responsive to angiotensin in patients with hyperplasia. Consequently, patients with adenoma tend to have higher plasma aldosterone in the early morning that decreases during the day, reflecting the diurnal rhythm of ACTH, whereas plasma aldosterone tends to increase with upright posture in patients with hyperplasia, reflecting the normal postural response of the renin-angiotensin-aldosterone axis. However, there is some overlap in the ability of these measurements to discriminate between adenoma and hyperplasia.

Adrenal computed tomography (CT) should be carried out in all patients diagnosed with primary aldosteronism. High-resolution CT may identify tumors as small as 0.3 cm and is positive for an adrenal tumor 90% of the time. If the CT is not diagnostic, an adenoma may be detected by adrenal scintigraphy with 6 β-[I^{131}] iodomethyl-19-norcholesterol after dexamethasone suppression (0.5 mg every 6 h for 7 days); however, this technique has decreased sensitivity for adenomas <1.5 cm.

When carried out by an experienced radiologist, bilateral adrenal venous sampling for measurement of plasma aldosterone is the most accurate means of differentiating unilateral from bilateral forms of primary aldosteronism. The sensitivity and specificity of adrenal venous sampling (95% and 100%, respectively) for detecting unilateral aldosterone hypersecretion are superior to those of adrenal CT; success rates are 90–96%, and complication rates are <2.5%. One frequently used protocol involves sampling for aldosterone and cortisol levels in response to ACTH stimulation. An ipsilateral/contralateral aldosterone ratio >4, with symmetric ACTH-stimulated cortisol levels, is indicative of unilateral aldosterone production.

Hypertension generally is responsive to surgery in patients with adenoma but not in patients with bilateral adrenal hyperplasia. Unilateral adrenalectomy, often done via a laparoscopic approach, is curative in 40–70% of patients with an adenoma. Surgery should be undertaken after blood pressure has been controlled and hypokalemia corrected. Transient hypoaldosteronism may occur up to 3 months postoperatively, resulting in hyperkalemia. Potassium should be monitored during this time, and hyperkalemia should be treated with potassium-wasting diuretics and with fludrocortisone, if needed. Patients with bilateral hyperplasia should be treated medically. The drug regimen for these patients, as well as for patients with an adenoma who are poor surgical candidates, should include an

aldosterone antagonist and, if necessary, other potassium-sparing diuretics.

Glucocorticoid-remediable hyperaldosteronism is a rare, monogenic autosomal dominant disorder characterized by moderate to severe hypertension, often occurring at an early age. These patients may have a family history of hemorrhagic stroke at a young age. Hypokalemia is usually mild or absent. Normally, angiotensin II stimulates aldosterone production by the adrenal zona glomerulosa, whereas ACTH stimulates cortisol production in the zona fasciculata. Owing to a chimeric gene on chromosome 8, ACTH also regulates aldosterone secretion by the zona fasciculata in patients with glucocorticoid-remediable hyperaldosteronism. The consequence is overproduction in the zona fasciculata of both aldosterone and hybrid steroids (18-hydroxycortisol and 18-oxocortisol) due to oxidation of cortisol. The diagnosis may be established by urine excretion rates of these hybrid steroids that are 20 to 30 times normal or by direct genetic testing. Therapeutically, suppression of ACTH with low-dose glucocorticoids corrects the hyperaldosteronism, hypertension, and hypokalemia. Spironolactone is also a therapeutic option.

CUSHING'S SYNDROME

Cushing's syndrome is related to excess cortisol production due either to excess ACTH secretion (from a pituitary tumor or an ectopic tumor) or to ACTH-independent adrenal production of cortisol. Hypertension occurs in 75–80% of patients with Cushing's syndrome. The mechanism of hypertension may be related to stimulation of mineralocorticoid receptors by cortisol and increased secretion of other adrenal steroids. If clinically suspected based on phenotypic characteristics, in patients not taking exogenous glucocorticoids, laboratory screening may be carried out with measurement of 24-h excretion rates of urine free cortisol or an overnight dexamethasone-suppression test. Recent evidence suggests that late night salivary cortisol is also a sensitive and convenient screening test. Further evaluation is required to confirm the diagnosis and identify the specific etiology of Cushing's syndrome. Appropriate therapy depends on the etiology.

PHEOCHROMOCYTOMA

Catecholamine-secreting tumors are located in the adrenal medulla (pheochromocytoma) or in extra-adrenal paraganglion tissue (paraganglioma) and account for hypertension in ~0.05% of patients. If unrecognized, pheochromocytoma may result in lethal cardiovascular consequences. Clinical manifestations, including hypertension, are primarily related to increased circulating catecholamines, although some of these tumors may secrete a number of other vasoactive substances. In a small percentage of patients, epinephrine is the predominant catecholamine secreted by the tumor, and these patients may present with hypotension rather than hypertension. The initial suspicion of the diagnosis is based on symptoms and/or the association of pheochromocytoma with other disorders **(Table 19-4)**. Approximately 20% of pheochromocytomas are familial with autosomal dominant inheritance. Inherited pheochromocytomas may be associated with multiple endocrine neoplasia (MEN) type 2A and type 2B, von Hippel-Lindau disease, and neurofibromatosis (Table 19-4). Each of these syndromes is related to specific, identifiable germ-line mutations. Additionally, mutations of succinate dehydrogenase genes are associated with paraganglioma syndromes, generally characterized by head and neck paragangliomas. Laboratory testing consists of measuring catecholamines in either urine or plasma. Genetic screening is available for evaluating patients and relatives suspected of harboring a pheochromocytoma associated with a familial syndrome. Surgical excision is the definitive treatment of pheochromocytoma and results in cure in ~90% of patients.

MISCELLANEOUS CAUSES OF HYPERTENSION

Hypertension due to *obstructive sleep apnea* is being recognized with increasing frequency. Independent of obesity, hypertension occurs in >50% of individuals with obstructive sleep apnea. The severity of hypertension correlates with the severity of sleep apnea. Approximately 70% of patients with obstructive sleep apnea are obese. Hypertension related to obstructive sleep apnea also should be considered in patients with drug-resistant hypertension and patients with a history of snoring. The diagnosis can be confirmed by polysomnography. In obese patients, weight loss may alleviate or cure sleep apnea and related hypertension. Continuous positive airway pressure (CPAP) administered during sleep is an effective therapy for obstructive sleep apnea. With CPAP, patients with apparently drug-resistant hypertension may be more responsive to antihypertensive agents.

Coarctation of the aorta is the most common congenital cardiovascular cause of hypertension. The incidence is 1–8 per 1000 live births. It is usually sporadic but occurs in 35% of children with Turner syndrome. Even when the anatomic lesion is surgically corrected in infancy, up to 30% of patients develop subsequent hypertension and are at risk of accelerated coronary artery disease and cerebrovascular events. Patients with less severe lesions may not be diagnosed until young adulthood. The physical findings are diagnostic and include diminished and delayed femoral pulses and a systolic pressure

TABLE 19-4

RARE MENDELIAN FORMS OF HYPERTENSION

DISEASE	PHENOTYPE	GENETIC CAUSE
Glucocorticoid-remediable hyperaldosteronism	Autosomal dominant Absent or mild hypokalemia	Chimeric 11β-hydroxylase/aldosterone gene on chromosome 8
17α-hydroxylase deficiency	Autosomal recessive Males: pseudohermaphroditism Females: primary amenorrhea, absent secondary sexual characteristics	Random mutations of the *CYP17* gene on chromosome 10
11β-hydroxylase deficiency	Autosomal recessive Masculinization	Mutations of the *CYP11B1* gene on chromosome 8q21-q22
11β-hydroxysteroid dehydrogenase deficiency (apparent mineralocorticoid excess syndrome)	Autosomal recessive Hypokalemia, low renin, low aldosterone	Mutations in the 11β-hydroxysteroid dehydrogenase gene
Liddle's syndrome	Autosomal dominant Hypokalemia, low renin, low aldosterone	Mutation subunits of the epithelial sodium channel *SCNN1B* and *SCNN1C* genes
Pseudohypoaldosteronism type II (Gordon's syndrome)	Autosomal dominant Hyperkalemia, normal glomerular filtration rate	Linkage to chromosomes 1q31-q42 and 17p11-q21
Hypertension exacerbated in pregnancy	Autosomal dominant Severe hypertension in early pregnancy	Missense mutation with substitution of leucine for serine at codon 810 (MRL_{810})
Polycystic kidney disease	Autosomal dominant Large cystic kidneys, renal failure, liver cysts, cerebral aneurysms, valvular heart disease	Mutations in the *PKD1* gene on chromosome 16 and *PKD2* gene on chromosome 4
Pheochromocytoma	Autosomal dominant (a) Multiple endocrine neoplasia, type 2A Medullary thyroid carcinoma, hyperparathyroidism (b) Multiple endocrine neoplasia, type 2B Medullary thyroid carcinoma, mucosal neuromas, thickened corneal nerves, alimentary ganglioneuromatoses, marfanoid habitus (c) von Hippel-Lindau disease Retinal angiomas, hemangioblastomas of the cerebellum and spinal cord, renal cell carcinoma (d) Neurofibromatosis type 1 Multiple neurofibromas, café-au-lait spots	 (a) Mutations in the RET protooncogene (b) Mutations in the RET protooncogene (c) Mutations in the VHL tumor-suppressor gene (d) Mutations in the NF1 tumor-suppressor gene

gradient between the right arm and the legs and, depending on the location of the coarctation, between the right and left arms. A blowing systolic murmur may be heard in the posterior left interscapular areas. The diagnosis may be confirmed by chest x-ray and transesophageal echocardiography. Therapeutic options include surgical repair and balloon angioplasty, with or without placement of an intravascular stent. Subsequently, many patients do not have a normal life expectancy but may have persistent hypertension, with death due to ischemic heart disease, cerebral hemorrhage, or aortic aneurysm.

Several additional endocrine disorders, including *thyroid diseases* and *acromegaly*, cause hypertension. Mild diastolic hypertension may be a consequence of hypothyroidism, whereas hyperthyroidism may result in systolic hypertension. *Hypercalcemia* of any etiology, the most common being primary hyperparathyroidism, may result in hypertension. Hypertension also may be related to a number of prescribed or over-the-counter *medications*.

MONOGENIC HYPERTENSION

A number of rare forms of monogenic hypertension have been identified (Table 19-4). These disorders may be recognized by their characteristic phenotypes, and in many instances the diagnosis may be confirmed by genetic analysis. Several inherited defects in adrenal

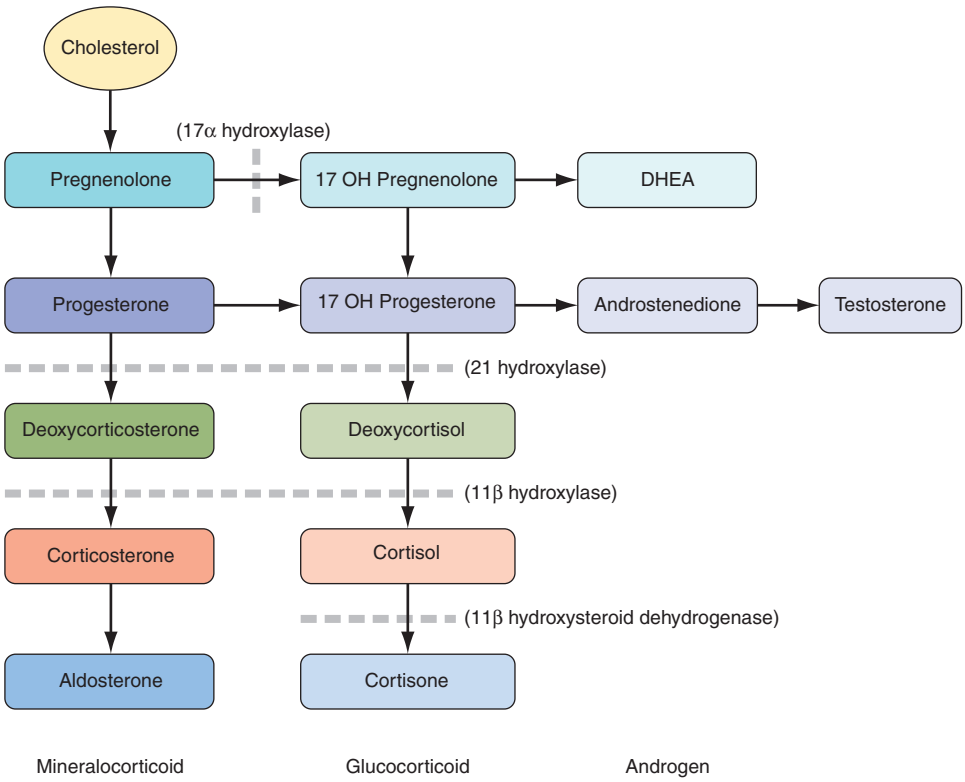


FIGURE 19-3
Adrenal enzymatic defects.

steroid biosynthesis and metabolism result in mineralocorticoid-induced hypertension and hypokalemia. In patients with a 17α-hydroxylase deficiency, synthesis of sex hormones and cortisol is decreased **(Fig. 19-3)**. Consequently, these individuals do not mature sexually; males may present with pseudohermaphroditism and females with primary amenorrhea and absent secondary sexual characteristics. Because cortisol-induced negative feedback on pituitary ACTH production is diminished, ACTH-stimulated adrenal steroid synthesis proximal to the enzymatic block is increased. Hypertension and hypokalemia are consequences of increased synthesis of mineralocorticoids proximal to the enzymatic block, particularly desoxycorticosterone. Increased steroid production and, hence, hypertension may be treated with low-dose glucocorticoids. An 11β-hydroxylase deficiency results in a salt-retaining adrenogenital syndrome that occurs in 1 in 100,000 live births. This enzymatic defect results in decreased cortisol synthesis, increased synthesis of mineralocorticoids (e.g., desoxycorticosterone), and shunting of steroid biosynthesis into the androgen pathway. In the severe form, the syndrome may present early in life, including the newborn period, with virilization and ambiguous genitalia in females and penile enlargement in males, or in older children as precocious puberty and short stature. Acne, hirsutism, and menstrual irregularities may be the presenting features when the disorder is first recognized in adolescence or early adulthood. Hypertension is less common in the late-onset forms. Patients with an 11β-hydroxysteroid dehydrogenase deficiency have an impaired capacity to metabolize cortisol to its inactive metabolite, cortisone, and hypertension is related to activation of mineralocorticoid receptors by cortisol. This defect may be inherited or acquired, due to licorice-containing glycyrrhizin acid. The same substance is present in the paste of several brands of chewing tobacco. The defect in Liddle's syndrome (Chap. 6) results from constitutive activation of amiloride-sensitive epithelial sodium channels on the distal renal tubule, resulting in excess sodium reabsorption; the syndrome is ameliorated by amiloride. Hypertension exacerbated in pregnancy is due to activation of the mineralocorticoid receptor by progesterone.

APPROACH TO THE PATIENT

Hypertension

HISTORY The initial assessment of a hypertensive patient should include a complete history and physical examination to confirm a diagnosis of hypertension, screen for other cardiovascular disease risk factors, screen for secondary causes of hypertension, identify cardiovascular consequences of hypertension and other comorbidities, assess blood pressure–related lifestyles, and determine the potential for intervention.

Most patients with hypertension have no specific symptoms referable to their blood pressure elevation. Although popularly considered a symptom of elevated arterial pressure, headache generally occurs only in patients with severe hypertension. Characteristically, a "hypertensive headache" occurs in the morning and

TABLE 19-5

PATIENT'S RELEVANT HISTORY
Duration of hypertension
Previous therapies: responses and side effects
Family history of hypertension and cardiovascular disease
Dietary and psychosocial history
Other risk factors: weight change, dyslipidemia, smoking, diabetes, physical inactivity
Evidence of secondary hypertension: history of renal disease; change in appearance; muscle weakness; spells of sweating, palpitations, tremor; erratic sleep, snoring, daytime somnolence; symptoms of hypo- or hyperthyroidism; use of agents that may increase blood pressure
Evidence of target organ damage: history of TIA, stroke, transient blindness; angina, myocardial infarction, congestive heart failure; sexual function
Other comorbidities

Abbreviation: TIA, transient ischemic attack.

is localized to the occipital region. Other nonspecific symptoms that may be related to elevated blood pressure include dizziness, palpitations, easy fatigability, and impotence. When symptoms are present, they are generally related to hypertensive cardiovascular disease or to manifestations of secondary hypertension. Table 19-5 lists salient features that should be addressed in obtaining a history from a hypertensive patient.

MEASUREMENT OF BLOOD PRESSURE Reliable measurements of blood pressure depend on attention to the details of the technique and conditions of the measurement. Proper training of observers, positioning of the patient, and selection of cuff size are essential. Owing to recent regulations preventing the use of mercury because of concerns about its potential toxicity, most office measurements are made with aneroid sphygmomanometers or with oscillometric devices. These instruments should be calibrated periodically, and their accuracy confirmed. Before the blood pressure measurement is taken, the individual should be seated quietly in a chair (not the exam table) with feet on the floor for 5 min in a private, quiet setting with a comfortable room temperature. At least two measurements should be made. The center of the cuff should be at heart level, and the width of the bladder cuff should equal at least 40% of the arm circumference; the length of the cuff bladder should be enough to encircle at least 80% of the arm circumference. It is important to pay attention to cuff placement, stethoscope placement, and the rate of deflation of the cuff (2 mmHg/s). Systolic blood pressure is the first of at least two regular "tapping" Korotkoff sounds, and diastolic blood pressure is the point at which the last regular Korotkoff sound is heard. In current practice, a diagnosis of hypertension generally is based on seated office measurements.

Currently available ambulatory monitors are fully automated, use the oscillometric technique, and typically are programmed to take readings every 15–30 min. Twenty-four-hour ambulatory blood pressure monitoring more reliably predicts cardiovascular disease risk than do office measurements. However, ambulatory monitoring is not used routinely in clinical practice and generally is reserved for patients in whom white coat hypertension is suspected. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has also recommended ambulatory monitoring for treatment resistance, symptomatic hypotension, autonomic failure, and episodic hypertension.

PHYSICAL EXAMINATION Body habitus, including weight and height, should be noted. At the initial examination, blood pressure should be measured in both arms and preferably in the supine, sitting, and standing positions to evaluate for postural hypotension. Even if the femoral pulse is normal to palpation, arterial pressure should be measured at least once in the lower extremity in patients in whom hypertension is discovered before age 30. Heart rate also should be recorded. Hypertensive individuals have an increased prevalence of atrial fibrillation. The neck should be palpated for an enlarged thyroid gland, and patients should be assessed for signs of hypo- and hyperthyroidism. Examination of blood vessels may provide clues about underlying vascular disease and should include funduscopic examination, auscultation for bruits over the carotid and femoral arteries, and palpation of femoral and pedal pulses. The retina is the only tissue in which arteries and arterioles can be examined directly. With increasing severity of hypertension and atherosclerotic disease, progressive funduscopic changes include increased arteriolar light reflex, arteriovenous crossing defects, hemorrhages and exudates, and, in patients with malignant hypertension, papilledema. Examination of the heart may reveal a loud second heart sound due to closure of the aortic valve and an S_4 gallop attributed to atrial contraction against a noncompliant left ventricle. Left ventricular hypertrophy may be detected by an enlarged, sustained, and laterally displaced apical impulse. An abdominal bruit, particularly a bruit that lateralizes and extends throughout systole into diastole, raises the possibility of renovascular hypertension. Kidneys of patients with polycystic kidney disease may be palpable in the abdomen. The physical examination also should include evaluation for signs of CHF and a neurologic examination.

LABORATORY TESTING Table 19-6 lists recommended laboratory tests in the initial evaluation of hypertensive patients. Repeat measurements of renal function, serum electrolytes, fasting glucose, and lipids

TABLE 19-6

BASIC LABORATORY TESTS FOR INITIAL EVALUATION

SYSTEM	TEST
Renal	Microscopic urinalysis, albumin excretion, serum BUN and/or creatinine
Endocrine	Serum sodium, potassium, calcium, ?TSH
Metabolic	Fasting blood glucose, total cholesterol, HDL and LDL (often computed) cholesterol, triglycerides
Other	Hematocrit, electrocardiogram

Abbreviations: BUN, blood urea nitrogen; HDL, LDL, high-/low-density lipoprotein; TSH, thyroid-stimulating hormone.

may be obtained after the introduction of a new antihypertensive agent and then annually or more frequently if clinically indicated. More extensive laboratory testing is appropriate for patients with apparent drug-resistant hypertension or when the clinical evaluation suggests a secondary form of hypertension.

TREATMENT Hypertension

LIFESTYLE INTERVENTIONS Implementation of lifestyles that favorably affect blood pressure has implications for both the prevention and the treatment of hypertension. Health-promoting lifestyle modifications are recommended for individuals with prehypertension and as an adjunct to drug therapy in hypertensive individuals. These interventions should address overall cardiovascular disease risk. Although the impact of lifestyle interventions on blood pressure is more pronounced in persons with hypertension, in short-term trials, weight loss and reduction of dietary NaCl have been shown to prevent the development of hypertension. In hypertensive individuals, even if these interventions do not produce a sufficient reduction in blood pressure to avoid drug therapy, the number of medications or doses required for blood pressure control may be reduced. Dietary modifications that effectively lower blood pressure are weight loss, reduced NaCl intake, increased potassium intake, moderation of alcohol consumption, and an overall healthy dietary pattern (Table 19-7).

Prevention and treatment of obesity are important for reducing blood pressure and cardiovascular disease risk. In short-term trials, even modest weight loss can lead to a reduction of blood pressure and an increase in insulin sensitivity. Average blood pressure reductions of 6.3/3.1 mmHg have been observed with a reduction in mean body weight of 9.2 kg. Regular physical activity facilitates weight loss, decreases blood pressure, and reduces the overall risk of cardiovascular disease.

TABLE 19-7

LIFESTYLE MODIFICATIONS TO MANAGE HYPERTENSION

Weight reduction	Attain and maintain BMI <25 kg/m^2
Dietary salt reduction	<6 g NaCl/d
Adapt DASH-type dietary plan	Diet rich in fruits, vegetables, and low-fat dairy products with reduced content of saturated and total fat
Moderation of alcohol consumption	For those who drink alcohol, consume ≤2 drinks/day in men and ≤1 drink/day in women
Physical activity	Regular aerobic activity, e.g., brisk walking for 30 min/d

Abbreviations: BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension (trial).

Blood pressure may be lowered by 30 min of moderately intense physical activity, such as brisk walking, 6–7 days a week, or by more intense, less frequent workouts.

There is individual variability in the sensitivity of blood pressure to NaCl, and this variability may have a genetic basis. Based on results of meta-analyses, lowering of blood pressure by limiting daily NaCl intake to 4.4–7.4 g (75–125 meq) results in blood pressure reductions of 3.7–4.9/0.9–2.9 mmHg in hypertensive individuals and lesser reductions in normotensive individuals. Dietary NaCl reduction also has been shown to reduce the long-term risk of cardiovascular events in adults with "prehypertension." Potassium and calcium supplementation have inconsistent, modest antihypertensive effects, and, independent of blood pressure, potassium supplementation may be associated with reduced stroke mortality. Alcohol use in persons consuming three or more drinks per day (a standard drink contains ~14 g ethanol) is associated with higher blood pressures, and a reduction of alcohol consumption is associated with a reduction of blood pressure. In patients with advanced renal disease, dietary protein restriction may have a modest effect in mitigating renal damage by reducing the intrarenal transmission of systemic arterial pressure.

The DASH (Dietary Approaches to Stop Hypertension) trial convincingly demonstrated that over an 8-week period a diet high in fruits, vegetables, and low-fat dairy products lowers blood pressure in individuals with high-normal blood pressures or mild hypertension. Reduction of daily NaCl intake to <6 g (100 meq) augmented the effect of this diet on blood pressure. Fruits and vegetables are enriched sources of potassium, magnesium, and fiber, and dairy products are an important source of calcium.

PHARMACOLOGIC THERAPY Drug therapy is recommended for individuals with blood pressures

≥140/90 mmHg. The degree of benefit derived from antihypertensive agents is related to the magnitude of the blood pressure reduction. Lowering systolic blood pressure by 10–12 mmHg and diastolic blood pressure by 5–6 mmHg confers relative risk reductions of 35–40% for stroke and 12–16% for CHD within 5 years of the initiation of treatment. Risk of heart failure is reduced by >50%. Hypertension control is the single most effective intervention for slowing the rate of progression of hypertension-related chronic kidney disease.

There is considerable variation in individual responses to different classes of antihypertensive agents, and the magnitude of response to any single agent may be limited by activation of counterregulatory mechanisms that oppose the hypotensive effect of the agent. Most available agents reduce systolic blood pressure by 7–13 mmHg and diastolic blood pressure by 4–8 mmHg when corrected for placebo effect. More often than not, combinations of agents, with complementary antihypertensive mechanisms, are required to achieve goal blood pressure reductions. Selection of antihypertensive agents and combinations of agents should be individualized, taking into account age, severity of hypertension, other cardiovascular disease risk factors, comorbid conditions, and practical considerations related to cost, side effects, and frequency of dosing (Table 19-8).

Diuretics Low-dose thiazide diuretics often are used as first-line agents alone or in combination with other antihypertensive drugs. Thiazides inhibit the Na^+/Cl^- pump in the distal convoluted tubule and hence increase sodium excretion. In the long term, they also may act as vasodilators. Thiazides are safe, efficacious, inexpensive, and reduce clinical events. They provide additive blood pressure–lowering effects when combined with beta blockers, angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs). In contrast, addition of a diuretic to a calcium channel blocker is less effective. Usual doses of hydrochlorothiazide range from 6.25–50 mg/d. Owing to an increased incidence of metabolic side effects (hypokalemia, insulin resistance, increased cholesterol), higher doses generally are not recommended. Two potassium-sparing diuretics, amiloride and triamterene, act by inhibiting epithelial sodium channels in the distal nephron. These agents are weak antihypertensive agents but may be used in combination with a thiazide to protect against hypokalemia. The main pharmacologic target for loop diuretics is the Na^+-K^+-$2Cl^-$ cotransporter in the thick ascending limb of the loop of Henle. Loop diuretics generally are reserved for hypertensive patients with reduced glomerular filtration rates [reflected in serum creatinine >220 μmol/L (>2.5 mg/dL)], CHF, or sodium retention and edema for some other reason, such as treatment with a potent vasodilator, e.g., minoxidil.

Blockers of the Renin-Angiotensin System ACEIs decrease the production of angiotensin II, increase bradykinin levels, and reduce sympathetic nervous system activity. ARBs provide selective blockade of AT_1 receptors, and the effect of angiotensin II on unblocked AT_2 receptors may augment their hypotensive effect. Both classes of agents are effective antihypertensive agents that may be used as monotherapy or in combination with diuretics, calcium antagonists, and alpha blocking agents. ACEIs and ARBs have been shown to improve insulin action and ameliorate the adverse effects of diuretics on glucose metabolism. Although the overall impact on the incidence of diabetes is modest, compared with amlodipine (a calcium antagonist), valsartan (an ARB) has been shown to reduce the risk of developing diabetes in high-risk hypertensive patients. ACEI/ARB combinations are less effective in lowering blood pressure than is the case when either class of these agents is used in combination with other classes of agents. In patients with vascular disease or a high risk of diabetes, combination ACEI/ARB therapy has been associated with more adverse events (e.g., cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure) without increases in benefit. However, in hypertensive patients with proteinuria, preliminary data suggest that reduction of proteinuria with ACEI/ARB combination treatment may be more effective than treatment with either agent alone.

Side effects of ACEIs and ARBs include functional renal insufficiency due to efferent renal arteriolar dilation in a kidney with a stenotic lesion of the renal artery. Additional predisposing conditions to renal insufficiency induced by these agents include dehydration, CHF, and use of nonsteroidal anti-inflammatory drugs. Dry cough occurs in ~15% of patients, and angioedema occurs in <1% of patients taking ACEIs. Angioedema occurs most commonly in individuals of Asian origin and more commonly in African Americans than in whites. Hyperkalemia due to hypoaldosteronism is an occasional side effect of both ACEIs and ARBs.

A new approach to blocking the renin-angiotensin system has been introduced into clinical practice for the treatment of hypertension: direct renin inhibitors. Blockade of the renin-angiotensin system is more complete with renin inhibitors than with ACEIs or ARBs. Aliskiren is the first of a class of oral, nonpeptide competitive inhibitors of the enzymatic activity of renin. Monotherapy with aliskiren seems to be as effective as an ACEI or ARB for lowering blood pressure, but not more effective. Further blood reductions may be achieved when aliskiren is used in combination with a thiazide diuretic, an ACEI,

TABLE 19-8

EXAMPLES OF ORAL DRUGS USED IN TREATMENT OF HYPERTENSION

DRUG CLASS	EXAMPLES	USUAL TOTAL DAILY DOSE[a] (DOSING FREQUENCY/DAY)	OTHER INDICATIONS	CONTRAINDICATIONS/ CAUTIONS
Diuretics				
Thiazides	Hydrochlorothiazide Chlorthalidone	6.25–50 mg (1–2) 25–50 mg (1)		Diabetes, dyslipidemia, hyperuricemia, gout, hypokalemia
Loop diuretics	Furosemide Ethacrynic acid	40–80 mg (2–3) 50–100 mg (2–3)	CHF due to systolic dysfunction, renal failure	Diabetes, dyslipidemia, hyperuricemia, gout, hypokalemia
Aldosterone antagonists	Spironolactone Eplerenone	25–100 mg (1–2) 50–100 mg (1–2)	CHF due to systolic dysfunction, primary aldosteronism	Renal failure, hyperkalemia
K^+ retaining	Amiloride Triamterene	5–10 mg (1–2) 50–100 mg (1–2)		Renal failure, hyperkalemia
Beta blockers				
Cardioselective	Atenolol Metoprolol	25–100 mg (1) 25–100 mg (1–2)	Angina, CHF due to systolic dysfunction, post-MI, sinus tachycardia, ventricular tachyarrhythmias	Asthma, COPD, 2nd- or 3rd-degree heart block, sick-sinus syndrome
Nonselective	Propranolol Propranolol LA	40–160 mg (2) 60–180 (1)		
Combined alpha/ beta	Labetalol Carvedilol	200–800 mg (2) 12.5–50 mg (2)	?Post-MI, CHF	
Alpha antagonists				
Selective	Prazosin Doxazosin Terazosin	2–20 mg (2–3) 1–16 mg (1) 1–10 mg (1–2)	Prostatism	
Nonselective	Phenoxybenzamine	20–120 mg (2–3)	Pheochromocytoma	
Sympatholytics				
Central	Clonidine Clonidine patch Methyldopa Reserpine Guanfacine	0.1–0.6 mg (2) 0.1–0.3 mg (1/week) 250–1000 mg (2) 0.05–0.25 mg (1) 0.5–2 mg (1)		
ACE inhibitors	Captopril Lisinopril Ramipril	25–200 mg (2) 10–40 mg (1) 2.5–20 mg (1–2)	Post-MI, coronary syndromes, CHF with low ejection fraction, nephropathy	Acute renal failure, bilateral renal artery stenosis, pregnancy, hyperkalemia
Angiotensin II antagonists	Losartan Valsartan Candesartan	25–100 mg (1–2) 80–320 mg (1) 2–32 mg (1–2)	CHF with low ejection fraction, nephropathy, ACE inhibitor cough	Renal failure, bilateral renal artery stenosis, pregnancy, hyperkalemia
Renin inhibitors	Aliskiren	150–300 mg (1)	Diabetic nephropathy	Pregnancy
Calcium antagonists				
Dihydropyridines	Nifedipine (long acting)	30–60 mg (1)		
Nondihydropyridines	Verapamil (long acting) Diltiazem (long acting)	120–360 mg (1–2) 180-420 mg (1)	Post-MI, supraventricular tachycardias, angina	2nd- or 3rd-degree heart block
Direct vasodilators	Hydralazine Minoxidil	25–100 mg (2) 2.5–80 mg (1–2)		Severe coronary artery disease

[a]At the initiation of therapy, lower doses may be preferable for elderly patients and for select combinations of antihypertensive agents.
Abbreviations: ACE, angiotensin-converting enzyme; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

an ARB, or calcium antagonists. Currently, aliskiren is not considered a first-line antihypertensive agent.

Aldosterone Antagonists Spironolactone is a nonselective aldosterone antagonist that may be used alone or in combination with a thiazide diuretic. It may be a particularly effective agent in patients with low-renin essential hypertension, resistant hypertension, and primary aldosteronism. In patients with CHF, low-dose spironolactone reduces mortality and hospitalizations for heart failure when given in addition to conventional therapy with ACEIs, digoxin, and loop diuretics. Because spironolactone binds to progesterone and androgen receptors, side effects may include gynecomastia, impotence, and menstrual abnormalities. These side effects are circumvented by a newer agent, eplerenone, which is a selective aldosterone antagonist. Eplerenone has recently been approved in the United States for the treatment of hypertension.

Beta Blockers β-Adrenergic receptor blockers lower blood pressure by decreasing cardiac output due to a reduction of heart rate and contractility. Other proposed mechanisms by which beta blockers lower blood pressure include a central nervous system effect and inhibition of renin release. Beta blockers are particularly effective in hypertensive patients with tachycardia, and their hypotensive potency is enhanced by coadministration with a diuretic. In lower doses, some beta blockers selectively inhibit cardiac β_1 receptors and have less influence on β_2 receptors on bronchial and vascular smooth muscle cells; however, there seems to be no difference in the antihypertensive potencies of cardioselective and nonselective beta blockers. Certain beta blockers have intrinsic sympathomimetic activity, and it is uncertain whether this constitutes an overall advantage or disadvantage in cardiac therapy. Beta blockers without intrinsic sympathomimetic activity decrease the rate of sudden death, overall mortality, and recurrent myocardial infarction. In patients with CHF, beta blockers have been shown to reduce the risks of hospitalization and mortality. Carvedilol and labetalol block both β receptors and peripheral α-adrenergic receptors. The potential advantages of combined β- and α-adrenergic blockade in treating hypertension remain to be determined.

α-Adrenergic Blockers Postsynaptic, selective α-adrenoreceptor antagonists lower blood pressure by decreasing peripheral vascular resistance. They are effective antihypertensive agents used either as monotherapy or in combination with other agents. However, in clinical trials of hypertensive patients, alpha blockade has not been shown to reduce cardiovascular morbidity and mortality or to provide as much protection against CHF as other classes of antihypertensive agents. These agents are also effective in treating lower urinary tract symptoms in men with prostatic hypertrophy. Nonselective α-adrenoreceptor antagonists bind to postsynaptic and presynaptic receptors and are used primarily for the management of patients with pheochromocytoma.

Sympatholytic Agents Centrally acting α_2 sympathetic agonists decrease peripheral resistance by inhibiting sympathetic outflow. They may be particularly useful in patients with autonomic neuropathy who have wide variations in blood pressure due to baroreceptor denervation. Drawbacks include somnolence, dry mouth, and rebound hypertension on withdrawal. Peripheral sympatholytics decrease peripheral resistance and venous constriction by depleting nerve terminal norepinephrine. Although they are potentially effective antihypertensive agents, their usefulness is limited by orthostatic hypotension, sexual dysfunction, and numerous drug-drug interactions.

Calcium Channel Blockers Calcium antagonists reduce vascular resistance through L-channel blockade, which reduces intracellular calcium and blunts vasoconstriction. This is a heterogeneous group of agents that includes drugs in the following three classes: phenylalkylamines (verapamil), benzothiazepines (diltiazem), and 1,4-dihydropyridines (nifedipine-like). Used alone and in combination with other agents (ACEIs, beta blockers, α_1-adrenergic blockers), calcium antagonists effectively lower blood pressure; however, it is unclear if adding a diuretic to a calcium blocker results in a further lowering of blood pressure. Side effects of flushing, headache, and edema with dihydropyridine use are related to their potencies as arteriolar dilators; edema is due to an increase in transcapillary pressure gradients, not to net salt and water retention.

Direct Vasodilators Direct vasodilators decrease peripheral resistance and concomitantly activate mechanisms that defend arterial pressure, notably the sympathetic nervous system, the renin-angiotensin-aldosterone system, and sodium retention. Usually, they are not considered first-line agents but are most effective when added to a combination that includes a diuretic and a beta blocker. Hydralazine is a potent direct vasodilator that has antioxidant and nitric oxide–enhancing actions, and minoxidil is a particularly potent agent and is used most frequently in patients with renal insufficiency who are refractory to all other drugs. Hydralazine may induce a lupus-like syndrome, and side effects of minoxidil include hypertrichosis and pericardial effusion.

COMPARISONS OF ANTIHYPERTENSIVES

Based on pooling results from clinical trials, meta-analyses of the efficacy of different classes of antihypertensive agents suggest essentially equivalent blood

pressure–lowering effects of the following six major classes of antihypertensive agents when used as monotherapy: thiazide diuretics, beta blockers, ACEIs, ARBs, calcium antagonists, and α_2 blockers. On average, standard doses of most antihypertensive agents reduce blood pressure by 8–10/4–7 mmHg; however, there may be subgroup differences in responsiveness. Younger patients may be more responsive to beta blockers and ACEIs, whereas patients over age 50 may be more responsive to diuretics and calcium antagonists. There is a limited relationship between plasma renin and blood pressure response. Patients with high-renin hypertension may be more responsive to ACEIs and ARBs than to other classes of agents, whereas patients with low-renin hypertension are more responsive to diuretics and calcium antagonists. Hypertensive African Americans tend to have low renin and may require higher doses of ACEIs and ARBs than whites for optimal blood pressure control, although this difference is abolished when these agents are combined with a diuretic. Beta blockers also appear to be less effective than thiazide diuretics in African Americans than in non-African Americans. Identification of genetic variants that influence blood pressure responsiveness would potentially provide a rational basis for the selection of a specific class of an antihypertensive agent in an individual patient. Early pharmacogenetic studies, utilizing either a candidate gene approach or genomewide scans, have shown associations of gene polymorphisms with blood pressure responsiveness to specific antihypertensive drugs. However, the reported effects have generally been too small to affect clinical decisions, and associated polymorphisms remain to be confirmed in subsequent studies. Currently, in practical terms, the presence of comorbidities often influences the selection of antihypertensive agents.

A recent meta-analysis of more than 30 randomized trials of blood pressure–lowering therapy indicates that for a given reduction in blood pressure, the major drug classes seem to produce similar overall net effects on total cardiovascular events. In both nondiabetic and diabetic hypertensive patients, most trials have failed to show significant differences in cardiovascular outcomes with different drug regimens as long as equivalent decreases in blood pressure were achieved. For example, the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT) demonstrated that the occurrence of coronary heart disease death and nonfatal myocardial infarction, as well as overall mortality, was virtually identical in hypertensive patients treated with either an ACEI (lisinopril), a diuretic (chlorthalidone), or a calcium antagonist (amlodipine).

However, in specific patient groups, ACEIs may have particular advantages, beyond that of blood pressure control, in reducing cardiovascular and renal outcomes. ACEIs and ARBs decrease intraglomerular pressure and proteinuria and may retard the rate of progression of renal insufficiency, not totally accounted for by their hypotensive effects, in both diabetic and nondiabetic renal diseases. Among African Americans with hypertension-related renal disease, ACEIs appear to be more effective than beta blockers or dihydropyridine calcium channel blockers in slowing, although not preventing, the decline of glomerular filtration rate. In experimental models of hypertension and diabetes, renal protection with aliskiren (a renin inhibitor) was comparable to that with ACEIs and ARBs. Independent of its blood pressure–lowering effect, aliskiren has renal protective effects in patients with hypertension, type 2 diabetes, and nephropathy. The renoprotective effect of these renin-angiotensin blockers, compared with other antihypertensive drugs, is less obvious at lower blood pressures. In most patients with hypertension and heart failure due to systolic and/or diastolic dysfunction, the use of diuretics, ACEIs or ARBs, and beta blockers is recommended to improve survival. Independent of blood pressure, in both hypertensive and normotensive individuals, ACEIs attenuate the development of left ventricular hypertrophy, improve symptomatology and risk of death from CHF, and reduce morbidity and mortality rates in post–myocardial infarction patients. Similar benefits in cardiovascular morbidity and mortality rates in patients with CHF have been observed with the use of ARBs. ACEIs provide better coronary protection than do calcium channel blockers, whereas calcium channel blockers provide more stroke protection than do either ACEIs or beta blockers. Results of a recent large, double-blind prospective clinical trial [Rationale and Design of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH Trial)] indicated that combination treatment with an ACEI (benazepril) plus a calcium antagonist (amlodipine) was superior to treatment with the ACEI plus a diuretic (hydrochlorothiazide) in reducing the risk of cardiovascular events and death among high-risk patients with hypertension. However, the combination of an ACEI and a diuretic has recently been shown to produce major reductions in morbidity and mortality in the very elderly.

After a stroke, combination therapy with an ACEI and a diuretic, but not with an ARB, reduces the rate of recurrent stroke. Some of these apparent differences may reflect differences in trial design and/or patient groups.

BLOOD PRESSURE GOALS OF ANTIHYPERTENSIVE THERAPY Based on clinical trial data, the maximum protection against combined cardiovascular endpoints is achieved with pressures <135–140 mmHg

for systolic blood pressure and <80–85 mmHg for diastolic blood pressure; however, treatment has not reduced cardiovascular disease risk to the level in nonhypertensive individuals. More aggressive blood pressure targets for blood pressure control (e.g., office or clinic blood pressure <130/80 mmHg) are generally recommended for patients with diabetes, coronary heart disease, chronic kidney disease, or additional cardiovascular disease risk factors. An even lower goal blood pressure (systolic blood pressure ~120 mmHg) may be desirable for patients with proteinuria (>1 g/d) since the decline of glomerular filtration rate in these patients is particularly blood pressure–dependent. In diabetic patients, effective blood pressure control reduces the risk of cardiovascular events and death as well as the risk for microvascular disease (nephropathy, retinopathy). Risk reduction is greater in diabetic than in nondiabetic individuals. Although the optimal target blood pressure in patients with heart failure has not been established, a reasonable goal is the lowest blood pressure that is not associated with evidence of hypoperfusion.

To achieve recommended blood pressure goals, the majority of individuals with hypertension will require treatment with more than one drug. Three or more drugs frequently are needed in patients with diabetes and renal insufficiency. For most agents, reduction of blood pressure at half-standard doses is only ~20% less than at standard doses. Appropriate combinations of agents at these lower doses may have additive or almost additive effects on blood pressure with a lower incidence of side effects.

Despite theoretical concerns about decreasing cerebral, coronary, and renal blood flow by overly aggressive antihypertensive therapy, clinical trials have found no evidence for a "J-curve" phenomenon; i.e., at blood pressure reductions achieved in clinical practice, there does *not* appear to be a lower threshold for increasing cardiovascular risk. A small nonprogressive increase in the serum creatinine concentration with blood pressure reduction may occur in patients with chronic renal insufficiency. This generally reflects a hemodynamic response, not structural renal injury, indicating that intraglomerular pressure has been reduced. Blood pressure control should not be allowed to deteriorate in order to prevent a modest rise in creatinine. Even among older patients with isolated systolic hypertension, further lowering of diastolic blood pressure does not result in harm. However, relatively little information is available concerning the risk-versus-benefit ratio of antihypertensive therapy in individuals >80 years, and in this population, gradual blood pressure reduction to less aggressive target levels of control may be appropriate.

The term *resistant hypertension* refers to patients with blood pressures persistently >140/90 mmHg despite taking three or more antihypertensive agents, including a diuretic, in a reasonable combination and at full doses. Resistant or difficult-to-control hypertension is more common in patients >60 years than in younger patients. Resistant hypertension may be related to "pseudoresistance" (high office blood pressures and lower home blood pressures), nonadherence to therapy, identifiable causes of hypertension (including obesity and excessive alcohol intake), and the use of any of a number of nonprescription and prescription drugs (Table 19-3). Rarely, in older patients, pseudohypertension may be related to the inability to measure blood pressure accurately in severely sclerotic arteries. This condition is suggested if the radial pulse remains palpable despite occlusion of the brachial artery by the cuff (Osler maneuver). The actual blood pressure can be determined by direct intra-arterial measurement. Evaluation of patients with resistant hypertension might include home blood pressure monitoring to determine if office blood pressures are representative of the usual blood pressure. A more extensive evaluation for a secondary form of hypertension should be undertaken if no other explanation for hypertension resistance becomes apparent.

HYPERTENSIVE EMERGENCIES Probably due to the widespread availability of antihypertensive therapy, in the United States there has been a decline in the numbers of patients presenting with "crisis levels" of blood pressure. Most patients who present with severe hypertension are chronically hypertensive, and in the absence of acute end organ damage, precipitous lowering of blood pressure may be associated with significant morbidity and should be avoided. The key to successful management of severe hypertension is to differentiate hypertensive crises from hypertensive urgencies. The degree of target organ damage, rather than the level of blood pressure alone, determines the rapidity with which blood pressure should be lowered. **Tables 19-9** and **19-10** list a number of hypertension-related emergencies and recommended therapies.

Malignant hypertension is a syndrome associated with an abrupt increase of blood pressure in a patient with underlying hypertension or related to the sudden onset of hypertension in a previously normotensive individual. The absolute level of blood pressure is not as important as its rate of rise. Pathologically, the syndrome is associated with diffuse necrotizing vasculitis, arteriolar thrombi, and fibrin deposition in arteriolar walls. Fibrinoid necrosis has been observed in arterioles of kidney, brain, retina, and other organs. Clinically, the syndrome is recognized by progressive retinopathy (arteriolar spasm, hemorrhages, exudates, and papilledema), deteriorating renal function with proteinuria, microangiopathic hemolytic anemia, and encephalopathy. In these

TABLE 19-9

PREFERRED PARENTERAL DRUGS FOR SELECTED HYPERTENSIVE EMERGENCIES

Hypertensive encephalopathy	Nitroprusside, nicardipine, labetalol
Malignant hypertension (when IV therapy is indicated)	Labetalol, nicardipine, nitroprusside, enalaprilat
Stroke	Nicardipine, labetalol, nitroprusside
Myocardial infarction/unstable angina	Nitroglycerin, nicardipine, labetalol, esmolol
Acute left ventricular failure	Nitroglycerin, enalaprilat, loop diuretics
Aortic dissection	Nitroprusside, esmolol, labetalol
Adrenergic crisis	Phentolamine, nitroprusside
Postoperative hypertension	Nitroglycerin, nitroprusside, labetalol, nicardipine
Preeclampsia/eclampsia of pregnancy	Hydralazine, labetalol, nicardipine

Source: Adapted from DG Vidt, in S Oparil, MA Weber (eds): *Hypertension*, 2nd ed. Philadelphia, Elsevier Saunders, 2005.

TABLE 19-10

USUAL INTRAVENOUS DOSES OF ANTIHYPERTENSIVE AGENTS USED IN HYPERTENSIVE EMERGENCIES[a]

ANTIHYPERTENSIVE AGENT	INTRAVENOUS DOSE
Nitroprusside	Initial 0.3 (μg/kg)/min; usual 2–4 (μg/kg)/min; maximum 10 (μg/kg)/min for 10 min
Nicardipine	Initial 5 mg/h; titrate by 2.5 mg/h at 5–15 min intervals; max 15 mg/h
Labetalol	2 mg/min up to 300 mg *or* 20 mg over 2 min, then 40–80 mg at 10-min intervals up to 300 mg total
Enalaprilat	Usual 0.625–1.25 mg over 5 min every 6–8 h; maximum 5 mg/dose
Esmolol	Initial 80–500 μg/kg over 1 min, then 50–300 (μg/kg)/min
Phentolamine	5–15 mg bolus
Nitroglycerin	Initial 5 μg/min, then titrate by 5 μg/min at 3–5-min intervals; if no response is seen at 20 μg/min, incremental increases of 10–20 μg/min may be used
Hydralazine	10–50 mg at 30-min intervals

[a]Constant blood pressure monitoring is required. Start with the lowest dose. Subsequent doses and intervals of administration should be adjusted according to the blood pressure response and duration of action of the specific agent.

patients, historic inquiry should include questions about the use of monamine oxidase inhibitors and recreational drugs (e.g., cocaine, amphetamines).

Although blood pressure should be lowered rapidly in patients with hypertensive encephalopathy, there are inherent risks of overly aggressive therapy. In hypertensive individuals, the upper and lower limits of autoregulation of cerebral blood flow are shifted to higher levels of arterial pressure, and rapid lowering of blood pressure to below the lower limit of autoregulation may precipitate cerebral ischemia or infarction as a consequence of decreased cerebral blood flow. Renal and coronary blood flows also may decrease with overly aggressive acute therapy. The initial goal of therapy is to reduce mean arterial blood pressure by no more than 25% within minutes to 2 h or to a blood pressure in the range of 160/100–110 mmHg. This may be accomplished with IV nitroprusside, a short-acting vasodilator with a rapid onset of action that allows for minute-to-minute control of blood pressure. Parenteral labetalol and nicardipine are also effective agents for the treatment of hypertensive encephalopathy.

In patients with malignant hypertension without encephalopathy or another catastrophic event, it is preferable to reduce blood pressure over hours or longer rather than minutes. This goal may effectively be achieved initially with frequent dosing of short-acting oral agents such as captopril, clonidine, and labetalol.

Acute, transient blood pressure elevations that last days to weeks frequently occur after thrombotic and hemorrhagic strokes. Autoregulation of cerebral blood flow is impaired in ischemic cerebral tissue, and higher arterial pressures may be required to maintain cerebral blood flow. Although specific blood pressure targets have not been defined for patients with acute cerebrovascular events, aggressive reductions of blood pressure are to be avoided. With the increasing availability of improved methods for measuring cerebral blood flow (using CT technology), studies are in progress to evaluate the effects of different classes of antihypertensive agents on both blood pressure and cerebral blood flow after an acute stroke. Currently, in the absence of other indications for acute therapy, for patients with cerebral infarction who are not candidates for thrombolytic therapy, one recommended guideline is to institute antihypertensive therapy only for patients with a systolic blood pressure >220 mmHg or a diastolic blood pressure >130 mmHg. If thrombolytic therapy is to be used, the recommended goal blood pressure is <185 mmHg systolic pressure and <110 mmHg diastolic pressure. In patients with hemorrhagic stroke, suggested guidelines for initiating antihypertensive therapy are systolic >180 mmHg or diastolic pressure >130 mmHg. The management

of hypertension after subarachnoid hemorrhage is controversial. Cautious reduction of blood pressure is indicated if mean arterial pressure is >130 mmHg.

In addition to pheochromocytoma, an adrenergic crisis due to catecholamine excess may be related to cocaine or amphetamine overdose, clonidine withdrawal, acute spinal cord injuries, and an interaction of tyramine-containing compounds with monamine oxidase inhibitors. These patients may be treated with phentolamine or nitroprusside.

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SECTION VI

URINARY TRACT INFECTIONS AND OBSTRUCTION

CHAPTER 20

URINARY TRACT INFECTIONS, PYELONEPHRITIS, AND PROSTATITIS

Kalpana Gupta ■ Barbara W. Trautner

Urinary tract infection (UTI) is a common and painful human illness that, fortunately, is rapidly responsive to modern antibiotic therapy. In the preantibiotic era, UTI caused significant morbidity. Hippocrates, writing about a disease that appears to have been acute cystitis, said that the illness could last for a year before either resolving or worsening to involve the kidneys. When chemotherapeutic agents used to treat UTI were introduced in the early twentieth century, they were relatively ineffective, and persistence of infection after 3 weeks of therapy was common. Nitrofurantoin, which became available in the 1950s, was the first tolerable and effective agent for the treatment of UTI.

Since the most common manifestation of UTI is acute cystitis, and since acute cystitis is far more prevalent among women than among men, most clinical research on UTI has involved women. Many studies have enrolled women from college campuses or large health maintenance organizations in the United States. Therefore, when reviewing the literature and recommendations concerning UTI, clinicians must consider whether the findings are applicable to their patient populations.

DEFINITIONS

UTI may be asymptomatic (subclinical infection) or symptomatic (disease). Thus, the term *UTI* encompasses a variety of clinical entities, including asymptomatic bacteriuria (ABU), cystitis, prostatitis, and pyelonephritis. The distinction between symptomatic UTI and ABU has major clinical implications. Both UTI and ABU connote the presence of bacteria in the urinary tract, usually accompanied by white blood cells and inflammatory cytokines in the urine. However, ABU occurs in the absence of symptoms attributable to the bacteria in the urinary tract and does not usually require treatment, while UTI has more typically been assumed to imply symptomatic disease that warrants antimicrobial therapy. Much of the literature concerning UTI, particularly catheter-associated infection, does not differentiate between UTI and ABU. In this chapter, the term *UTI* denotes symptomatic disease; *cystitis*, symptomatic infection of the bladder; and *pyelonephritis*, symptomatic infection of the kidneys. *Uncomplicated UTI* refers to acute cystitis or pyelonephritis in nonpregnant outpatient women without anatomic abnormalities or instrumentation of the urinary tract; *complicated UTI* is a catch-all term that encompasses all other types of UTI. *Recurrent UTI* is not necessarily complicated; individual episodes can be uncomplicated and treated as such. *Catheter-associated bacteriuria* can be either symptomatic (CAUTI) or asymptomatic.

EPIDEMIOLOGY AND RISK FACTORS

Except among infants and the elderly, UTI occurs far more commonly in females than in males. During the neonatal period, the incidence of UTI is slightly higher among males than among females because male infants more commonly have congenital urinary tract anomalies. After 50 years of age, obstruction from prostatic hypertrophy becomes common in men, and the incidence of UTI is almost as high among men as among women. Between 1 year and ~50 years of age, UTI and recurrent UTI are predominantly diseases of females. The prevalence of ABU is ~5% among women between ages 20 and 40 and may be as high as 40–50% among elderly women and men.

As many as 50–80% of women in the general population acquire at least one UTI during their lifetime—uncomplicated cystitis in most cases. Recent use of a

diaphragm with spermicide, frequent sexual intercourse, and a history of UTI are independent risk factors for acute cystitis. Cystitis is temporally related to recent sexual intercourse, with a sixtyfold increase in the relative odds of acute cystitis in the 48 h after intercourse. In healthy postmenopausal women, sexual activity, diabetes mellitus, and incontinence are risk factors for UTI.

Many factors predisposing women to cystitis also increase the risk of pyelonephritis. Factors independently associated with pyelonephritis in young healthy women include frequent sexual intercourse, a new sexual partner, a UTI in the previous 12 months, a maternal history of UTI, diabetes, and incontinence. The common risk factors for cystitis and pyelonephritis are not surprising given that pyelonephritis typically arises through the ascent of bacteria from the bladder to the upper urinary tract. However, pyelonephritis can occur without clear antecedent cystitis.

About 20–30% of women who have had one episode of UTI will have recurrent episodes. Early recurrence (within 2 weeks) is usually regarded as relapse rather than reinfection and may indicate the need to evaluate the patient for a sequestered focus. Intracellular pods of infecting organisms within the bladder epithelium have been demonstrated in animal models of UTI, but the importance of this phenomenon in humans is not yet clear. The rate of recurrence ranges from 0.3 to 7.6 infections per patient per year, with an average of 2.6 infections per year. It is not uncommon for multiple recurrences to follow an initial infection, resulting in clustering of episodes. Clustering may be related temporally to the presence of a new risk factor or to the sloughing of the protective outer bladder epithelial layer in response to bacterial attachment during acute cystitis. The likelihood of a recurrence decreases with increasing time since the last infection. A case-control study of predominantly white premenopausal women with recurrent UTI identified frequent sexual intercourse, use of spermicide, a new sexual partner, a first UTI before 15 years of age, and a maternal history of UTI as independent risk factors for recurrent UTI. The only consistently documented behavioral risk factors for recurrent UTI include frequent sexual intercourse and spermicide use. In postmenopausal women, anatomic factors affecting bladder emptying, such as cystoceles, urinary incontinence, and residual urine, are most strongly associated with recurrent UTI.

In pregnant women, ABU has clinical consequences, and both screening for and treatment of this condition are indicated. Specifically, ABU during pregnancy is associated with preterm birth and perinatal mortality for the fetus and with pyelonephritis for the mother. A Cochrane meta-analysis found that treatment of ABU in pregnant women decreased the risk of pyelonephritis by 75%.

The majority of men with UTI have a functional or anatomic abnormality of the urinary tract, most commonly urinary obstruction secondary to prostatic hypertrophy. That said, not all men with UTI have detectable urinary abnormalities; this point is particularly relevant for men ≤45 years of age. Lack of circumcision is also associated with an increased risk of UTI, because *Escherichia coli* is more likely to colonize the glans and prepuce, and subsequently migrate into the urinary tract.

Women—but not men—with diabetes have a two- to threefold higher rate of ABU and UTI than women without diabetes. Increased duration of diabetes and the use of insulin rather than oral medication are also associated with a higher risk of UTI among women with diabetes. Poor bladder function, obstruction in urinary flow, and incomplete voiding are additional factors commonly found in patients with diabetes that increase the risk of UTI. Impaired cytokine secretion may contribute to ABU in diabetic women.

ETIOLOGY

The uropathogens causing UTI vary by clinical syndrome but are usually enteric gram-negative rods that have migrated to the urinary tract. The susceptibility patterns of these organisms vary by clinical syndrome and by geography. In acute uncomplicated cystitis in the United States, the etiologic agents are highly predictable: *E. coli* accounts for 75–90% of isolates; *Staphylococcus saprophyticus* for 5–15% (with particularly frequent isolation from younger women); and *Klebsiella* species, *Proteus* species, *Enterococcus* species, *Citrobacter* species, and other organisms for 5–10%. Similar etiologic agents are found in Europe and Brazil. The spectrum of agents causing uncomplicated pyelonephritis is similar, with *E. coli* predominating. In complicated UTI (e.g., CAUTI), *E. coli* remains the predominant organism, but other aerobic gram-negative rods, such as *Klebsiella* species, *Proteus* species, *Citrobacter* species, *Acinetobacter* species, *Morganella* species, and *Pseudomonas aeruginosa*, also are frequently isolated. Gram-positive bacteria (e.g., enterococci and *Staphylococcus aureus*) and yeasts are also important pathogens in complicated UTI. Data on etiology and resistance are generally obtained from laboratory surveys and should be understood in the context that organism identification is performed only in cases in which urine is sent for culture—i.e., typically when complicated UTI or pyelonephritis is suspected. The available data demonstrate a worldwide increase in the resistance of *E. coli* to antibiotics commonly used to treat UTI. North American and European surveys of *E. coli* isolates from women with acute cystitis have documented rates of resistance to trimethoprim-sulfamethoxazole (TMP-SMX) greater than 20% and rates of resistance to ciprofloxacin between 5% and 10% in some regions.

Since resistance rates vary by local geographic region, with individual patient characteristics, and over time, it is important to use current and local data when choosing a treatment regimen.

PATHOGENESIS

The urinary tract can be viewed as an anatomic unit united by a continuous column of urine extending from the urethra to the kidneys. In the majority of UTIs, bacteria establish infection by ascending from the urethra to the bladder. Continuing ascent up the ureter to the kidney is the pathway for most renal parenchymal infections. However, introduction of bacteria into the bladder does not inevitably lead to sustained and symptomatic infection. The interplay of host, pathogen, and environmental factors determines whether tissue invasion and symptomatic infection will ensue **(Fig. 20-1)**. For example, bacteria often enter the bladder after sexual intercourse, but normal voiding and innate host defense mechanisms in the bladder eliminate these organisms. Any foreign body in the urinary tract, such as a urinary catheter or stone, provides an inert surface for bacterial colonization. Abnormal micturition and/or significant residual urine volume promotes true infection. In the simplest of terms, anything that increases the likelihood of bacteria entering the bladder and staying there increases the risk of UTI.

Bacteria can also gain access to the urinary tract through the bloodstream. However, hematogenous spread accounts for <2% of documented UTIs and usually results from bacteremia caused by relatively virulent organisms, such as *Salmonella* and *S. aureus*. Indeed, the isolation of either of these pathogens from a patient without a catheter or other instrumentation warrants a search for a bloodstream source. Hematogenous infections may produce focal abscesses or areas of pyelonephritis within a kidney and result in positive urine cultures. The pathogenesis of candiduria is distinct in that the hematogenous route is common. The presence of *Candida* in the urine of a noninstrumented immunocompetent patient implies either genital contamination or potentially widespread visceral dissemination.

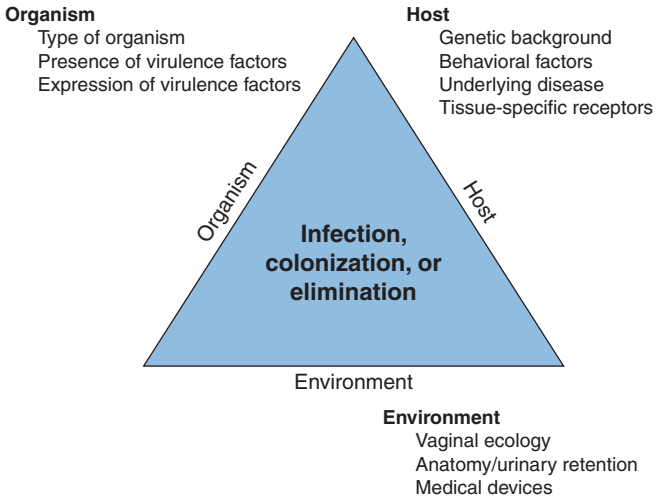


FIGURE 20-1
Pathogenesis of urinary tract infection. The relationship between specific host, pathogen, and environmental factors determines the clinical outcome.

Environmental factors

Vaginal ecology

In women, vaginal ecology is an important environmental factor affecting the risk of UTI. Colonization of the vaginal introitus and perirurethral area with organisms from the intestinal flora (usually *E. coli*) is the critical initial step in the pathogenesis of UTI. Sexual intercourse is associated with an increased risk of vaginal colonization with *E. coli* and thereby increases the risk of UTI. Nonoxynol-9 in spermicide is toxic to the normal vaginal microflora and thus is likewise associated with an increased risk of *E. coli* vaginal colonization and bacteriuria. In postmenopausal women, the previously predominant vaginal lactobacilli are replaced with gram-negative colonization. The use of topical estrogens to prevent UTI in postmenopausal women is controversial; given the side effects of systemic hormone replacement, oral estrogens should not be used to prevent UTI.

Anatomic and functional abnormalities

Any condition that permits urinary stasis or obstruction predisposes the individual to UTI. Foreign bodies such as stones or urinary catheters provide an inert surface for bacterial colonization and formation of a persistent biofilm. Thus, vesicoureteral reflux, ureteral obstruction secondary to prostatic hypertrophy, neurogenic bladder, and urinary diversion surgery create an environment favorable to UTI. In persons with such conditions, *E. coli* strains lacking typical urinary virulence factors are often the cause of infection. Inhibition of ureteral peristalsis and decreased ureteral tone leading to vesicoureteral reflux are important in the pathogenesis of pyelonephritis in pregnant women. Anatomic factors—specifically, the distance of the urethra from the anus—are considered to be the primary reason why UTI is predominantly an illness of young women rather than of young men.

Host factors

The genetic background of the host influences the individual's susceptibility to recurrent UTI, at least among women. A familial disposition to UTI and to pyelonephritis is well documented. Women with recurrent UTI are more likely to have had their first UTI before age 15 years and to have a maternal history

of UTI. A component of the underlying pathogenesis of this familial predisposition to recurrent UTI may be persistent vaginal colonization with *E. coli*, even during asymptomatic periods. Vaginal and periurethral mucosal cells from women with recurrent UTI bind threefold more uropathogenic bacteria than do mucosal cells from women without recurrent infection. Epithelial cells from susceptible women may possess specific types or greater numbers of receptors to which *E. coli* can bind, thereby facilitating colonization and invasion. Mutations in host response genes (e.g., those coding for toll-like receptors and the interleukin 8 receptor) have also been linked to recurrent UTI and pyelonephritis. Polymorphisms in the interleukin 8–specific receptor gene *CXCR1* are associated with increased susceptibility to pyelonephritis. Lower-level expression of *CXCR1* on the surface of neutrophils impairs neutrophil-dependent host defense against bacterial invasion of the renal parenchyma.

Microbial factors

An anatomically normal urinary tract presents a stronger barrier to infection than a compromised urinary tract. Thus, strains of *E. coli* that cause invasive symptomatic infection of the urinary tract in otherwise normal hosts often possess and express genetic virulence factors, including surface adhesins that mediate binding to specific receptors on the surface of uroepithelial cells. The best-studied adhesins are the P fimbriae, hairlike protein structures that interact with a specific receptor on renal epithelial cells. (The letter *P* denotes the ability of these fimbriae to bind to blood group antigen P, which contains a D-galactose-D-galactose residue.) P fimbriae are important in the pathogenesis of pyelonephritis and subsequent bloodstream invasion from the kidney.

Another adhesin is the type 1 pilus (fimbria), which all *E. coli* strains possess but not all *E. coli* strains express. Type 1 pili are thought to play a key role in initiating *E. coli* bladder infection; they mediate binding to uroplakins on the luminal surface of bladder uroepithelial cells. The binding of type 1 fimbriae of *E. coli* to receptors on uroepithelial cells initiates a complex series of signaling events that leads to apoptosis and exfoliation of uroepithelial cells, with the attached *E. coli* organisms carried away in the urine.

APPROACH TO THE PATIENT

Clinical Manifestations

The most important issue to be addressed when a UTI is suspected is the characterization of the clinical syndrome as ABU, uncomplicated cystitis, pyelonephritis, prostatitis, or complicated UTI. This information will shape the diagnostic and therapeutic approach.

Asymptomatic Bacteriuria A diagnosis of ABU can be considered only when the patient does not have local or systemic symptoms referable to the urinary tract. The clinical presentation is usually that of a patient who undergoes a screening urine culture for a reason unrelated to the genitourinary tract and is incidentally found to have bacteriuria. The presence of systemic signs or symptoms such as fever, altered mental status, and leukocytosis in the setting of a positive urine culture does not merit a diagnosis of symptomatic UTI unless other potential etiologies have been considered.

Cystitis The typical symptoms of cystitis are dysuria, urinary frequency, and urgency. Nocturia, hesitancy, suprapubic discomfort, and gross hematuria are often noted as well. Unilateral back or flank pain is generally an indication that the upper urinary tract is involved. Fever is also an indication of invasive infection of either the kidney or the prostate.

Pyelonephritis Mild pyelonephritis can present as low-grade fever with or without lower-back or costovertebral-angle pain, whereas severe pyelonephritis can manifest as high fever, rigors, nausea, vomiting, and flank and/or loin pain. Symptoms are generally acute in onset, and symptoms of cystitis may not be present. Fever is the main feature distinguishing cystitis and pyelonephritis. The fever of pyelonephritis typically exhibits a high, spiking "picket-fence" pattern and resolves over 72 h of therapy. Bacteremia develops in 20–30% of cases of pyelonephritis. Patients with diabetes may present with obstructive uropathy associated with acute papillary necrosis when the sloughed papillae obstruct the ureter. Papillary necrosis may also be evident in some cases of pyelonephritis complicated by obstruction, sickle cell disease, analgesic nephropathy, or combinations of these conditions. In the rare cases of bilateral papillary necrosis, a rapid rise in the serum creatinine level may be the first indication of the condition. *Emphysematous* pyelonephritis is a particularly severe form of the disease that is associated with the production of gas in renal and perinephric tissues and occurs almost exclusively in diabetic patients (Fig. 20-2). *Xanthogranulomatous* pyelonephritis occurs when chronic urinary obstruction (often by staghorn calculi), together with chronic infection, leads to suppurative destruction of renal tissue (Fig. 20-3). On pathologic examination, the residual renal tissue frequently has a yellow coloration with infiltration by lipid-laden macrophages. Pyelonephritis can also be complicated by intraparenchymal abscess formation; this situation should be suspected when a patient has continued fever and/or bacteremia despite antibacterial therapy.

Prostatitis Prostatitis includes both infectious and noninfectious abnormalities of the prostate gland. Infections can be acute or chronic, are almost always

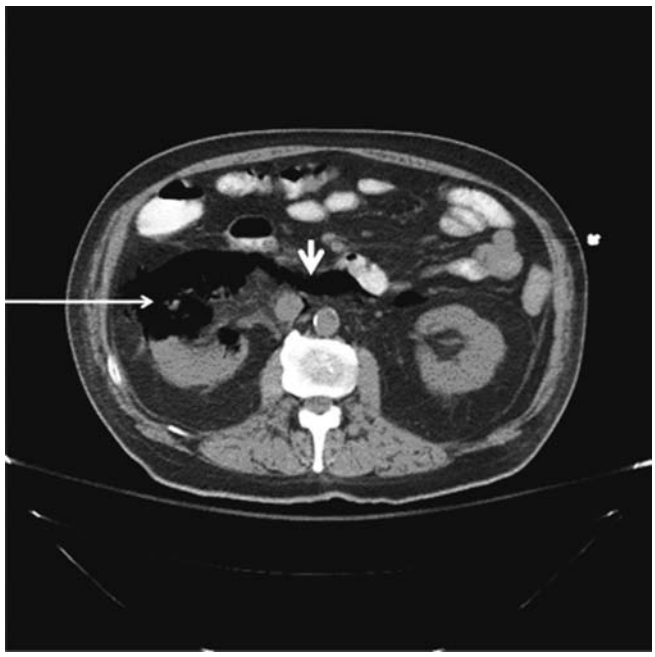


FIGURE 20-2

Emphysematous pyelonephritis. Infection of the right kidney of a diabetic man by *Escherichia coli*, a gas-forming, facultative anaerobic uropathogen, has led to destruction of the renal parenchyma (*arrow*) and tracking of gas through the retroperitoneal space (*arrowhead*).

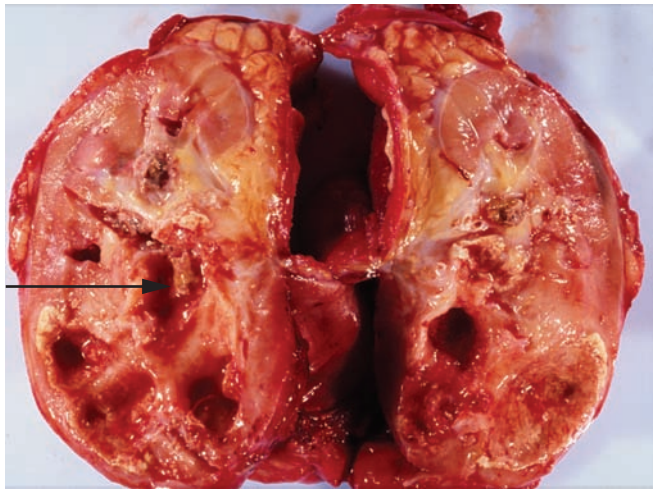
bacterial in nature, and are far less common than the noninfectious entity of chronic pelvic pain syndrome (formerly known as chronic prostatitis). Acute bacterial prostatitis presents as dysuria, frequency, and pain in the prostatic, pelvic, or perineal area. Fever and chills are usually present, and symptoms of bladder outlet obstruction are common. Chronic bacterial prostatitis presents more insidiously as recurrent episodes of cystitis, sometimes with associated pelvic and perineal pain. Men who present with recurrent cystitis should be evaluated for a prostatic focus.

Complicated UTI Complicated UTI presents as a symptomatic episode of cystitis or pyelonephritis in a man or woman with an anatomic predisposition to infection, with a foreign body in the urinary tract, or with factors predisposing to a delayed response to therapy.

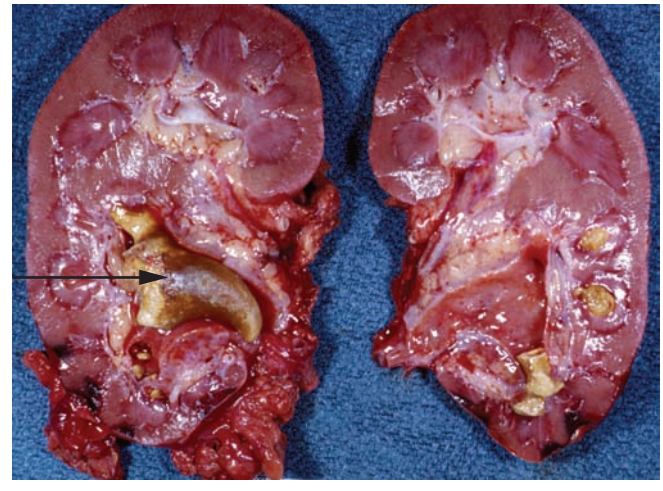
DIAGNOSTIC TOOLS

History

The diagnosis of any of the UTI syndromes or ABU begins with a detailed history **(Fig. 20-4)**. The history given by the patient has a high predictive value in uncomplicated cystitis. A meta-analysis evaluating the probability of acute UTI on the basis of history and physical findings concluded that, in women presenting with at least one symptom of UTI (dysuria, frequency, hematuria, or back pain) and without complicating factors, the probability of acute cystitis or pyelonephritis is 50%. The even higher rates of accuracy of self-diagnosis among women with recurrent UTI probably account for the success of patient-initiated treatment of recurrent cystitis. If vaginal discharge and complicating factors are absent and risk factors for UTI are present, then the probability of UTI is close to 90%, and no laboratory evaluation is needed. Similarly, a combination of



A



B

FIGURE 20-3

Xanthogranulomatous pyelonephritis. *A.* This photograph shows extensive destruction of renal parenchyma due to long-standing suppurative inflammation. The precipitating factor was obstruction by a staghorn calculus, which has been removed, leaving a depression (*arrow*). The mass effect of xanthogranulomatous pyelonephritis can mimic renal malignancy. ***B.*** A large staghorn calculus (*arrow*) is seen obstructing the renal pelvis and calyceal system. The lower pole of the kidney shows areas of hemorrhage and necrosis with collapse of cortical areas. (*Both images courtesy of Dharam M. Ramnani, MD, Virginia Urology Pathology Laboratory, Richmond, VA.*)

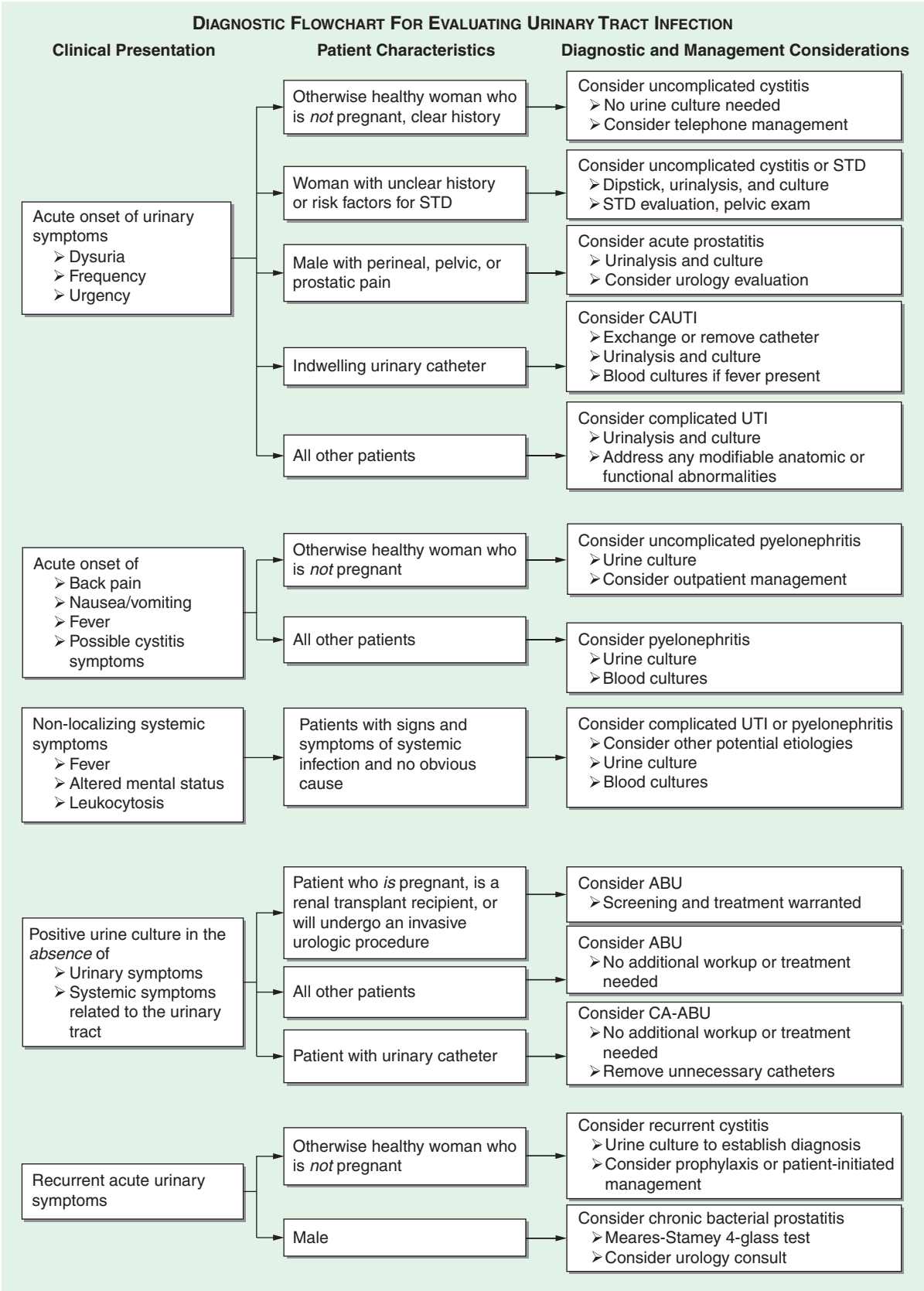


FIGURE 20-4

Diagnostic approach to urinary tract infection. ABU, asymptomatic bacteriuria; CA-ABU, catheter-associated ABU; CAUTI, catheter-associated UTI; STD, sexually transmitted disease.

dysuria and urinary frequency in the absence of vaginal discharge increases the probability of UTI to 96%. Further laboratory evaluation with dipstick testing or urine culture is not necessary in such patients before the initiation of definitive therapy.

When the patient's history is applied as a diagnostic tool, it is important to recall that the studies included in the meta-analysis cited above did not enroll children, adolescents, pregnant women, men, or patients with complicated UTI. One significant concern is that sexually transmitted disease—that caused by *Chlamydia trachomatis* in particular—may be inappropriately treated as UTI. This concern is particularly relevant for female patients under the age of 25. The differential diagnosis to be considered when women present with dysuria includes cervicitis (*C. trachomatis*, *Neisseria gonorrhoeae*), vaginitis (*Candida albicans*, *Trichomonas vaginalis*), herpetic urethritis, interstitial cystitis, and noninfectious vaginal or vulvar irritation. Women with more than one sexual partner and inconsistent use of condoms are at high risk for both UTI and sexually transmitted disease, and symptoms alone do not always distinguish between these conditions.

The urine dipstick test, urinalysis, and urine culture

Useful diagnostic tools include the urine dipstick test and urinalysis, both of which provide point-of-care information, and the urine culture, which can retrospectively confirm a prior diagnosis. Understanding the parameters of the dipstick test is important in interpreting its results. Only members of the family Enterobacteriaceae convert nitrate to nitrite, and enough nitrite must accumulate in the urine to reach the threshold of detection. If a woman with acute cystitis is forcing fluids and voiding frequently, the dipstick test for nitrite is less likely to be positive, even when *E. coli* is present. The leukocyte esterase test detects this enzyme in the host's polymorphonuclear leukocytes in the urine, whether the cells are intact or lysed. Many reviews have attempted to describe the diagnostic accuracy of dipstick testing. The bottom line for clinicians is that a urine dipstick test can confirm the diagnosis of uncomplicated cystitis in a patient with a reasonably high pretest probability of this disease. Either nitrite or leukocyte esterase positivity can be interpreted as a positive result. Blood in the urine may also suggest a diagnosis of UTI. A dipstick test negative for both nitrite and leukocyte esterase in the same type of patient should prompt consideration of other explanations for the patient's symptoms and collection of urine for culture. A negative dipstick test is not sufficiently sensitive to rule out bacteriuria in pregnant women, in whom it is important to detect all episodes of bacteriuria. Performance characteristics of the dipstick test differ in men (highly specific) and in noncatheterized nursing home residents (highly sensitive).

Urine microscopy reveals pyuria in nearly all cases of cystitis and hematuria in ~30% of cases. In current practice, most hospital laboratories use an automated system rather than manual examination for urine microscopy. A machine aspirates a sample of the urine and then classifies the particles in the urine by size, shape, contrast, light scatter, volume, and other properties. These automated systems can be overwhelmed by high numbers of dysmorphic red blood cells, white blood cells, or crystals; in general, counts of bacteria are less accurate than are counts of red and white blood cells. Our clinical recommendation is that the patient's symptoms and presentation should outweigh an incongruent result on automated urinalysis.

The detection of bacteria in a urine culture is the diagnostic "gold standard" for UTI; unfortunately, however, culture results do not become available until 24 h after the patient's presentation. Identifying specific organism(s) can require an additional 24 h. Studies of women with symptoms of cystitis have found that a colony count threshold of $>10^2$ bacteria/mL is more sensitive (95%) and specific (85%) than a threshold of 10^5/mL for the diagnosis of acute cystitis in women. In men, the minimal level indicating infection appears to be 10^3/mL. Urine specimens frequently become contaminated with the normal microbial flora of the distal urethra, vagina, or skin. These contaminants can grow to high numbers if the collected urine is allowed to stand at room temperature. In most instances, a culture that yields mixed bacterial species is contaminated except in settings of long-term catheterization, chronic urinary retention, or the presence of a fistula between the urinary tract and the gastrointestinal or genital tract.

DIAGNOSIS

The approach to diagnosis is influenced by which of the clinical UTI syndromes is suspected (Fig. 20-4).

Uncomplicated cystitis in women

Uncomplicated cystitis in women can be treated on the basis of history alone. However, if the symptoms are not specific or if a reliable history cannot be obtained, then a urine dipstick test should be performed. A positive nitrite or leukocyte esterase result in a woman with one symptom of UTI increases the probability of UTI from 50% to ~80%, and empirical treatment can be considered without further testing. In this setting, a negative dipstick result does not rule out UTI, and a urine culture, close clinical follow-up, and possibly a pelvic examination are recommended. These recommendations are made with the caveat that factors associated with complicated UTI, such as pregnancy, are not present.

Cystitis in men

The signs and symptoms of cystitis in men are similar to those in women, but this disease differs in several important ways in the male population. Collection of urine for culture is strongly recommended when a man has symptoms of UTI, as the documentation of bacteriuria can differentiate the less common syndromes of acute and chronic bacterial prostatitis from the very common entity of chronic pelvic pain syndrome, which is not associated with bacteriuria and thus is not usually responsive to antibacterial therapy. If the diagnosis is unclear, localization cultures using the two- or four-glass Meares-Stamey test (urine collection after prostate massage) should be undertaken to differentiate between bacterial and nonbacterial prostatic syndromes, and the patient should be referred to a urologist. Men with febrile UTI often have an elevated serum level of prostate-specific antigen as well as an enlarged prostate and enlarged seminal vesicles on ultrasound—findings indicative of prostate involvement. In 85 men with febrile UTI, symptoms of urinary retention, early recurrence of UTI, hematuria at follow-up, and voiding difficulties were predictive of surgically correctable disorders. Men with none of these symptoms had normal upper and lower urinary tracts on urologic workup.

Asymptomatic bacteriuria

The diagnosis of ABU involves both microbiologic and clinical criteria. The microbiologic criterion is usually $\geq 10^5$ bacterial cfu/mL except in catheter-associated disease, in which case $\geq 10^2$ cfu/mL is the cutoff. The clinical criterion is that the person has no signs or symptoms referable to UTI.

TREATMENT Urinary Tract Infections

Antimicrobial therapy is warranted for any symptomatic UTI. The choice of antimicrobial agent and the dose and duration of therapy depend on the site of infection and the presence or absence of complicating conditions. Each category of UTI warrants a different approach based on the particular clinical syndrome.

UNCOMPLICATED CYSTITIS IN WOMEN

Since the species and antimicrobial susceptibilities of the bacteria that cause acute uncomplicated cystitis are highly predictable, many episodes of uncomplicated cystitis can be managed over the telephone (Fig. 20-4). Most patients with other UTI syndromes require further diagnostic evaluation. Although the risk of serious complications with telephone management appears to be low, studies of telephone management algorithms generally have involved otherwise healthy white women who are at low risk for complications of UTI.

In 1999, TMP-SMX was recommended as the first-line agent for treatment of uncomplicated UTI in the published guidelines of the Infectious Diseases Society of America. Antibiotic resistance among uropathogens causing uncomplicated cystitis has since increased, appreciation of the importance of collateral damage (as defined below) has increased, and newer agents have been studied. Unfortunately, there is no longer a single best agent for acute uncomplicated cystitis.

Collateral damage refers to the adverse ecologic effects of antimicrobial therapy, including killing of the normal flora and selection of drug-resistant organisms. Outbreaks of *Clostridium difficile* infection offer an example of collateral damage in the hospital environment. The implication of collateral damage in this context is that a drug that is highly efficacious for the treatment of UTI is not necessarily the optimal first-line agent if it also has pronounced secondary effects on the normal flora or is likely to change resistance patterns. Drugs used for UTI that have a minimal effect on fecal flora include pivmecillinam, fosfomycin, and nitrofurantoin. In contrast, trimethoprim, TMP-SMX, quinolones, and ampicillin affect the fecal flora more significantly; these drugs are notably the agents for which rising resistance levels have been documented.

Several effective therapeutic regimens are available for acute uncomplicated cystitis in women (Table 20-1). Well-studied first-line agents include TMP-SMX and nitrofurantoin. Second-line agents include fluoroquinolone and β-lactam compounds. Single-dose fosfomycin treatment for acute cystitis is widely used in Europe but has produced mixed results in randomized trials. Pivmecillinam is not currently available in the United States or Canada but is a popular agent in some European countries. The pros and cons of other therapies are discussed briefly below.

Traditionally, TMP-SMX has been recommended as first-line treatment for acute cystitis, and it remains appropriate to consider the use of this drug in regions with resistance rates not exceeding 20%. TMP-SMX resistance has clinical significance: in TMP-SMX–treated patients with resistant isolates, the time to symptom resolution is longer, and rates of both clinical and microbiologic failure are higher. Individual host factors associated with an elevated risk of UTI caused by a strain of *E. coli* resistant to TMP-SMX include recent use of TMP-SMX or another antimicrobial agent and recent travel to an area with high rates of TMP-SMX resistance. The optimal setting for empirical use of TMP-SMX is uncomplicated UTI in a female patient who has an established relationship

TABLE 20-1

TREATMENT STRATEGIES FOR ACUTE UNCOMPLICATED CYSTITIS

DRUG AND DOSE	ESTIMATED CLINICAL EFFICACY (%)	ESTIMATED BACTERIAL EFFICACY (%)	COMMON SIDE EFFECTS
Nitrofurantoin, 100 mg bid × 5–7 d	84–95	86–92	Nausea, headache
TMP-SMX, 1 DS tablet bid × 3 d	90–100	91–100	Rash, urticaria, nausea, vomiting, hematologic abnormalities
Fosfomycin, 3-g single-dose sachet	70–91	78–83	Diarrhea, nausea, headache
Pivmecillinam, 400 mg bid × 3–7 d	55–82	74–84	Nausea, vomiting, diarrhea
Fluoroquinolones, dose varies by agent; 3-d regimen	85–95	81–98	Nausea, vomiting, diarrhea, headache, drowsiness, insomnia
β-Lactams, dose varies by agent; 5- to 7-d regimen	79–98	74–98	Diarrhea, nausea, vomiting, rash, urticaria

Note: Efficacy rates are averages or ranges calculated from the data and studies included in the 2010 Infectious Diseases Society of America/European Society of Clinical Microbiology and Infectious Diseases Guideline for Treatment of Uncomplicated UTI. DS, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole.

with the practitioner and who can thus seek further care if her symptoms do not respond promptly.

Resistance to nitrofurantoin remains low despite >60 years of use. Since this drug affects bacterial metabolism in multiple pathways, several mutational steps are required for the development of resistance. Nitrofurantoin remains highly active against *E. coli* and most non–*E. coli* isolates. *Proteus*, *Pseudomonas*, *Serratia*, *Enterobacter*, and yeasts are all intrinsically resistant to this drug. Although nitrofurantoin has traditionally been prescribed as a 7-day regimen, similar microbiologic and clinical efficacies are noted with a 5-day course of nitrofurantoin or a 3-day course of TMP-SMX for treatment of women with acute cystitis; 3-day courses of nitrofurantoin are not recommended for acute cystitis. Nitrofurantoin does not reach significant levels in tissue and cannot be used to treat pyelonephritis.

Most fluoroquinolones are highly effective for short-course therapy for cystitis; the exception is moxifloxacin, which does not achieve adequate urinary levels. The fluoroquinolones commonly used for UTI include ofloxacin, ciprofloxacin, and levofloxacin. The main concern about fluoroquinolone use for acute cystitis is the propagation of fluoroquinolone resistance, not only among uropathogens but also among other organisms causing more serious and difficult-to-treat infections at other sites. Fluoroquinolone use is also a factor driving the emergence of *C. difficile* outbreaks in hospital settings. Most experts now call for restricting fluoroquinolones to specific instances of uncomplicated cystitis in which other antimicrobial agents are not suitable. Quinolone use in the elderly has been associated with an increased risk of Achilles tendon rupture.

Except for pivmecillinam, β-lactam agents generally have not performed as well as TMP-SMX or fluoroquinolones in acute cystitis. Rates of pathogen eradication are lower and relapse rates are higher with β-lactam drugs. The generally accepted explanation is that β-lactams fail to eradicate uropathogens from the vaginal reservoir. A proposed role for intracellular biofilm communities is intriguing. Many strains of *E. coli* that are resistant to TMP-SMX are also resistant to amoxicillin and cephalexin; thus, these drugs should be used only for patients infected with susceptible strains.

Urinary analgesics are appropriate in certain situations to speed resolution of bladder discomfort. The urinary tract analgesic phenazopyridine is widely used but can cause significant nausea. Combination analgesics containing urinary antiseptics (methenamine, methylene blue), a urine-acidifying agent (sodium phosphate), and an antispasmodic agent (hyoscyamine) are also available.

PYELONEPHRITIS Since patients with pyelonephritis have tissue-invasive disease, the treatment regimen chosen should have a very high likelihood of eradicating the causative organism and should reach therapeutic blood levels quickly. High rates of TMP-SMX–resistant *E. coli* in patients with pyelonephritis have made fluoroquinolones the first-line therapy for acute uncomplicated pyelonephritis. Whether the fluoroquinolones are given orally or parenterally depends on the patient's tolerance for oral intake. A randomized clinical trial demonstrated that a 7-day course of therapy with oral ciprofloxacin (500 mg twice daily, with or without an initial IV 400-mg dose) was highly effective for the initial management of pyelonephritis in the outpatient setting. Oral TMP-SMX (one double-strength tablet twice daily for 14 days) is also effective for treatment of acute uncomplicated pyelonephritis if the

uropathogen is known to be susceptible. If the pathogen's susceptibility is not known and TMP-SMX is used, an initial IV 1-g dose of ceftriaxone is recommended. Oral β-lactam agents are less effective than the fluoroquinolones and should be used with caution and close follow-up. Options for parenteral therapy for uncomplicated pyelonephritis include fluoroquinolones, an aminoglycoside with or without ampicillin, an extended-spectrum cephalosporin with or without an aminoglycoside, or a carbapenem. Combinations of a β-lactam and a β-lactamase inhibitor (e.g., ampicillin-sulbactam, ticarcillin-clavulanate, and piperacillin-tazobactam) or imipenem-cilastatin can be used in patients with more complicated histories, previous episodes of pyelonephritis, or recent urinary tract manipulations; in general, the treatment of such patients should be guided by urine culture results. Once the patient has responded clinically, oral therapy should be substituted for parenteral therapy.

UTI IN PREGNANT WOMEN Nitrofurantoin, ampicillin, and the cephalosporins are considered relatively safe in early pregnancy. One retrospective case-control study suggesting an association between nitrofurantoin and birth defects awaits confirmation. Sulfonamides should clearly be avoided both in the first trimester (because of possible teratogenic effects) and near term (because of a possible role in the development of kernicterus). Fluoroquinolones are avoided because of possible adverse effects on fetal cartilage development. Ampicillin and the cephalosporins have been used extensively in pregnancy and are the drugs of choice for the treatment of asymptomatic or symptomatic UTI in this group of patients. For pregnant women with overt pyelonephritis, parenteral β-lactam therapy with or without aminoglycosides is the standard of care.

UTI IN MEN Since the prostate is involved in the majority of cases of febrile UTI in men, the goal in these patients is to eradicate the prostatic infection as well as the bladder infection. In men with apparently uncomplicated UTI, a 7- to 14-day course of a fluoroquinolone or TMP-SMX is recommended. If acute bacterial prostatitis is suspected, antimicrobial therapy should be initiated after urine and blood are obtained for cultures. Therapy can be tailored to urine culture results and should be continued for 2–4 weeks. For documented chronic bacterial prostatitis, a 4- to 6-week course of antibiotics is often necessary. Recurrences, which are not uncommon in chronic prostatitis, often warrant a 12-week course of treatment.

COMPLICATED UTI Complicated UTI (other than that discussed previously) occurs in a heterogeneous group of patients with a wide variety of structural and functional abnormalities of the urinary tract and kidneys. The range of species and their susceptibility to antimicrobial agents are likewise heterogeneous. As a consequence, therapy for complicated UTI must be individualized and guided by urine culture results. Frequently, a patient with complicated UTI will have prior urine culture data that can be used to guide empirical therapy while current culture results are awaited. Xanthogranulomatous pyelonephritis is treated with nephrectomy. Percutaneous drainage can be used as the initial therapy in emphysematous pyelonephritis and can be followed by elective nephrectomy as needed. Papillary necrosis with obstruction requires intervention to relieve the obstruction and to preserve renal function.

ASYMPTOMATIC BACTERIURIA Treatment of ABU does not decrease the frequency of symptomatic infections or complications except in pregnant women, persons undergoing urologic surgery, and perhaps neutropenic patients and renal transplant recipients. Treatment of ABU in pregnant women and patients undergoing urologic procedures should be directed by urine culture results. In all other populations, screening for and treatment of ABU are discouraged. The majority of cases of catheter-associated bacteriuria are asymptomatic and do not warrant antimicrobial therapy.

CATHETER-ASSOCIATED UTI Multiple institutions have released guidelines for the treatment of CAUTI, which is defined by bacteriuria and symptoms in a catheterized patient. The signs and symptoms either are localized to the urinary tract or can include otherwise unexplained systemic manifestations, such as fever. The accepted threshold for bacteriuria varies from $\geq 10^3$ cfu/mL to $\geq 10^5$ cfu/mL.

The formation of biofilm—a living layer of uropathogens—on the urinary catheter is central to the pathogenesis of CAUTI and affects both therapeutic and preventive strategies. Organisms in a biofilm are relatively resistant to killing by antibiotics, and eradication of a catheter-associated biofilm is difficult without removal of the device itself. Furthermore, because catheters provide a conduit for bacteria to enter the bladder, bacteriuria is inevitable with long-term catheter use.

The typical signs and symptoms of UTI, including pain, urgency, dysuria, fever, peripheral leukocytosis, and pyuria, have less predictive value for the diagnosis of infection in catheterized patients. Furthermore, the presence of bacteria in the urine of a patient who is febrile and catheterized does not necessarily predict CAUTI, and other explanations for the fever should be considered.

The etiology of CAUTI is diverse, and urine culture results are essential to guide treatment. Fairly good evidence supports the practice of catheter change during treatment for CAUTI. The goal is to remove biofilm-associated organisms that could serve as a nidus for reinfection. Pathology studies reveal that many patients with long-term catheters have occult pyelonephritis.

A randomized trial in persons with spinal cord injury who were practicing intermittent catheterization found that relapse was more common after 3 days of therapy than after 14 days. In general, a 7- to 14-day course of antibiotics is recommended, but further studies on the optimal duration of therapy are needed.

In the setting of long-term catheter use, systemic antibiotics, bladder-acidifying agents, antimicrobial bladder washes, topical disinfectants, and antimicrobial drainage-bag solutions have all been ineffective at preventing the onset of bacteriuria and have been associated with the emergence of resistant organisms. The best strategy for prevention of CAUTI is to avoid insertion of unnecessary catheters and to remove catheters once they are no longer necessary. Evidence is insufficient to recommend suprapubic catheters and condom catheters as alternatives to indwelling urinary catheters as a means to prevent CAUTI. However, intermittent catheterization may be preferable to long-term indwelling urethral catheterization in certain populations (e.g., spinal cord–injured persons) to prevent both infectious and anatomic complications. Antimicrobial catheters impregnated with silver or nitrofurazone have not been shown to provide significant clinical benefit in terms of reducing rates of symptomatic UTI.

CANDIDURIA The appearance of *Candida* in the urine is an increasingly common complication of indwelling catheterization, particularly for patients in the intensive care unit, those taking broad-spectrum antimicrobial drugs, and those with underlying diabetes mellitus. *C. albicans* is still the most common isolate, although *C. glabrata* and other non-*albicans* species are also isolated frequently. The clinical presentation varies from an asymptomatic laboratory finding to pyelonephritis and even sepsis. In asymptomatic patients, removal of the urethral catheter results in resolution of candiduria in more than one-third of cases. Treatment is recommended for patients who have symptomatic cystitis or pyelonephritis and for those who are at high risk for disseminated disease. High-risk patients include those with neutropenia, those who are undergoing urologic manipulation, and low-birth-weight infants. Fluconazole (200–400 mg/d for 14 days) achieves high levels in urine and is the first-line regimen for *Candida* infections of the urinary tract. The newer azoles and echinocandins are characterized by only low-level urinary excretion and thus are not recommended, although cases of successful eradication of candiduria with some of these agents have been reported. For *Candida* isolates with high levels of resistance to fluconazole, oral flucytosine and/or parenteral amphotericin B are options. Bladder irrigation with amphotericin B generally is not recommended.

PREVENTION OF RECURRENT UTI IN WOMEN

Recurrence of uncomplicated cystitis in reproductive-age women is common, and a preventive strategy is indicated if recurrent UTIs are interfering with a patient's lifestyle. The threshold of two or more symptomatic episodes per year is not absolute; decisions about interventions should take the patient's preferences into account.

Three prophylactic strategies are available: continuous, postcoital, or patient-initiated therapy. Continuous prophylaxis and postcoital prophylaxis usually entail low doses of TMP-SMX, a fluoroquinolone, or nitrofurantoin. These regimens are all highly effective during the period of active antibiotic intake. Typically, a prophylactic regimen is prescribed for 6 months and then discontinued, at which point the rate of recurrent UTI often returns to baseline. If bothersome infections recur, the prophylactic program can be reinstituted for a longer period.

Patient-initiated therapy involves supplying the patient with materials for urine culture and self-medication with a course of antibiotics at the first symptoms of infection. The urine culture is refrigerated and delivered to the physician's office for confirmation of the diagnosis. When an established and reliable patient-provider relationship exists, the urine culture can be omitted as long as the symptomatic episodes respond completely to short-course therapy and are not followed by relapse.

PROGNOSIS

Cystitis is a risk factor for recurrent cystitis and pyelonephritis. ABU is common among elderly and catheterized patients but does not in itself increase the risk of death. The relationships among recurrent UTI, chronic pyelonephritis, and renal insufficiency have been widely studied. In the absence of anatomic abnormalities, recurrent infection in children and adults does not lead to chronic pyelonephritis or to renal failure. Moreover, infection does not play a primary role in chronic interstitial nephritis; the primary etiologic factors in this condition are analgesic abuse, obstruction, reflux, and toxin exposure. In the presence of underlying renal abnormalities (particularly obstructing stones), infection as a secondary factor can accelerate renal parenchymal damage. In spinal cord–injured patients, use of a long-term indwelling bladder catheter is a well-documented risk factor for bladder cancer. Chronic bacteriuria resulting in chronic inflammation is one possible explanation for this observation.

CHAPTER 21

URINARY TRACT OBSTRUCTION

Julian L. Seifter

Obstruction to the flow of urine, with attendant stasis and elevation in urinary tract pressure, impairs renal and urinary conduit functions and is a common cause of acute and chronic kidney disease (obstructive nephropathy). With early relief of obstruction, the defects in function usually disappear completely. However, chronic obstruction may produce permanent loss of renal mass (renal atrophy) and excretory capability, as well as enhanced susceptibility to local infection and stone formation. Early diagnosis and prompt therapy are therefore essential to minimize the otherwise devastating effects of obstruction on kidney structure and function.

ETIOLOGY

Obstruction to urine flow can result from *intrinsic* or *extrinsic mechanical blockade* as well as from *functional defects* not associated with fixed occlusion of the urinary drainage system. Mechanical obstruction can occur at any level of the urinary tract, from the renal calyces to the external urethral meatus. Normal points of narrowing, such as the ureteropelvic and ureterovesical junctions, bladder neck, and urethral meatus, are common sites of obstruction. When obstruction is above the level of the bladder, unilateral dilatation of the ureter (*hydroureter*) and renal pyelocalyceal system (*hydronephrosis*) occur; lesions at or below the level of the bladder cause bilateral involvement.

Common forms of obstruction are listed in Table 21-1. Childhood causes include *congenital malformations*, such as narrowing of the ureteropelvic junction and abnormal insertion of the ureter into the bladder, the most common cause. Vesicoureteral reflux in the absence of urinary tract infection or bladder neck obstruction often resolves with age. Reinsertion of the ureter into the bladder is indicated if reflux is severe and unlikely to improve spontaneously, if renal function deteriorates, or if urinary tract infections recur despite chronic antimicrobial therapy. Vesicoureteral reflux may cause prenatal hydronephrosis and, if severe, can lead to recurrent urinary infections and renal scarring in childhood. Posterior urethral valves are the most common cause of bilateral hydronephrosis in boys. In adults, urinary tract obstruction (UTO) is due mainly to *acquired defects*. Pelvic tumors, calculi, and urethral stricture predominate. Ligation of or injury to the ureter during pelvic or colonic surgery can lead to hydronephrosis which, if unilateral, may remain undetected. Obstructive uropathy may also result from extrinsic neoplastic (carcinoma of cervix or colon) or inflammatory disorders. Lymphomas and pelvic or colonic neoplasms with retroperitoneal involvement are causes of ureteral obstruction.

Functional impairment of urine flow usually results from disorders that involve both the ureter and bladder. Causes include neurogenic bladder, often with adynamic ureter, and vesicoureteral reflux. Reflux in children may result in severe unilateral or bilateral hydroureter and hydronephrosis. Urinary retention may be the consequence of α-adrenergic and anticholinergic agents, as well as opiates. Hydronephrosis in pregnancy is due to relaxational effects of progesterone on smooth muscle of the renal pelvis, as well as ureteral compression by the enlarged uterus.

CLINICAL FEATURES AND PATHOPHYSIOLOGY

The pathophysiology and clinical features of UTO are summarized in Table 21-2. *Pain*, the symptom that most commonly leads to medical attention, is due to distention of the collecting system or renal capsule. Pain severity is influenced more by the rate at which distention develops than by the degree of distention. Acute supravesical

TABLE 21-1

COMMON MECHANICAL CAUSES OF URINARY TRACT OBSTRUCTION

URETER	BLADDER OUTLET	URETHRA
Congenital		
Ureteropelvic junction narrowing or obstruction Ureterovesical junction narrowing or obstruction and reflux Ureterocele Retrocaval ureter	Bladder neck obstruction Ureterocele	Posterior urethral valves Anterior urethral valves Stricture Meatal stenosis Phimosis
Acquired Intrinsic Defects		
Calculi Inflammation Infection Trauma Sloughed papillae Tumor Blood clots	Benign prostatic hyperplasia Cancer of prostate Cancer of bladder Calculi Diabetic neuropathy Spinal cord disease Anticholinergic drugs and α-adrenergic antagonists	Stricture Tumor Calculi Trauma Phimosis
Acquired Extrinsic Defects		
Pregnant uterus Retroperitoneal fibrosis Aortic aneurysm Uterine leiomyomata Carcinoma of uterus, prostate, bladder, colon, rectum Lymphoma Pelvic inflammatory disease, endometriosis Accidental surgical ligation	Carcinoma of cervix, colon Trauma	Trauma

TABLE 21-2

PATHOPHYSIOLOGY OF BILATERAL URETERAL OBSTRUCTION

HEMODYNAMIC EFFECTS	TUBULE EFFECTS	CLINICAL FEATURES
Acute		
↑ Renal blood flow ↓ GFR ↓ Medullary blood flow ↑ Vasodilator prostaglandins, nitric oxide	↑ Ureteral and tubule pressures ↑ Reabsorption of Na^+, urea, water	Pain (capsule distention) Azotemia Oliguria or anuria
Chronic		
↓ Renal blood flow ↓↓ GFR ↑ Vasoconstrictor prostaglandins ↑ Renin-angiotensin production	↓ Medullary osmolarity ↓ Concentrating ability Structural damage; parenchymal atrophy ↓ Transport functions for Na^+, K^+, H^+	Azotemia Hypertension AVP-insensitive polyuria Natriuresis Hyperkalemic, hyperchloremic acidosis
Release of Obstruction		
Slow ↑ in GFR (variable)	↓ Tubule pressure ↑ Solute load per nephron (urea, NaCl) Natriuretic factors present	Postobstructive diuresis Potential for volume depletion and electrolyte imbalance due to losses of Na^+, K^+, PO_4^{2-}, Mg^{2+}, and water

Abbreviations: AVP, arginine vasopressin; GFR, glomerular filtration rate.

obstruction, as from a stone lodged in a ureter (see Chap. 9), is associated with excruciating pain, known as *renal colic*. This pain often radiates to the lower abdomen, testes, or labia. By contrast, more insidious causes of obstruction, such as chronic narrowing of the ureteropelvic junction, may produce little or no pain and yet result in total destruction of the affected kidney. Flank pain that occurs only with micturition is pathognomonic of vesicoureteral reflux. Hesitancy and straining to initiate the urinary stream, postvoid dribbling, urinary frequency, and incontinence are common with obstruction at or below the level of the bladder.

Obstruction of urine flow results in an increase in hydrostatic pressures proximal to the site of obstruction. It is this buildup of pressure that leads to the accompanying pain, distention of the collecting system in the kidney, and elevated intratubular pressures that initiate tubular dysfunction. As the increased hydrostatic pressure is expressed in the urinary space of the glomeruli, further filtration decreases or stops completely.

Azotemia develops when overall excretory function is impaired, often in the setting of bladder outlet obstruction, bilateral renal pelvic or ureteric obstruction, or unilateral disease in a patient with a solitary functioning kidney. Complete bilateral obstruction should be suspected when acute renal failure is accompanied by anuria. Any patient with renal failure otherwise unexplained, or with a history of nephrolithiasis, hematuria, diabetes mellitus, prostatic enlargement, pelvic surgery, trauma, or tumor should be evaluated for UTO.

In the acute setting, partial, bilateral obstruction may mimic prerenal azotemia with concentrated urine and sodium retention. However, with more prolonged obstruction, symptoms of *polyuria* and *nocturia* commonly accompany partial UTO and result from diminished renal concentrating ability. Impairment of transcellular salt reabsorption in the proximal tubule, medullary thick ascending limb of Henle, and collecting duct cells is due to down regulation of transport proteins including the Na^+, K^+ adenosine triphosphatase (ATPase), $NaKCl_2$ cotransporter (NKCC) in the thick ascending limb, and the epithelial Na^+ channel (ENaC) in collecting duct cells. Consequences include failure to produce urine free of salt (natriuresis) and loss of medullary hypertonicity producing a urinary concentrating defect. In addition to direct effects on renal transport mechanisms, increased PGE2 (due to induction of COX-2), angiotensin-II (with its downregulation of Na^+ transporters), and atrial natriuretic peptide (ANP) (due to volume expansion in the azotemic patient) contribute to the decreased salt reabsorption along the nephron.

Dysregulation of aquaporin-2 water channels in the collecting duct contributes to the polyuria. The defect usually does not improve with administration of vasopressin and is therefore a form of acquired nephrogenic diabetes insipidus.

Wide fluctuations in urine output in a patient with azotemia should always raise the possibility of intermittent or partial UTO. If fluid intake is inadequate, severe dehydration and hypernatremia may develop. However, as with other causes of poor renal function, excesses of salt and water intake may result in edema and hyponatremia.

Partial bilateral UTO often results in *acquired distal renal tubular acidosis*, *hyperkalemia*, and *renal salt wasting*. The H^+-ATPase, situated on the apical membrane of the intercalated cells of the collecting duct, is critical for distal H^+ secretion. The trafficking of intracellular H^+ pumps from the cytoplasm to the cell membrane is disrupted in UTO. The decreased function of the ENaC, in the apical membrane of neighboring collecting duct principal cells, contributes to decreased Na^+ reabsorption (salt wasting), decreased electronegativity of the tubule lumen, and therefore decreased K^+ secretion via K^+ channels (hyperkalemia) and H^+ secretion via the H^+-ATPases [distal renal tubular acidosis (RTA)]. Proximal tubule ammoniagenesis, important to the elimination of H^+ as $NH4^+$, is impaired. These defects in tubule function are often accompanied by renal tubulointerstitial damage. Azotemia with hyperkalemia and metabolic acidosis should prompt consideration of UTO.

The renal interstitium becomes edematous and infiltrated with mononuclear inflammatory cells early in UTO. Later, interstitial fibrosis and atrophy of the papillae and medulla occur and precede these processes in the cortex. The increase in angiotensin-II noted in UTO contributes to the inflammatory response and fibroblast accumulation through mechanisms involving profibrotic cytokines. With time, this process leads to chronic kidney damage.

UTO must always be considered in patients with urinary tract infections or urolithiasis. Urinary stasis encourages the growth of organisms. Urea-splitting bacteria are associated with magnesium ammonium phosphate (struvite) calculi. *Hypertension* is frequent in acute and subacute unilateral obstruction and is usually a consequence of increased release of renin by the involved kidney. Chronic kidney disease from bilateral UTO, often associated with extracellular volume expansion, may result in significant hypertension. *Erythrocytosis*, an infrequent complication of obstructive uropathy, is secondary to increased erythropoietin production.

DIAGNOSIS

A history of difficulty in voiding, pain, infection, or change in urinary volume is common. Evidence for distention of the kidney or urinary bladder can often be obtained by palpation and percussion of the abdomen. A careful rectal and genital examination may reveal enlargement or nodularity of the prostate, abnormal rectal sphincter tone, or a rectal or pelvic mass.

Urinalysis may reveal hematuria, pyuria, and bacteriuria. The urine sediment is often normal, even when obstruction leads to marked azotemia and extensive structural damage. An abdominal scout film may detect nephrocalcinosis or a radiopaque stone. As indicated in **Fig. 21-1**, if UTO is suspected, a bladder catheter should be inserted. Abdominal ultrasonography should be performed to evaluate renal and bladder size, as well as pyelocalyceal contour. Ultrasonography is approximately 90% specific and sensitive for detection of hydronephrosis. False-positive results are associated with diuresis, renal cysts, or the presence of an extrarenal pelvis, a normal congenital variant. Congenital ureteropelvic junction (UPJ) obstruction may be mistaken for renal cystic disease. Hydronephrosis may be absent on ultrasound when obstruction is less than 48 hours in duration or associated with volume contraction, staghorn calculi, retroperitoneal fibrosis, or infiltrative renal disease. Duplex Doppler ultrasonography may detect an increased resistive index in urinary obstruction.

Recent advances in technology have led to alternatives to the once standard intravenous urogram in the further evaluation of UTO. The high-resolution multidetector row CT scan in particular has advantages of visualizing the retroperitoneum, as well as identifying both intrinsic and extrinsic sites of obstruction. Noncontrast CT scans improve visualization of the urinary tract in the patient with renal impairment and are safer for patients at risk for contrast nephropathy. MR urography is a promising technique but at this time not superior to the CT scan and carries the risk of certain gadolinium agents in patients with renal insufficiency, i.e., nephrogenic systemic fibrosis. The intravenous urogram may define the site of obstruction and demonstrate dilatation of the calyces, renal pelvis, and ureter above the obstruction. The ureter may be tortuous in chronic obstruction. Radionuclide scans are able to give differential renal function but give less anatomic detail than CT or intravenous urography (IVU).

To facilitate visualization of a suspected lesion in a ureter or renal pelvis, *retrograde* or *antegrade urography* should be attempted. These procedures do not carry the risk of contrast-induced acute renal failure in patients with renal insufficiency. The retrograde approach involves catheterization of the involved ureter under cystoscopic control, while the antegrade technique necessitates percutaneous placement of a catheter into the renal pelvis. While the antegrade approach may provide immediate decompression of a unilateral obstructing lesion, many urologists initially attempt the retrograde approach unless the catheterization is unsuccessful.

Voiding cystourethrography is of value in the diagnosis of vesicoureteral reflux and bladder neck and urethral obstructions. Postvoiding films reveal residual urine. Endoscopic visualization by the urologist often permits precise identification of lesions involving the urethra, prostate, bladder, and ureteral orifices.

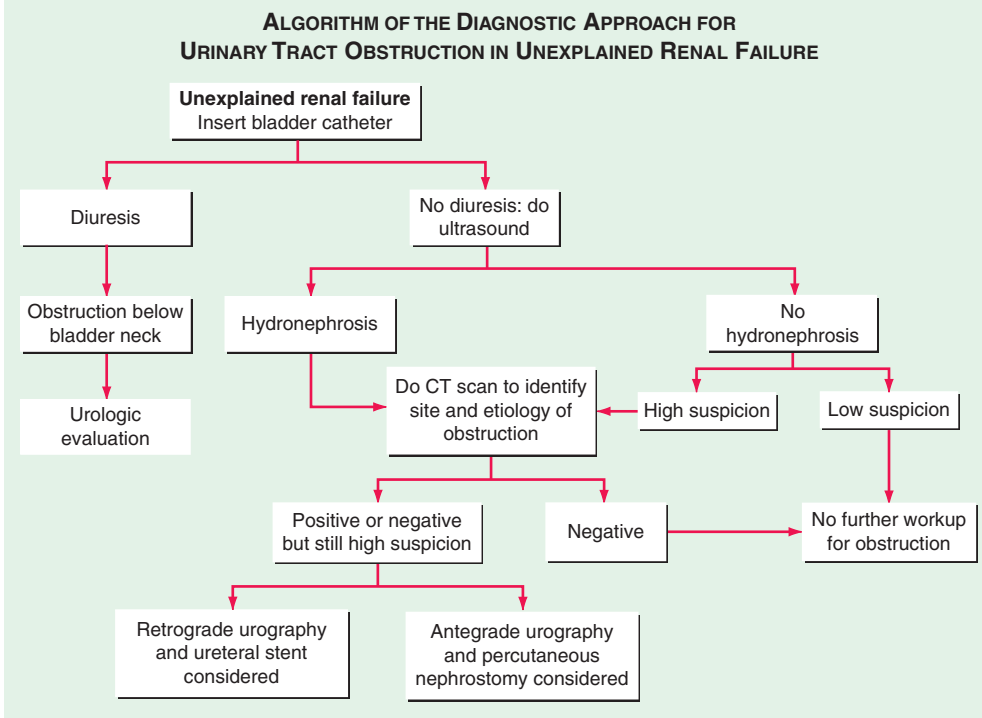


FIGURE 21-1
Diagnostic approach for urinary tract obstruction in unexplained renal failure. CT, computed tomography.

TREATMENT **Urinary Tract Obstruction**

UTO complicated by infection requires immediate relief of obstruction to prevent the development of generalized sepsis and progressive renal damage. Sepsis necessitates prompt urologic intervention. Drainage may be achieved by nephrostomy, ureterostomy, or ureteral, urethral, or suprapubic catheterization. Prolonged antibiotic treatment may be necessary. Chronic or recurrent infections in a poorly functioning obstructed kidney may necessitate nephrectomy. When infection is not present, surgery is often delayed until acid-base, fluid, and electrolyte status is restored. Nevertheless, the site of obstruction should be ascertained as soon as feasible. Elective relief of obstruction is usually recommended in patients with urinary retention, recurrent urinary tract infections, persistent pain, or progressive loss of renal function. Benign prostatic hypertrophy may be treated medically with α-adrenergic blockers and 5α-reductase inhibitors. Functional obstruction secondary to neurogenic bladder may be decreased with the combination of frequent voiding and cholinergic drugs.

PROGNOSIS

With relief of obstruction, the prognosis regarding return of renal function depends largely on whether irreversible renal damage has occurred. When obstruction is not relieved, the course will depend mainly on whether the obstruction is complete or incomplete and bilateral or unilateral, as well as whether or not urinary tract infection is also present. Complete obstruction with infection can lead to total destruction of the kidney within days. Partial return of glomerular filtration rate may follow relief of complete obstruction of 1 and 2 weeks' duration, but after 8 weeks of obstruction, recovery is unlikely. In the absence of definitive evidence of irreversibility, every effort should be made to decompress the obstruction in the hope of restoring renal function at least partially. A renal radionuclide scan, performed after a prolonged period of decompression, may be used to predict the reversibility of renal dysfunction.

POSTOBSTRUCTIVE DIURESIS

Relief of bilateral, but not unilateral, complete obstruction commonly results in polyuria, which may be massive. The urine is usually hypotonic and may contain large amounts of sodium chloride, potassium, phosphate, and magnesium. The natriuresis is due in part to the excretion of retained urea (osmotic diuresis), natriuretic factors accumulated during uremia and depressed salt and water reabsorption when urine flow is reestablished. In the majority of patients this diuresis results in the *appropriate* excretion of the excesses of retained salt and water. When extracellular volume and composition return to normal, the diuresis usually abates spontaneously. Occasionally, iatrogenic expansion of extracellular volume is responsible for or sustains the diuresis observed in the postobstructive period. Replacement with intravenous fluids in amounts less than urinary losses usually avoids this complication. More aggressive fluid management is required in the setting of hypovolemia, hypotension, or disturbances in serum electrolyte concentrations.

The loss of electrolyte-free water with urea may result in hypernatremia. Serum and urine sodium and osmolal concentrations should guide the use of appropriate intravenous replacement. Often replacement with 0.45% saline is required. Relief of obstruction may be followed by urinary salt and water losses severe enough to provoke profound dehydration and vascular collapse. In these patients, decreased tubule reabsorptive capacity is probably responsible for the marked diuresis. Appropriate therapy in such patients includes intravenous administration of salt-containing solutions to replace sodium and volume deficits.

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SECTION VII

CANCER OF THE KIDNEY AND URINARY TRACT

CHAPTER 22

BLADDER AND RENAL CELL CARCINOMAS

Howard I. Scher ■ Robert J. Motzer

BLADDER CANCER

A transitional cell epithelium lines the urinary tract from the renal pelvis to the ureter, urinary bladder, and the proximal two-thirds of the urethra. Cancers can occur at any point: 90% of malignancies develop in the bladder, 8% in the renal pelvis, and the remaining 2% in the ureter or urethra. Bladder cancer is the fourth most common cancer in men and the thirteenth in women, with an estimated 70,530 new cases and 14,680 deaths in the United States predicted for the year 2010. The almost 5:1 ratio of incidence to mortality reflects the higher frequency of the less lethal superficial variants compared to the more lethal invasive and metastatic variants. The incidence is three times higher in men than in women and twofold higher in whites than blacks, with a median age at diagnosis of 65 years.

Once diagnosed, urothelial tumors exhibit polychronotropism—the tendency to recur over time and in new locations in the urothelial tract. As long as urothelium is present, continuous monitoring of the tract is required.

EPIDEMIOLOGY

Cigarette smoking is believed to contribute to up to 50% of the diagnosed urothelial cancers in men and up to 40% in women. The risk of developing a urothelial malignancy in male smokers is increased two- to fourfold relative to nonsmokers and continues for 10 years or longer after cessation. Other implicated agents include the aniline dyes, the drugs phenacetin and chlornaphazine, and external beam radiation. Chronic cyclophosphamide exposure may also increase risk, whereas vitamin A supplements appear to be protective. Exposure to *Schistosoma haematobium*, a parasite found in many developing countries, is associated with an increase in both squamous and transitional cell carcinomas of the bladder.

PATHOLOGY

Clinical subtypes are grouped into three categories: 75% are superficial, 20% invade muscle, and 5% are metastatic at presentation. Staging of the tumor within the bladder is based on the pattern of growth and depth of invasion: Ta lesions grow as exophytic lesions; carcinoma in situ (CIS) lesions start on the surface and tend to invade. The revised tumor, node, metastasis (TNM) staging system is illustrated in **Fig. 22-1**. About half of invasive tumors presented originally as superficial lesions that later progressed. Tumors are also rated by grade. Grade I lesions (highly differentiated tumors) rarely progress to a higher stage, whereas grade III tumors do.

More than 95% of urothelial tumors in the United States are transitional cell in origin. Pure squamous cancers with keratinization constitute 3%, adenocarcinomas 2%, and small cell tumors (with paraneoplastic syndromes) <1%. Adenocarcinomas develop primarily in the urachal remnant in the dome of the bladder or in the periurethral tissues; some assume a signet cell histology. Lymphomas and melanomas are rare. Of the transitional cell tumors, low-grade papillary lesions that grow on a central stalk are most common. These tumors are very friable, have a tendency to bleed, are at high risk for recurrence, and yet rarely progress to the more lethal invasive variety. In contrast, CIS is a high-grade tumor that is considered a precursor of the more lethal muscle-invasive disease.

PATHOGENESIS

The multicentric nature of the disease and high rate of recurrence has led to the hypothesis of a field defect in the urothelium that results in a predisposition to cancer. Molecular genetic analyses suggest that the superficial and invasive lesions develop along distinct molecular pathways in which primary tumorigenic aberrations

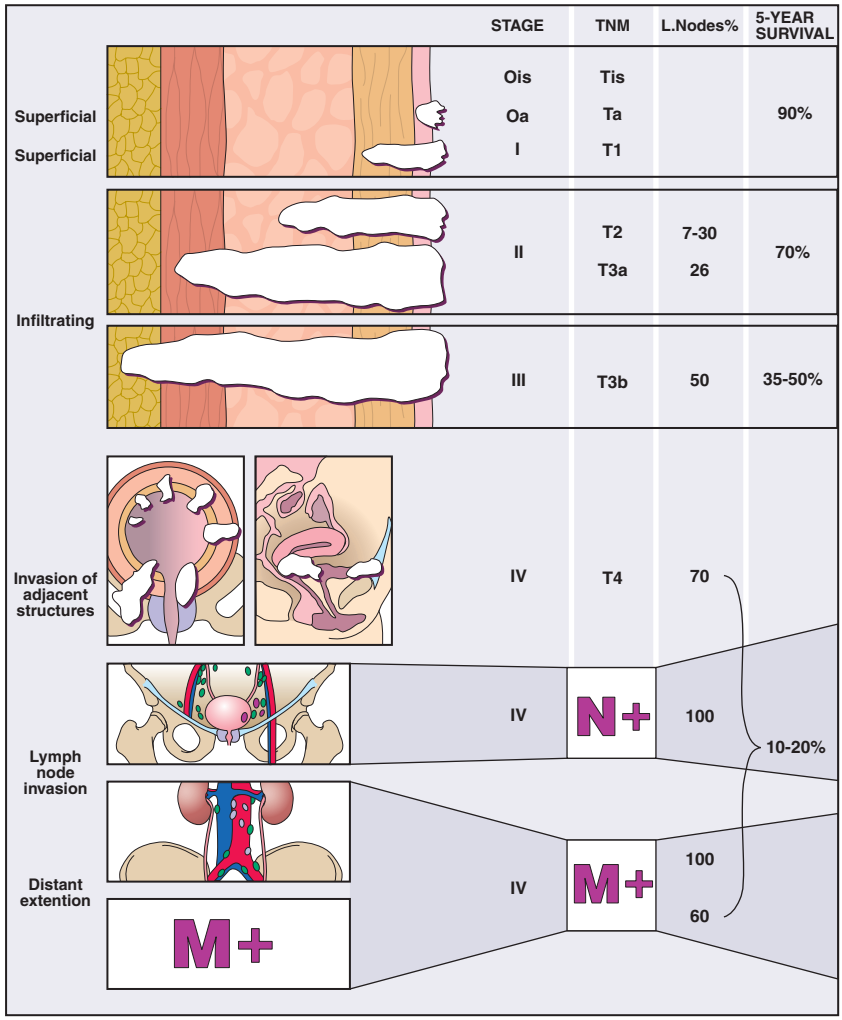

FIGURE 22-1
Bladder staging. TNM, tumor, node, metastasis.

precede secondary changes associated with progression to a more advanced stage. Low-grade papillary tumors that do not tend to invade or metastasize harbor constitutive activation of the receptor-tyrosine kinase-Ras signal transduction pathway and a high frequency of fibroblast growth factor receptor 3 (FGFR3) mutations. In contrast, CIS and invasive tumors have a higher frequency of *TP53* and *RB* gene alternations. Within all clinical stages, including Tis, T1, and T2 or greater lesions, tumors with alterations in *p53*, *p21*, and/or *RB* have a higher probability of recurrence, metastasis, and death from disease.

CLINICAL PRESENTATION, DIAGNOSIS, AND STAGING

Hematuria occurs in 80–90% of patients and often reflects exophytic tumors. The bladder is the most common source of gross hematuria (40%), but benign cystitis (22%) is a more common cause than bladder cancer (15%) (Chap. 3). Microscopic hematuria is more commonly of prostate origin (25%); only 2% of bladder cancers produce microscopic hematuria. Once hematuria is documented, a urinary cytology, visualization of the urothelial tract by CT or intravenous pyelogram, and cystoscopy are recommended if no other etiology is found. Screening asymptomatic individuals for hematuria increases the diagnosis of tumors at an early stage but has not been shown to prolong life. After hematuria, irritative symptoms are the next most common presentation, which may reflect in situ disease. Obstruction of the ureters may cause flank pain. Symptoms of metastatic disease are rarely the first presenting sign.

The endoscopic evaluation includes an examination under anesthesia to determine whether a palpable mass is present. A flexible endoscope is inserted into the bladder, and bladder barbotage is performed. The visual inspection includes mapping the location, size, and number of lesions, as well as a description of the growth pattern (solid vs. papillary). An intraoperative

video is often recorded. All visible tumors should be resected, and a sample of the muscle underlying the tumor should be obtained to assess the depth of invasion. Normal-appearing areas are biopsied at random to ensure no field defect. A notation is made as to whether a tumor was completely or incompletely resected. Selective catheterization and visualization of the upper tracts should be performed if the cytology is positive and no disease is visible in the bladder. Ultrasonography, CT, and/or MRI may help to determine whether a tumor extends to perivesical fat (T3) and to document nodal spread. Distant metastases are assessed by CT of the chest and abdomen, MRI, or radionuclide imaging of the skeleton.

TREATMENT Bladder Cancer

Management depends on whether the tumor invades muscle and whether it has spread to the regional lymph nodes and beyond. The probability of spread increases with increasing T stage.

SUPERFICIAL DISEASE At a minimum, the management of a superficial tumor is complete endoscopic resection with or without intravesical therapy. The decision to recommend intravesical therapy depends on the histologic subtype, number of lesions, depth of invasion, presence or absence of CIS, and antecedent history. Recurrences develop in upward of 50% of cases, of which 5–20% progress to a more advanced stage. In general, solitary papillary lesions are managed by transurethral surgery alone. CIS and recurrent disease are treated by transurethral surgery followed by intravesical therapy.

Intravesical therapies are used in two general contexts: as an adjuvant to a complete endoscopic resection to prevent recurrence or, less commonly, to eliminate disease that cannot be controlled by endoscopic resection alone. Intravesical treatments are advised for patients with recurrent disease, >40% involvement of the bladder surface by tumor, diffuse CIS, or T1 disease. The standard intravesical therapy, based on randomized comparisons, is bacillus Calmette-Guerin (BCG) in six weekly instillations, followed by monthly maintenance administrations for ≥1 year. Other agents with activity include mitomycin-C, interferon (IFN), and gemcitabine. The side effects of intravesical therapies include dysuria, urinary frequency, and, depending on the drug, myelosuppression or contact dermatitis. Rarely, intravesical BCG may produce a systemic illness associated with granulomatous infections in multiple sites that requires antituberculin therapy.

Following the endoscopic resection, patients are monitored for recurrence at 3-month intervals during the first year. Recurrence may develop anywhere along the urothelial tract, including the renal pelvis, ureter, or urethra. A consequence of the "successful" treatment of tumors in the bladder is an increase in the frequency of extravesical recurrences (e.g., urethra or ureter). Those with persistent disease in the bladder or new tumors are generally considered for a second course of BCG or for intravesical chemotherapy with valrubicin or gemcitabine. In some cases, cystectomy is recommended, although the specific indications vary. Tumors in the ureter or renal pelvis are typically managed by resection during retrograde examination or, in some cases, by instillation through the renal pelvis. Tumors of the prostatic urethra may require cystectomy if the tumor cannot be resected completely.

INVASIVE DISEASE The treatment of a tumor that has invaded muscle can be separated into control of the primary tumor and, depending on the pathologic findings at surgery, systemic chemotherapy to treat micrometastatic disease. Radical cystectomy is the standard, although in selected cases a bladder-sparing approach is used; this approach includes complete endoscopic resection; partial cystectomy; or a combination of resection, systemic chemotherapy, and external beam radiation therapy. In some countries, external beam radiation therapy is considered standard. In the United States, its role is limited to those patients deemed unfit for cystectomy, those with unresectable local disease, or as part of an experimental bladder-sparing approach.

Indications for cystectomy include muscle-invading tumors not suitable for segmental resection; low-stage tumors unsuitable for conservative management (e.g., due to multicentric and frequent recurrences resistant to intravesical instillations); high-grade tumors (T1G3) associated with CIS; and bladder symptoms, such as frequency or hemorrhage, that impair quality of life.

Radical cystectomy is major surgery that requires appropriate preoperative evaluation and management. The procedure involves removal of the bladder and pelvic lymph nodes and creation of a conduit or reservoir for urinary flow. Grossly abnormal lymph nodes are evaluated by frozen section. If metastases are confirmed, the procedure is often aborted. In males, radical cystectomy includes the removal of the prostate, seminal vesicles, and proximal urethra. Impotence is universal unless the nerves responsible for erectile function are preserved. In females, the procedure includes removal of the bladder, urethra, uterus, fallopian tubes, ovaries, anterior vaginal wall, and surrounding fascia.

Previously, urine flow was managed by directing the ureters to the abdominal wall, where it was collected in an external appliance. Currently, most patients receive either a continent cutaneous reservoir constructed from detubularized bowel or an orthotopic neobladder.

Some 70% of men receive a neobladder. With a continent reservoir, 65–85% of men will be continent at night and 85–90% during the day. Cutaneous reservoirs are drained by intermittent catheterization; orthotopic neobladders are drained more naturally. Contraindications to a neobladder include renal insufficiency, an inability to self-catheterize, or an exophytic tumor or CIS in the urethra. Diffuse CIS in the bladder is a relative contraindication based on the risk of a urethral recurrence. Concurrent ulcerative colitis or Crohn's disease may hinder the use of resected bowel.

A partial cystectomy may be considered when the disease is limited to the dome of the bladder, a margin of at least 2 cm can be achieved, there is no CIS in other sites, and the bladder capacity is adequate after the tumor has been removed. This occurs in 5–10% of cases. Carcinomas in the ureter or in the renal pelvis are treated with nephroureterectomy with a bladder cuff to remove the tumor.

The probability of recurrence following surgery is predicted on the basis of pathologic stage, presence or absence of lymphatic or vascular invasion, and nodal spread. Among those whose cancers recur, the recurrence develops in a median of 1 year (range 0.04–11.1 years). Long-term outcomes vary by pathologic stage and histology (Table 22-1). The number of lymph nodes removed is also prognostic, whether or not the nodes contained tumor.

Chemotherapy (described in a later section) has been shown to prolong the survival of patients with invasive disease, but only when combined with definitive treatment of the bladder by radical cystectomy or radiation therapy. Thus, for the majority of patients, chemotherapy alone is inadequate to clear the bladder of disease. Experimental studies are evaluating bladder preservation strategies by combining chemotherapy and radiation therapy in patients whose tumors were endoscopically removed.

METASTATIC DISEASE The primary goal of treatment for metastatic disease is to achieve complete remission with chemotherapy alone or with a combined-modality approach of chemotherapy followed by surgical resection of residual disease, as is done routinely for the treatment of germ cell tumors. One can define a goal in terms of cure or palliation on the basis of the probability of achieving a complete response to chemotherapy using prognostic factors, such as Karnofsky Performance Status (KPS) (<80%), and whether the pattern of spread is nodal or visceral (liver, lung, or bone). For those with zero, one, or two risk factors, the probability of complete remission is 38, 25, and 5%, respectively, and median survival is 33, 13.4, and 9.3 months, respectively. Patients who are functionally compromised or who have visceral disease or bone metastases rarely achieve long-term survival. The toxicities also vary as a function of risk, and treatment-related mortality rates are as high as 3–4% using some combinations in these poor-risk patient groups.

TABLE 22-1

SURVIVAL FOLLOWING SURGERY FOR BLADDER CANCER

PATHOLOGIC STAGE	5-YEAR SURVIVAL, %	10-YEAR SURVIVAL, %
T2,N0	89	87
T3a,N0	78	76
T3b,N0	62	61
T4,N0	50	45
Any T,N1	35	34

CHEMOTHERAPY A number of chemotherapeutic drugs have shown activity as single agents; cisplatin, paclitaxel, and gemcitabine are considered most active. Standard therapy consists of two-, three-, or four-drug combinations. Overall response rates of >50% have been reported using combinations such as methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC); cisplatin and paclitaxel (PT); gemcitabine and cisplatin (GC); or gemcitabine, paclitaxel, and cisplatin (GTC). M-VAC was considered standard, but the toxicities of neutropenia and fever, mucositis, diminished renal and auditory function, and peripheral neuropathy led to the development of alternative regimens. At present, GC is used more commonly than M-VAC, based on the results of a comparative trial of M-VAC versus GC that showed less neutropenia and fever, and less mucositis for the GC regimen. Anemia and thrombocytopenia were more common with GC. GTC is not more effective than GC.

Chemotherapy has also been evaluated in the neoadjuvant and adjuvant settings. In a randomized trial, patients receiving three cycles of neoadjuvant M-VAC followed by cystectomy had a significantly better median (6.2 years) and 5-year survival (57%) compared to cystectomy alone (median survival 3.8 years; 5-year survival 42%). Similar results were obtained in an international study of three cycles of cisplatin, methotrexate, and vinblastine (CMV) followed by either radical cystectomy or radiation therapy. The decision to administer adjuvant therapy is based on the risk of recurrence after cystectomy. Indications for adjuvant chemotherapy include the presence of nodal disease, extravesical tumor extension, or vascular invasion in the resected specimen. Another study of adjuvant therapy found that four cycles of CMV delayed recurrence, although an effect on survival was less clear. Additional trials are studying taxane- and gemcitabine-based combinations.

The management of bladder cancer is summarized in Table 22-2.

TABLE 22-2

MANAGEMENT OF BLADDER CANCER

NATURE OF LESION	MANAGEMENT APPROACH
Superficial	Endoscopic removal, usually with intravesical therapy
Invasive disease	Cystectomy ± systemic chemotherapy (before or after surgery)
Metastatic disease	Curative or palliative chemotherapy (based on prognostic factors) ± surgery

CARCINOMA OF THE RENAL PELVIS AND URETER

About 2500 cases of renal pelvis and ureter cancer occur each year; nearly all are transitional cell carcinomas similar to bladder cancer in biology and appearance. This tumor is also associated with chronic phenacetin abuse and with Balkan nephropathy, a chronic interstitial nephritis endemic in Bulgaria, Greece, Bosnia-Herzegovina, and Romania.

The most common symptom is painless gross hematuria, and the disease is usually detected on intravenous pyelogram during the workup for hematuria. Patterns of spread are like those in bladder cancer. For low-grade disease localized to the renal pelvis and ureter, nephroureterectomy (including excision of the distal ureter with a portion of the bladder) is associated with 5-year survival of 80–90%. More invasive or histologically poorly differentiated tumors are more likely to recur locally and to metastasize. Metastatic disease is treated with the chemotherapy used in bladder cancer, and the outcome is similar to that of metastatic transitional-cell cancer of bladder origin.

RENAL CELL CARCINOMA

Renal cell carcinomas account for 90–95% of malignant neoplasms arising from the kidney. Notable features include resistance to cytotoxic agents, infrequent responses to biologic response modifiers such as interleukin (IL)-2, robust activity to antiangiogenesis targeted agents, and a variable clinical course for patients with metastatic disease, including anecdotal reports of spontaneous regression.

EPIDEMIOLOGY

The incidence of renal cell carcinoma continues to rise and is now nearly 58,000 cases annually in the United States, resulting in 13,000 deaths. The male-to-female ratio is 2:1. Incidence peaks between the ages of 50 and 70 years, although this malignancy may be diagnosed at any age. Many environmental factors have been investigated as possible contributing causes; the strongest association is with cigarette smoking. Risk is also increased for patients who have acquired cystic disease of the kidney associated with end-stage renal disease, and for those with tuberous sclerosis. Most cases are sporadic, although familial forms have been reported. One is associated with von Hippel-Lindau (VHL) syndrome. VHL syndrome is an autosomal dominant disorder. Genetic studies identified the *VHL* gene on the short arm of chromosome 3. Approximately 35% of individuals with VHL disease develop clear cell renal cell carcinoma. Other associated neoplasms include retinal hemangioma, hemangioblastoma of the spinal cord and cerebellum, pheochromocytoma, neuroendocrine tumors and cysts, and cysts in the epididymis of the testis in men and the broad ligament in women. Subtypes vary according to low risk (type 1) or high risk (type 2) of developing pheochromocytoma.

PATHOLOGY AND GENETICS

Renal cell neoplasia represents a heterogeneous group of tumors with distinct histopathologic, genetic, and clinical features ranging from benign to high-grade malignant (Table 22-3). They are classified on the basis of morphology and histology. Categories include clear cell carcinoma (60% of cases), papillary tumors (5–15%), chromophobic tumors (5–10%), oncocytomas (5–10%), and collecting or Bellini duct tumors (<1%). Papillary

TABLE 22-3

CLASSIFICATION OF EPITHELIAL NEOPLASMS ARISING FROM THE KIDNEY

CARCINOMA TYPE	GROWTH PATTERN	CELL OF ORIGIN	CYTOGENETICS
Clear cell	Acinar or sarcomatoid	Proximal tubule	3p–
Papillary	Papillary or sarcomatoid	Proximal tubule	+7, +17, –Y
Chromophobic	Solid, tubular, or sarcomatoid	Cortical collecting duct	Hypodiploid
Oncocytic	Tumor nests	Cortical collecting duct	Undetermined
Collecting duct	Papillary or sarcomatoid	Medullary collecting duct	Undetermined

tumors tend to be bilateral and multifocal. Chromophobic tumors have a more indolent clinical course, and oncocytomas are considered benign neoplasms. In contrast, Bellini duct carcinomas, which are thought to arise from the collecting ducts within the renal medulla, are very rare but very aggressive. Clear cell tumors, the predominant histology, are found in >80% of patients who develop metastases. Clear cell tumors arise from the epithelial cells of the proximal tubules and usually show chromosome 3p deletions. Deletions of 3p21–26 (where the *VHL* gene maps) are identified in patients with familial as well as sporadic tumors. *VHL* encodes a tumor-suppressor protein that is involved in regulating the transcription of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and a number of other hypoxia-inducible proteins. Inactivation of *VHL* leads to overexpression of these agonists of the VEGF and PDGF receptors, which promote tumor angiogenesis and tumor growth. Agents that inhibit proangiogenic growth factor activity show antitumor effects.

CLINICAL PRESENTATION

The presenting signs and symptoms include hematuria, abdominal pain, and a flank or abdominal mass. This classic triad occurs in 10–20% of patients. Other symptoms are fever, weight loss, anemia, and a varicocele. The tumor is most commonly detected as an incidental finding on a radiograph. Widespread use of radiologic cross-sectional imaging procedures (CT, ultrasound, MRI) contributes to earlier detection, including incidental renal masses detected during evaluation for other medical conditions. The increasing number of incidentally discovered low-stage tumors has contributed to an improved 5-year survival for patients with renal cell carcinoma and increased use of nephron-sparing surgery (partial nephrectomy). A spectrum of paraneoplastic syndromes has been associated with these malignancies, including erythrocytosis, hypercalcemia, nonmetastatic hepatic dysfunction (Stauffer syndrome), and acquired dysfibrinogenemia. Erythrocytosis is noted at presentation in only about 3% of patients. Anemia, a sign of advanced disease, is more common.

The standard evaluation of patients with suspected renal cell tumors includes a CT scan of the abdomen and pelvis, chest radiograph, urine analysis, and urine cytology. If metastatic disease is suspected from the chest radiograph, a CT of the chest is warranted. MRI is useful in evaluating the inferior vena cava in cases of suspected tumor involvement or invasion by thrombus. In clinical practice, any solid renal masses should be considered malignant until proven otherwise; a definitive diagnosis is required. If no metastases are demonstrated, surgery is indicated, even if the renal vein is invaded. The differential diagnosis of a renal mass includes cysts, benign neoplasms (adenoma, angiomyolipoma, oncocytoma), inflammatory lesions (pyelonephritis or abscesses), and other primary or metastatic cancers. Other malignancies that may involve the kidney include transitional cell carcinoma of the renal pelvis, sarcoma, lymphoma, and Wilms' tumor. All of these are less common causes of renal masses than is renal cell cancer.

STAGING AND PROGNOSIS

Staging is based on the American Joint Committee on Cancer (AJCC) staging system **(Fig. 22-2)**. Stage I tumors are <7 cm in greatest diameter and confined to the kidney, stage II tumors are ≥7 cm and confined to the kidney, stage III tumors extend through the renal capsule but are confined to Gerota's fascia (IIIa) or involve a single hilar lymph node (N1), and stage IV disease includes tumors that have invaded adjacent organs (excluding the adrenal gland) or involve multiple lymph nodes or distant metastases. The rate of 5-year survival varies by stage: >90% for stage I, 85% for stage II, 60% for stage III, and 10% for stage IV.

TREATMENT Renal Cell Carcinoma

LOCALIZED TUMORS The standard management for stage I or II tumors and selected cases of stage III disease is radical nephrectomy. This procedure involves en bloc removal of Gerota's fascia and its contents, including the kidney, the ipsilateral adrenal gland, and adjacent hilar lymph nodes. The role of a regional lymphadenectomy is controversial. Extension into the renal vein or inferior vena cava (stage III disease) does not preclude resection even if cardiopulmonary bypass is required. If the tumor is resected, half of these patients have prolonged survival.

Nephron-sparing approaches via open or laparoscopic surgery may be appropriate for patients who have only one kidney, depending on the size and location of the lesion. A nephron-sparing approach can also be used for patients with bilateral tumors, accompanied by a radical nephrectomy on the opposite side. Partial nephrectomy techniques are applied electively to resect small masses for patients with a normal contralateral kidney. Adjuvant therapy following this surgery does not improve outcome, even in cases with a poor prognosis.

ADVANCED DISEASE Surgery has a limited role for patients with metastatic disease. However, long-term survival may occur in patients who relapse after nephrectomy in a solitary site that can be removed. One indication for nephrectomy with metastases at initial presentation is to alleviate pain or hemorrhage of a

TNM	Involvement	Extent of Disease
TX	Primary not involved	
T1	≤7 cm	limited to kidney
T1a	≤4 cm	
T1b	≥4 cm	
T2	>7 cm	limited to kidney
T2a	>7 cm to ≤10 cm	
T2b	>10 cm	
T3	into major veins or perinephric tissues	not beyond Gerota's fascia
T3a	in renal vein or renal sinus fat	not beyond Gerota's fascia
T3b	into vena cava	below diaphragm
T3c	into vena cava	above diaphragm
T4	invasion beyond Gerota's fascia	including contiguous extentions & into ipsilateral adrenal gland

Regional

NX	Regional lymph not assessed
N0	No lymph involvment
N1	Regional lymph involvment

Distant Metastases

M0	No distant metastases
M1	Distant metastases

Anatomic Stage / Prognostic Groups			
I	T1	N0	M0
II	T2	N0	M0
III	T1 or T2,	N1	M0
	T3	N0 or N1	M0
IV	T4	Any N	M0
	Any T	Any N	M1

FIGURE 22-2
Renal cell carcinoma staging. TNM, tumor, node, metastasis

primary tumor. Also, a cytoreductive nephrectomy before systemic treatment improves survival for carefully selected patients with stage IV tumors.

Metastatic renal cell carcinoma is highly refractory to chemotherapy. Cytokine therapy with IL-2 or IFN-α produces regressions in 10–20% of patients. IL-2 produces durable complete remission in a small proportion of cases. In general, cytokine therapy is considered unsatisfactory for most patients.

The situation changed dramatically when two large-scale randomized trials established a role for antiangiogenic therapy in this disease, as predicted by the genetic studies. These trials separately evaluated two orally administered antiangiogenic agents, sorafenib and sunitinib, that inhibited receptor tyrosine kinase signaling through the VEGF and PDGF receptors. Both showed efficacy as second-line treatment following progression during cytokine treatment, resulting in approval by regulatory authorities for the treatment of advanced renal cell carcinoma. A randomized phase 3 trial comparing sunitinib to IFN-α showed superior efficacy for sunitinib with an acceptable safety profile. The trial resulted in a change in the standard first-line treatment from IFN to sunitinib. Sunitinib is usually given orally at a dose of 50 mg/d for 4 weeks out of 6. Diarrhea is the main toxicity. Sorafenib is usually given orally at a dose of 400 mg bid. In addition to diarrhea, toxicities include rash, fatigue, and hand-foot syndrome. Temsirolimus and everolimus, inhibitors of the mammalian target of rapamycin (mTOR), show activity in patients with untreated poor-prognosis tumors and in sunitinib/sorafenib refractory tumors.

The prognosis of metastatic renal cell carcinoma is variable. In one analysis, no prior nephrectomy, a KPS <80, low hemoglobin, high corrected calcium, and abnormal lactate dehydrogenase were poor prognostic factors. Patients with zero, one or two, and three or more factors had a median survival of 24, 12, and 5 months, respectively. These tumors may follow an unpredictable and protracted clinical course. It may be best to document progression before considering systemic treatment.

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APPENDIX

LABORATORY VALUES OF CLINICAL IMPORTANCE

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This Appendix contains tables of reference values for laboratory tests, special analytes, and special function tests. A variety of factors can influence reference values. Such variables include the population studied, the duration and means of specimen transport, laboratory methods and instrumentation, and even the type of container used for the collection of the specimen. The reference or "normal" ranges given in this appendix may therefore not be appropriate for all laboratories, and these values should only be used as general guidelines. Whenever possible, reference values provided by the laboratory performing the testing should be utilized in the interpretation of laboratory data. Values supplied in this Appendix reflect typical reference ranges in adults. Pediatric reference ranges may vary significantly from adult values.

In preparing the Appendix, the authors have taken into account the fact that the system of international units (SI, système international d'unités) is used in most countries and in some medical journals. However, clinical laboratories may continue to report values in "traditional" or conventional units. Therefore, both systems are provided in the Appendix. The dual system is also used in the text except for (1) those instances in which the numbers remain the same but only the terminology is changed (mmol/L for meq/L or IU/L for mIU/mL), when only the SI units are given; and (2) most pressure measurements (e.g., blood and cerebrospinal fluid pressures), when the traditional units (mmHg, mmH_2O) are used. In all other instances in the text the SI unit is followed by the traditional unit in parentheses.

REFERENCE VALUES FOR LABORATORY TESTS

TABLE 1

HEMATOLOGY AND COAGULATION

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Activated clotting time	WB	70–180 s	70–180 s
Activated protein C resistance (factor V Leiden)	P	Not applicable	Ratio >2.1
ADAMTS13 activity	P	≥0.67	≥67%
ADAMTS13 inhibitor activity	P	Not applicable	≤0.4 U
ADAMTS13 antibody	P	Not applicable	≤18 U
$Alpha_2$ antiplasmin	P	0.87–1.55	87–155%
Antiphospholipid antibody panel			
PTT-LA (lupus anticoagulant screen)	P	Negative	Negative
Platelet neutralization procedure	P	Negative	Negative
Dilute viper venom screen	P	Negative	Negative
Anticardiolipin antibody	S		
IgG		0–15 arbitrary units	0–15 GPL
IgM		0–15 arbitrary units	0–15 MPL

(*continued*)

TABLE 1

HEMATOLOGY AND COAGULATION (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Antithrombin III	P		
Antigenic		220–390 mg/L	22–39 mg/dL
Functional		0.7–1.30 U/L	70–130%
Anti-Xa assay (heparin assay)	P		
Unfractionated heparin		0.3–0.7 kIU/L	0.3–0.7 IU/mL
Low-molecular-weight heparin		0.5–1.0 kIU/L	0.5–1.0 IU/mL
Danaparoid (Orgaran)		0.5–0.8 kIU/L	0.5–0.8 IU/mL
Autohemolysis test	WB	0.004–0.045	0.4–4.50%
Autohemolysis test with glucose	WB	0.003–0.007	0.3–0.7%
Bleeding time (adult)		<7.1 min	<7.1 min
Bone marrow			
Clot retraction	WB	0.50–1.00/2 h	50–100%/2 h
Cryofibrinogen	P	Negative	Negative
D-dimer	P	220–740 ng/mL FEU	220–740 ng/mL FEU
Differential blood count	WB		
Relative counts:			
Neutrophils		0.40–0.70	40–70%
Bands		0.0–0.05	0–5%
Lymphocytes		0.20–0.50	20–50%
Monocytes		0.04–0.08	4–8%
Eosinophils		0.0–0.6	0–6%
Basophils		0.0–0.02	0–2%
Absolute counts:			
Neutrophils		$1.42–6.34 \times 10^9$/L	1420–6340/mm^3
Bands		$0–0.45 \times 10^9$/L	0–450/mm^3
Lymphocytes		$0.71–4.53 \times 10^9$/L	710–4530/mm^3
Monocytes		$0.14–0.72 \times 10^9$/L	140–720/mm^3
Eosinophils		$0–0.54 \times 10^9$/L	0–540/mm^3
Basophils		$0–0.18 \times 10^9$/L	0–180/mm^3
Erythrocyte count	WB		
Adult males		$4.30–5.60 \times 10^{12}$/L	$4.30–5.60 \times 10^6$/mm^3
Adult females		$4.00–5.20 \times 10^{12}$/L	$4.00–5.20 \times 10^6$/mm^3
Erythrocyte life span	WB		
Normal survival		120 days	120 days
Chromium labeled, half-life ($t_{1/2}$)		25–35 days	25–35 days
Erythrocyte sedimentation rate	WB		
Females		0–20 mm/h	0–20 mm/h
Males		0–15 mm/h	0–15 mm/h
Euglobulin lysis time	P	7200–14,400 s	120–240 min
Factor II, prothrombin	P	0.50–1.50	50–150%
Factor V	P	0.50–1.50	50–150%
Factor VII	P	0.50–1.50	50–150%
Factor VIII	P	0.50–1.50	50–150%
Factor IX	P	0.50–1.50	50–150%
Factor X	P	0.50–1.50	50–150%
Factor XI	P	0.50–1.50	50–150%
Factor XII	P	0.50–1.50	50–150%
Factor XIII screen	P	Not applicable	Present
Factor inhibitor assay	P	<0.5 Bethesda Units	<0.5 Bethesda Units
Fibrin(ogen) degradation products	P	0–1 mg/L	0–1 μg/mL
Fibrinogen	P	2.33–4.96 g/L	233–496 mg/dL
Glucose-6-phosphate dehydrogenase (erythrocyte)	WB	<2400 s	<40 min
Ham's test (acid serum)	WB	Negative	Negative

(*continued*)

TABLE 1

HEMATOLOGY AND COAGULATION (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Hematocrit	WB		
Adult males		0.388–0.464	38.8–46.4
Adult females		0.354–0.444	35.4–44.4
Hemoglobin			
Plasma	P	6–50 mg/L	0.6–5.0 mg/dL
Whole blood:	WB		
Adult males		133–162 g/L	13.3–16.2 g/dL
Adult females		120–158 g/L	12.0–15.8 g/dL
Hemoglobin electrophoresis	WB		
Hemoglobin A		0.95–0.98	95–98%
Hemoglobin A_2		0.015–0.031	1.5–3.1%
Hemoglobin F		0–0.02	0–2.0%
Hemoglobins other than A, A_2, or F		Absent	Absent
Heparin-induced thrombocytopenia antibody	P	Negative	Negative
Immature platelet fraction (IPF)	WB	0.011–0.061	1.1–6.1%
Joint fluid crystal	JF	Not applicable	No crystals seen
Joint fluid mucin	JF	Not applicable	Only type I mucin present
Leukocytes			
Alkaline phosphatase (LAP)	WB	0.2–1.6 μkat/L	13–100 μ/L
Count (WBC)	WB	3.54–9.06 × 10^9/L	3.54–9.06 × 10^3/mm^3
Mean corpuscular hemoglobin (MCH)	WB	26.7–31.9 pg/cell	26.7–31.9 pg/cell
Mean corpuscular hemoglobin concentration (MCHC)	WB	323–359 g/L	32.3–35.9 g/dL
Mean corpuscular hemoglobin of reticulocytes (CH)	WB	24–36 pg	24–36 pg
Mean corpuscular volume (MCV)	WB	79–93.3 fL	79–93.3 μm^3
Mean platelet volume (MPV)	WB	9.00–12.95 fL	9.00–12.95
Osmotic fragility of erythrocytes	WB		
Direct		0.0035–0.0045	0.35–0.45%
Indirect		0.0030–0.0065	0.30–0.65%
Partial thromboplastin time, activated	P	26.3–39.4 s	26.3–39.4 s
Plasminogen	P		
Antigen		84–140 mg/L	8.4–14.0 mg/dL
Functional		0.70–1.30	70–130%
Plasminogen activator inhibitor 1	P	4–43 μg/L	4–43 ng/mL
Platelet aggregation	PRP	Not applicable	>65% aggregation in response to adenosine diphosphate, epinephrine, collagen, ristocetin, and arachidonic acid
Platelet count	WB	165–415 × 10^9/L	165–415 × 10^3/mm^3
Platelet, mean volume	WB	6.4–11 fL	6.4–11.0 μm^3
Prekallikrein assay	P	0.50–1.5	50–150%
Prekallikrein screen	P		No deficiency detected
Protein C	P		
Total antigen		0.70–1.40	70–140%
Functional		0.70–1.30	70–130%
Protein S	P		
Total antigen		0.70–1.40	70–140%
Functional		0.65–1.40	65–140%
Free antigen P		0.70–1.40	70–140%
Prothrombin gene mutation G20210A	WB	Not applicable	Not present
Prothrombin time	P	12.7–15.4 s	12.7–15.4 s

(*continued*)

TABLE 1

HEMATOLOGY AND COAGULATION (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Protoporphyrin, free erythrocyte	WB	0.28–0.64 μmol/L of red blood cells	16–36 μg/dL of red blood cells
Red cell distribution width	WB	<0.145	<14.5%
Reptilase time	P	16–23.6 s	16–23.6 s
Reticulocyte count	WB		
Adult males		0.008–0.023 red cells	0.8–2.3% red cells
Adult females		0.008–0.020 red cells	0.8–2.0% red cells
Reticulocyte hemoglobin content	WB	>26 pg/cell	>26 pg/cell
Ristocetin cofactor (functional von Willebrand factor)	P		
Blood group O		0.75 mean of normal	75% mean of normal
Blood group A		1.05 mean of normal	105% mean of normal
Blood group B		1.15 mean of normal	115% mean of normal
Blood group AB		1.25 mean of normal	125% mean of normal
Serotonin release assay	S	<0.2 release	<20% release
Sickle cell test	WB	Negative	Negative
Sucrose hemolysis	WB	<0.1	<10% hemolysis
Thrombin time	P	15.3–18.5 s	15.3–18.5 s
Total eosinophils	WB	150–300 × 10^6/L	150–300/mm^3
Transferrin receptor	S, P	9.6–29.6 nmol/L	9.6–29.6 nmol/L
Viscosity			
Plasma	P	1.7–2.1	1.7–2.1
Serum	S	1.4–1.8	1.4–1.8
von Willebrand factor (vWF) antigen (factor VIII:R antigen)			
Blood group O		0.75 mean of normal	75% mean of normal
Blood group A		1.05 mean of normal	105% mean of normal
Blood group B		1.15 mean of normal	115% mean of normal
Blood group AB		1.25 mean of normal	125% mean of normal
von Willebrand factor multimers	P	Normal distribution	Normal distribution
White blood cells: see “Leukocytes”			

Abbreviations: JF, joint fluid; P, plasma; PRP, platelet-rich plasma; S, serum; WB, whole blood.

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Acetoacetate	P	49–294 μmol/L	0.5–3.0 mg/dL
Adrenocorticotropin (ACTH)	P	1.3–16.7 pmol/L	6.0–76.0 pg/mL
Alanine aminotransferase (ALT, SGPT)	S	0.12–0.70 μkat/L	7–41 U/L
Albumin	S	40–50 g/L	4.0–5.0 mg/dL
Aldolase	S	26–138 nkat/L	1.5–8.1 U/L
Aldosterone (adult)			
Supine, normal sodium diet	S, P	<443 pmol/L	<16 ng/dL
Upright, normal	S, P	111–858 pmol/L	4–31 ng/dL
Alpha fetoprotein (adult)	S	0–8.5 μg/L	0–8.5 ng/mL
$Alpha_1$ antitrypsin	S	1.0–2.0 g/L	100–200 mg/dL
Ammonia, as NH_3	P	11–35 μmol/L	19–60 μg/dL
Amylase (method dependent)	S	0.34–1.6 μkat/L	20–96 U/L

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Androstendione (adult)	S		
Males		0.81–3.1 nmol/L	23–89 ng/dL
Females			
Premenopausal		0.91–7.5 nmol/L	26–214 ng/dL
Postmenopausal		0.46–2.9 nmol/L	13–82 ng/dL
Angiotensin-converting enzyme (ACE)	S	0.15–1.1 µkat/L	9–67 U/L
Anion gap	S	7–16 mmol/L	7–16 mmol/L
Apolipoprotein A-1	S		
Male		0.94–1.78 g/L	94–178 mg/dL
Female		1.01–1.99 g/L	101–199 mg/dL
Apolipoprotein B	S		
Male		0.55–1.40 g/L	55–140 mg/dL
Female		0.55–1.25 g/L	55–125 mg/dL
Arterial blood gases	WB		
$[HCO_3^-]$		22–30 mmol/L	22–30 meq/L
PCO_2		4.3–6.0 kPa	32–45 mmHg
pH		7.35–7.45	7.35–7.45
Po_2		9.6–13.8 kPa	72–104 mmHg
Aspartate aminotransferase (AST, SGOT)	S	0.20–0.65 µkat/L	12–38 U/L
Autoantibodies	S		
Anti-centromere antibody IgG		≤29 AU/mL	≤29 AU/mL
Anti-double-strand (native) DNA		<25 IU/L	<25 IU/L
Anti-glomerular basement membrane antibodies			
Qualitative IgG, IgA		Negative	Negative
Quantitative IgG antibody		≤19 AU/mL	≤19 AU/mL
Anti-histone antibodies		<1.0 U	<1.0 U
Anti-Jo-1 antibody		≤29 AU/mL	≤29 AU/mL
Anti-mitochondrial antibody		Not applicable	<20 Units
Anti-neutrophil cytoplasmic autoantibodies		Not applicable	<1:20
Serine proteinase 3 antibodies		≤19 AU/mL	≤19 AU/mL
Myeloperoxidase antibodies		≤19 AU/mL	≤19 AU/mL
Antinuclear antibody		Not applicable	Negative at 1:40
Anti-parietal cell antibody		Not applicable	None detected
Anti-RNP antibody		Not applicable	<1.0 U
Anti-Scl 70 antibody		Not applicable	<1.0 U
Anti-Smith antibody		Not applicable	<1.0 U
Anti–smooth muscle antibody		Not applicable	<1.0 U
Anti-SSA antibody		Not applicable	<1.0 U
Anti-SSB antibody		Not applicable	Negative
Anti-thyroglobulin antibody		<40 KIU/L	<40 IU/mL
Anti-thyroid peroxidase antibody		<35 KIU/L	<35 IU/mL
B-type natriuretic peptide (BNP)	P	Age and gender specific: <100 ng/L	Age and gender specific: <100 pg/mL
Bence Jones protein, serum qualitative	S	Not applicable	None detected
Bence Jones protein, serum quantitative	S		
Free kappa		3.3–19.4 mg/L	0.33–1.94 mg/dL
Free lambda		5.7–26.3 mg/L	0.57–2.63 mg/dL
K/L ratio		0.26–1.65	0.26–1.65
Beta-2-microglobulin	S	1.1–2.4 mg/L	1.1–2.4 mg/L
Bilirubin	S		
Total		5.1–22 µmol/L	0.3–1.3 mg/dL
Direct		1.7–6.8 µmol/L	0.1–0.4 mg/dL
Indirect		3.4–15.2 µmol/L	0.2–0.9 mg/dL

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
C peptide	S	0.27–1.19 nmol/L	0.8–3.5 ng/mL
C1-esterase-inhibitor protein	S	210–390 mg/L	21–39 mg/dL
CA 125	S	<35 kU/L	<35 U/mL
CA 19-9	S	<37 kU/L	<37 U/mL
CA 15-3	S	<33 kU/L	<33 U/mL
CA 27-29	S	0–40 kU/L	0–40 U/mL
Calcitonin	S		
Male		0–7.5 ng/L	0–7.5 pg/mL
Female		0–5.1 ng/L	0–5.1 pg/mL
Calcium	S	2.2–2.6 mmol/L	8.7–10.2 mg/dL
Calcium, ionized	WB	1.12–1.32 mmol/L	4.5–5.3 mg/dL
Carbon dioxide content (TCO_2)	P (sea level)	22–30 mmol/L	22–30 meq/L
Carboxyhemoglobin (carbon monoxide content)	WB		
Nonsmokers		0.0–0.015	0–1.5%
Smokers		0.04–0.09	4–9%
Loss of consciousness and death		>0.50	>50%
Carcinoembryonic antigen (CEA)	S		
Nonsmokers		0.0–3.0 µg/L	0.0–3.0 ng/mL
Smokers		0.0–5.0 µg/L	0.0–5.0 ng/mL
Ceruloplasmin	S	250–630 mg/L	25–63 mg/dL
Chloride	S	102–109 mmol/L	102–109 meq/L
Cholesterol: see Table 5			
Cholinesterase	S	5–12 kU/L	5–12 U/mL
Chromogranin A	S	0–50 µg/L	0–50 ng/mL
Complement	S		
C3		0.83–1.77 g/L	83–177 mg/dL
C4		0.16–0.47 g/L	16–47 mg/dL
Complement total		60–144 CAE units	60–144 CAE units
Cortisol			
Fasting, 8 A.M.–12 noon	S	138–690 nmol/L	5–25 µg/dL
12 noon–8 P.M.		138–414 nmol/L	5–15 µg/dL
8 P.M.–8 A.M.		0–276 nmol/L	0–10 µg/dL
C-reactive protein	S	<10 mg/L	<10 mg/L
C-reactive protein, high sensitivity	S	Cardiac risk Low: <1.0 mg/L Average: 1.0–3.0 mg/L High: >3.0 mg/L	Cardiac risk Low: <1.0 mg/L Average: 1.0–3.0 mg/L High: >3.0 mg/L
Creatine kinase (total)	S		
Females		0.66–4.0 µkat/L	39–238 U/L
Males		0.87–5.0 µkat/L	51–294 U/L
Creatine kinase-MB	S		
Mass		0.0–5.5 µg/L	0.0–5.5 ng/mL
Fraction of total activity (by electrophoresis)		0–0.04	0–4.0%
Creatinine	S		
Female		44–80 µmol/L	0.5–0.9 mg/dL
Male		53–106 µmol/L	0.6–1.2 mg/dL
Cryoglobulins	S	Not applicable	None detected
Cystatin C	S	0.5–1.0 mg/L	0.5–1.0 mg/L

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Dehydroepiandrosterone (DHEA) (adult)	S		
Male		6.2–43.4 nmol/L	180–1250 ng/dL
Female		4.5–34.0 nmol/L	130–980 ng/dL
Dehydroepiandrosterone (DHEA) sulfate	S		
Male (adult)		100–6190 µg/L	10–619 µg/dL
Female (adult, premenopausal)		120–5350 µg/L	12–535 µg/dL
Female (adult, postmenopausal)		300–2600 µg/L	30–260 µg/dL
11-Deoxycortisol (adult) (compound S)	S	0.34–4.56 nmol/L	12–158 ng/dL
Dihydrotestosterone	S, P		
Male		1.03–2.92 nmol/L	30–85 ng/dL
Female		0.14–0.76 nmol/L	4–22 ng/dL
Dopamine	P	0–130 pmol/L	0–20 pg/mL
Epinephrine	P		
Supine (30 min)		<273 pmol/L	<50 pg/mL
Sitting		<328 pmol/L	<60 pg/mL
Standing (30 min)		<491 pmol/L	<90 pg/mL
Erythropoietin	S	4–27 U/L	4–27 U/L
Estradiol	S, P		
Female			
Menstruating:			
Follicular phase		74–532 pmol/L	<20–145 pg/mL
Midcycle peak		411–1626 pmol/L	112–443 pg/mL
Luteal phase		74–885 pmol/L	<20–241 pg/mL
Postmenopausal		217 pmol/L	<59 pg/mL
Male		74 pmol/L	<20 pg/mL
Estrone	S, P		
Female			
Menstruating:			
Follicular phase		<555 pmol/L	<150 pg/mL
Luteal phase		<740 pmol/L	<200 pg/mL
Postmenopausal		11–118 pmol/L	3–32 pg/mL
Male		33–133 pmol/L	9–36 pg/mL
Fatty acids, free (nonesterified)	P	0.1–0.6 mmol/L	2.8–16.8 mg/dL
Ferritin	S		
Female		10–150 µg/L	10–150 ng/mL
Male		29–248 µg/L	29–248 ng/mL
Follicle-stimulating hormone (FSH)	S, P		
Female			
Menstruating			
Follicular phase		3.0–20.0 IU/L	3.0–20.0 mIU/mL
Ovulatory phase		9.0–26.0 IU/L	9.0–26.0 mIU/mL
Luteal phase		1.0–12.0 IU/L	1.0–12.0 mIU/mL
Postmenopausal		18.0–153.0 IU/L	18.0–153.0 mIU/mL
Male		1.0–12.0 IU/L	1.0–12.0 mIU/mL
Fructosamine	S	<285 umol/L	<285 umol/L
Gamma glutamyltransferase	S	0.15–0.99 µkat/L	9–58 U/L
Gastrin	S	<100 ng/L	<100 pg/mL
Glucagon	P	40–130 ng/L	40–130 pg/mL

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Glucose	WB	3.6–5.3 mmol/L	65–95 mg/dL
Glucose (fasting)	P		
Normal		4.2–5.6 mmol/L	75–100 mg/dL
Increased risk for diabetes		5.6–6.9 mmol/L	100–125 mg/dL
Diabetes mellitus		Fasting >7.0 mmol/L A 2-hour level of >11.1 mmol/L during an oral glucose tolerance test A random glucose level of ≥11.1 mmol/L in patients with symptoms of hyperglycemia	Fasting >126 mg/dL A 2-hour level of ≥200 mg/dL during an oral glucose tolerance test A random glucose level of ≥200 mg/dL in patients with symptoms of hyperglycemia
Growth hormone	S	0–5 µg/L	0–5 ng/mL
Hemoglobin A_{lc}	WB	0.04–0.06 HgB fraction	4.0–5.6%
Pre-diabetes		0.057–0.064 HgB fraction	5.7–6.4%
Diabetes mellitus		A hemoglobin A_{1c} level of ≥0.065 Hgb fraction as suggested by the American Diabetes Association	A hemoglobin A_{1c} level of ≥6.5% as suggested by the American Diabetes Association
Hemoglobin A_{1c} with estimated average glucose (eAg)	WB	eAg mmoL/L = 1.59 × HbA_{1c} – 2.59	eAg (mg/dL) = 28.7 × HbA_{1c} – 46.7
High-density lipoprotein (HDL) (see Table 5)			
Homocysteine	P	4.4–10.8 µmol/L	4.4–10.8 µmol/L
Human chorionic gonadotropin (HCG)	S		
Nonpregnant female		<5 IU/L	<5 mIU/mL
1–2 weeks postconception		9–130 IU/L	9–130 mIU/mL
2–3 weeks postconception		75–2600 IU/L	75–2600 mIU/mL
3–4 weeks postconception		850–20,800 IU/L	850–20,800 mIU/mL
4–5 weeks postconception		4000–100,200 IU/L	4000–100,200 mIU/mL
5–10 weeks postconception		11,500–289,000 IU/L	11,500–289,000 mIU/mL
10–14 weeks postconception		18,300–137,000 IU/L	18,300–137,000 mIU/mL
Second trimester		1400–53,000 IU/L	1400–53,000 mIU/mL
Third trimester		940–60,000 IU/L	940–60,000 mIU/mL
β-Hydroxybutyrate	P	60–170 µmol/L	0.6–1.8 mg/dL
17-Hydroxyprogesterone (adult)	S		
Male		<4.17 nmol/L	<139 ng/dL
Female			
Follicular phase		0.45–2.1 nmol/L	15–70 ng/dL
Luteal phase		1.05–8.7 nmol/L	35–290 ng/dL
Immunofixation	S	Not applicable	No bands detected
Immunoglobulin, quantitation (adult)			
IgA	S	0.70–3.50 g/L	70–350 mg/dL
IgD	S	0–140 mg/L	0–14 mg/dL
IgE	S	1–87 KIU/L	1–87 IU/mL
IgG	S	7.0–17.0 g/L	700–1700 mg/dL
IgG_1	S	2.7–17.4 g/L	270–1740 mg/dL
IgG_2	S	0.3–6.3 g/L	30–630 mg/dL
IgG_3	S	0.13–3.2 g/L	13–320 mg/dL
IgG_4	S	0.11–6.2 g/L	11–620 mg/dL
IgM	S	0.50–3.0 g/L	50–300 mg/dL
Insulin	S, P	14.35–143.5 pmol/L	2–20 µU/mL
Iron	S	7–25 µmol/L	41–141 µg/dL

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Iron-binding capacity	S	45–73 µmol/L	251–406 µg/dL
Iron-binding capacity saturation	S	0.16–0.35	16–35%
Ischemia modified albumin	S	<85 KU/L	<85 U/mL
Joint fluid crystal	JF	Not applicable	No crystals seen
Joint fluid mucin	JF	Not applicable	Only type I mucin present
Ketone (acetone)	S	Negative	Negative
Lactate	P, arterial P, venous	0.5–1.6 mmol/L 0.5–2.2 mmol/L	4.5–14.4 mg/dL 4.5–19.8 mg/dL
Lactate dehydrogenase	S	2.0–3.8 µkat/L	115–221 U/L
Lipase	S	0.51–0.73 µkat/L	3–43 U/L
Lipids: see Table 5			
Lipoprotein (a)	S	0–300 mg/L	0–30 mg/dL
Low-density lipoprotein (LDL) (see Table 5)			
Luteinizing hormone (LH) Female Menstruating Follicular phase Ovulatory phase Luteal phase Postmenopausal Male	S, P 	 2.0–15.0 U/L 22.0–105.0 U/L 0.6–19.0 U/L 16.0–64.0 U/L 2.0–12.0 U/L	 2.0–15.0 mIU/mL 22.0–105.0 mIU/mL 0.6–19.0 mIU/mL 16.0–64.0 mIU/mL 2.0–12.0 mIU/mL
Magnesium	S	0.62–0.95 mmol/L	1.5–2.3 mg/dL
Metanephrine	P	<0.5 nmol/L	<100 pg/mL
Methemoglobin	WB	0.0–0.01	0–1%
Myoglobin Male Female	S 	 20–71 µg/L 25–58 µg/L	 20–71 µg/L 25–58 µg/L
Norepinephrine Supine (30 min) Sitting Standing (30 min)	P 	 650–2423 pmol/L 709–4019 pmol/L 739–4137 pmol/L	 110–410 pg/mL 120–680 pg/mL 125–700 pg/mL
N-telopeptide (cross-linked), NTx Female, premenopausal Male BCE = bone collagen equivalent	S 	 6.2–19.0 nmol BCE 5.4–24.2 nmol BCE	 6.2–19.0 nmol BCE 5.4–24.2 nmol BCE
NT-Pro BNP	S, P	<125 ng/L up to 75 years <450 ng/L >75 years	<125 pg/mL up to 75 years <450 pg/mL >75 years
5′ Nucleotidase	S	0.00–0.19 µkat/L	0–11 U/L
Osmolality	P	275–295 mosmol/kg serum water	275–295 mosmol/kg serum water
Osteocalcin	S	11–50 µg/L	11–50 ng/mL
Oxygen content Arterial (sea level) Venous (sea level)	WB 	 17–21 10–16	 17–21 vol% 10–16 vol%
Oxygen saturation (sea level) Arterial Venous, arm	WB 	Fraction: 0.94–1.0 0.60–0.85	Percent: 94–100% 60–85%
Parathyroid hormone (intact)	S	8–51 ng/L	8–51 pg/mL

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Phosphatase, alkaline	S	0.56–1.63 μkat/L	33–96 U/L
Phosphorus, inorganic	S	0.81–1.4 mmol/L	2.5–4.3 mg/dL
Potassium	S	3.5–5.0 mmol/L	3.5–5.0 meq/L
Prealbumin	S	170–340 mg/L	17–34 mg/dL
Procalcitonin	S	<0.1 μg/L	<0.1 ng/mL
Progesterone	S, P		
Female: Follicular		<3.18 nmol/L	<1.0 ng/mL
Midluteal		9.54–63.6 nmol/L	3–20 ng/mL
Male		<3.18 nmol/L	<1.0 ng/mL
Prolactin	S		
Male		53–360 mg/L	2.5–17 ng/mL
Female		40–530 mg/L	1.9–25 ng/mL
Prostate-specific antigen (PSA)	S	0.0–4.0 μg/L	0.0–4.0 ng/mL
Prostate-specific antigen, free	S	With total PSA between 4 and 10 μg/L and when the free PSA is: >0.25 decreased risk of prostate cancer <0.10 increased risk of prostate cancer	With total PSA between 4 and 10 ng/mL and when the free PSA is: >25% decreased risk of prostate cancer <10% increased risk of prostate cancer
Protein fractions:	S		
Albumin		35–55 g/L	3.5–5.5 g/dL (50–60%)
Globulin		20–35 g/L	2.0–3.5 g/dL (40–50%)
$Alpha_1$		2–4 g/L	0.2–0.4 g/dL (4.2–7.2%)
$Alpha_2$		5–9 g/L	0.5–0.9 g/dL (6.8–12%)
Beta		6–11 g/L	0.6–1.1 g/dL (9.3–15%)
Gamma		7–17 g/L	0.7–1.7 g/dL (13–23%)
Protein, total	S	67–86 g/L	6.7–8.6 g/dL
Pyruvate	P	40–130 μmol/L	0.35–1.14 mg/dL
Rheumatoid factor	S	<15 kIU/L	<15 IU/mL
Serotonin	WB	0.28–1.14 umol/L	50–200 ng/mL
Serum protein electrophoresis	S	Not applicable	Normal pattern
Sex hormone–binding globulin (adult)	S		
Male		11–80 nmol/L	11–80 nmol/L
Female		30–135 nmol/L	30–135 nmol/L
Sodium	S	136–146 mmol/L	136–146 meq/L
Somatomedin-C (IGF-1) (adult)	S		
16 years		226–903 μg/L	226–903 ng/mL
17 years		193–731 μg/L	193–731 ng/mL
18 years		163–584 μg/L	163–584 ng/mL
19 years		141–483 μg/L	141–483 ng/mL
20 years		127–424 μg/L	127–424 ng/mL
21–25 years		116–358 μg/L	116–358 ng/mL
26–30 years		117–329 μg/L	117–329 ng/mL
31–35 years		115–307 μg/L	115–307 ng/mL
36–40 years		119–204 μg/L	119–204 ng/mL
41–45 years		101–267 μg/L	101–267 ng/mL
46–50 years		94–252 μg/L	94–252 ng/mL
51–55 years		87–238 μg/L	87–238 ng/mL
56–60 years		81–225 μg/L	81–225 ng/mL
61–65 years		75–212 μg/L	75–212 ng/mL

(*continued*)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (*CONTINUED*)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
66–70 years		69–200 µg/L	69–200 ng/mL
71–75 years		64–188 µg/L	64–188 ng/mL
76–80 years		59–177 µg/L	59–177 ng/mL
81–85 years		55–166 µg/L	55–166 ng/mL
Somatostatin	P	<25 ng/L	<25 pg/mL
Testosterone, free	S		
Female, adult		10.4–65.9 pmol/L	3–19 pg/mL
Male, adult		312–1041 pmol/L	90–300 pg/mL
Testosterone, total,	S		
Female		0.21–2.98 nmol/L	6–86 ng/dL
Male		9.36–37.10 nmol/L	270–1070 ng/dL
Thyroglobulin	S	1.3–31.8 µg/L	1.3–31.8 ng/mL
Thyroid-binding globulin	S	13–30 mg/L	1.3–3.0 mg/dL
Thyroid-stimulating hormone	S	0.34–4.25 mIU/L	0.34–4.25 µIU/mL
Thyroxine, free (fT4)	S	9.0–16 pmol/L	0.7–1.24 ng/dL
Thyroxine, total (T4)	S	70–151 nmol/L	5.4–11.7 µg/dL
Thyroxine index (free)	S	6.7–10.9	6.7–10.9
Transferrin	S	2.0–4.0 g/L	200–400 mg/dL
Triglycerides (see Table 5)	S	0.34–2.26 mmol/L	30–200 mg/dL
Triiodothyronine, free (fT3)	S	3.7–6.5 pmol/L	2.4–4.2 pg/mL
Triiodothyronine, total (T3)	S	1.2–2.1 nmol/L	77–135 ng/dL
Troponin I (method dependent)	S, P		
99th percentile of a healthy population		0–0.04 µg/L	0–0.04 ng/mL
Troponin T	S, P		
99th percentile of a healthy population		0–0.01 µg/L	0–0.01 ng/mL
Urea nitrogen	S	2.5–7.1 mmol/L	7–20 mg/dL
Uric acid	S		
Females		0.15–0.33 mmol/L	2.5–5.6 mg/dL
Males		0.18–0.41 mmol/L	3.1–7.0 mg/dL
Vasoactive intestinal polypeptide	P	0–60 ng/L	0–60 pg/mL
Zinc protoporphyrin	WB	0–400 µg/L	0–40 µg/dL
Zinc protoporphyrin (ZPP)-to-heme ratio	WB	0–69 µmol ZPP/mol heme	0–69 µmol ZPP/mol heme

Abbreviations: P, plasma; S, serum; WB, whole blood.

TABLE 3

TOXICOLOGY AND THERAPEUTIC DRUG MONITORING

	THERAPEUTIC RANGE		TOXIC LEVEL	
DRUG	**SI UNITS**	**CONVENTIONAL UNITS**	**SI UNITS**	**CONVENTIONAL UNITS**
Acetaminophen	66–199 µmol/L	10–30 µg/mL	>1320 µmol/L	>200 µg/mL
Amikacin				
Peak	34–51 µmol/L	20–30 µg/mL	>60 µmol/L	>35 µg/mL
Trough	0–17 µmol/L	0–10 µg/mL	>17 µmol/L	>10 µg/mL
Amitriptyline/nortriptyline (total drug)	430–900 nmol/L	120–250 ng/mL	>1800 nmol/L	>500 ng/mL
Amphetamine	150–220 nmol/L	20–30 ng/mL	>1500 nmol/L	>200 ng/mL
Bromide	9.4–18.7 mmol/L	75–150 mg/dL	>18.8 mmol/L	>150 mg/dL
Mild toxicity			6.4–18.8 mmol/L	51–150 mg/dL
Severe toxicity			>18.8 mmol/L	>150 mg/dL
Lethal			>37.5 mmol/L	>300 mg/dL
Caffeine	25.8–103 µmol/L	5–20 µg/mL	>206 µmol/L	>40 µg/mL
Carbamazepine	17–42 µmol/L	4–10 µg/mL	>85 µmol/L	>20 µg/mL
Chloramphenicol				
Peak	31–62 µmol/L	10–20 µg/mL	>77 µmol/L	>25 µg/mL
Trough	15–31 µmol/L	5–10 µg/mL	>46 µmol/L	>15 µg/mL
Chlordiazepoxide	1.7–10 µmol/L	0.5–3.0 µg/mL	>17 µmol/L	>5.0 µg/mL
Clonazepam	32–240 nmol/L	10–75 ng/mL	>320 nmol/L	>100 ng/mL
Clozapine	0.6–2.1 µmol/L	200–700 ng/mL	>3.7 µmol/L	>1200 ng/mL
Cocaine			>3.3 µmol/L	>1.0 µg/mL
Codeine	43–110 nmol/mL	13–33 ng/mL	>3700 nmol/mL	>1100 ng/mL (lethal)
Cyclosporine				
Renal transplant				
0–6 months	208–312 nmol/L	250–375 ng/mL	>312 nmol/L	>375 ng/mL
6–12 months after transplant	166–250 nmol/L	200–300 ng/mL	>250 nmol/L	>300 ng/mL
>12 months	83–125 nmol/L	100–150 ng/mL	>125 nmol/L	>150 ng/mL
Cardiac transplant				
0–6 months	208–291 nmol/L	250–350 ng/mL	>291 nmol/L	>350 ng/mL
6–12 months after transplant	125–208 nmol/L	150–250 ng/mL	>208 nmol/L	>250 ng/mL
>12 months	83–125 nmol/L	100–150 ng/mL	>125 nmol/L	150 ng/mL
Lung transplant				
0–6 months	250–374 nmol/L	300–450 ng/mL	>374 nmol/L	>450 ng/mL
Liver transplant				
Initiation	208–291 nmol/L	250–350 ng/mL	>291 nmol/L	>350 ng/mL
Maintenance	83–166 nmol/L	100–200 ng/mL	>166 nmol/L	>200 ng/mL
Desipramine	375–1130 nmol/L	100–300 ng/mL	>1880 nmol/L	>500 ng/mL
Diazepam (and metabolite)				
Diazepam	0.7–3.5 µmol/L	0.2–1.0 µg/mL	>7.0 µmol/L	>2.0 µg/mL
Nordiazepam	0.4–6.6 µmol/L	0.1–1.8 µg/mL	>9.2 µmol/L	>2.5 µg/mL
Digoxin	0.64–2.6 nmol/L	0.5–2.0 ng/mL	>5.0 nmol/L	>3.9 ng/mL
Disopyramide	5.3–14.7 µmol/L	2–5 µg/mL	>20.6 µmol/L	>7 µg/mL
Doxepin and nordoxepin				
Doxepin	0.36–0.98 µmol/L	101–274 ng/mL	>1.8 µmol/L	>503 ng/mL
Nordoxepin	0.38–1.04 µmol/L	106–291 ng/mL	>1.9 µmol/L	>531 ng/mL
Ethanol				
Behavioral changes			>4.3 mmol/L	>20 mg/dL
Legal limit			≥17 mmol/L	≥80 mg/dL
Critical with acute exposure			>54 mmol/L	>250 mg/dL
Ethylene glycol				
Toxic			>2 mmol/L	>12 mg/dL
Lethal			>20 mmol/L	>120 mg/dL

(*continued*)

TABLE 3

TOXICOLOGY AND THERAPEUTIC DRUG MONITORING (*CONTINUED*)

	THERAPEUTIC RANGE		TOXIC LEVEL	
DRUG	**SI UNITS**	**CONVENTIONAL UNITS**	**SI UNITS**	**CONVENTIONAL UNITS**
Ethosuximide	280–700 µmol/L	40–100 µg/mL	>700 µmol/L	>100 µg/mL
Everolimus	3.13–8.35 nmol/L	3–8 ng/mL	>12.5 nmol/L	>12 ng/mL
Flecainide	0.5–2.4 µmol/L	0.2–1.0 µg/mL	>3.6 µmol/L	>1.5 µg/mL
Gentamicin				
Peak	10–21 µmol/mL	5–10 µg/mL	>25 µmol/mL	>12 µg/mL
Trough	0–4.2 µmol/mL	0–2 µg/mL	>4.2 µmol/mL	>2 µg/mL
Heroin (diacetyl morphine)			>700 µmol/L	>200 ng/mL (as morphine)
Ibuprofen	49–243 µmol/L	10–50 µg/mL	>970 µmol/L	>200 µg/mL
Imipramine (and metabolite)				
Desimipramine	375–1130 nmol/L	100–300 ng/mL	>1880 nmol/L	>500 ng/mL
Total imipramine + desimipramine	563–1130 nmol/L	150–300 ng/mL	>1880 nmol/L	>500 ng/mL
Lamotrigine	11.7–54.7 µmol/L	3–14 µg/mL	>58.7 µmol/L	>15 µg/mL
Lidocaine	5.1–21.3 µmol/L	1.2–5.0 µg/mL	>38.4 µmol/L	>9.0 µg/mL
Lithium	0.5–1.3 mmol/L	0.5–1.3 meq/L	>2 mmol/L	>2 meq/L
Methadone	1.0–3.2 µmol/L	0.3–1.0 µg/mL	>6.5 µmol/L	>2 µg/mL
Methamphetamine	0.07–0.34 µmol/L	0.01–0.05 µg/mL	>3.35 µmol/L	>0.5µg/mL
Methanol			>6 mmol/L	>20 mg/dL
Methotrexate				
Low-dose	0.01–0.1 µmol/L	0.01–0.1 µmol/L	>0.1 mmol/L	>0.1 mmol/L
High-dose (24 h)	<5.0 µmol/L	<5.0 µmol/L	>5.0 µmol/L	>5.0 µmol/L
High-dose (48 h)	<0.50 µmol/L	<0.50 µmol/L	>0.5 µmol/L	>0.5 µmol/L
High-dose (72 h)	<0.10 µmol/L	<0.10 µmol/L	>0.1 µmol/L	>0.1 µmol/L
Morphine	232–286 µmol/L	65–80 ng/mL	>720 µmol/L	>200 ng/mL
Mycophenolic acid	3.1–10.9 µmol/L	1.0–3.5 ng/mL	>37 µmol/L	>12 ng/mL
Nitroprusside (as thiocyanate)	103–499 µmol/L	6–29 µg/mL	860 µmol/L	>50 µg/mL
Nortriptyline	190–569 nmol/L	50–150 ng/mL	>1900 nmol/L	>500 ng/mL
Phenobarbital	65–172 µmol/L	15–40 µg/mL	>258 µmol/L	>60 µg/mL
Phenytoin	40–79 µmol/L	10–20 µg/mL	>158 µmol/L	>40 µg/mL
Phenytoin, free	4.0–7.9 µg/mL	1–2 µg/mL	>13.9 µg/mL	>3.5 µg/mL
% Free	0.08–0.14	8–14%		
Primidone and metabolite				
Primidone	23–55 µmol/L	5–12 µg/mL	>69 µmol/L	>15 µg/mL
Phenobarbital	65–172 µmol/L	15–40 µg/mL	>215 µmol/L	>50 µg/mL
Procainamide				
Procainamide	17–42 µmol/L	4–10 µg/mL	>43 µmol/L	>10 µg/mL
NAPA (*N*-acetylprocainamide)	22–72 µmol/L	6–20 µg/mL	>126 µmol/L	>35 µg/mL
Quinidine	6.2–15.4 µmol/L	2.0–5.0 µg/mL	>19 µmol/L	>6 µg/mL
Salicylates	145–2100 µmol/L	2–29 mg/dL	>2900 µmol/L	>40 mg/dL
Sirolimus (trough level)				
Kidney transplant	4.4–15.4 nmol/L	4–14 ng/mL	>16 nmol/L	>15 ng/mL
Tacrolimus (FK506) (trough)				
Kidney and liver				
Initiation	12–19 nmol/L	10–15 ng/mL	>25 nmol/L	>20 ng/mL
Maintenance	6–12 nmol/L	5–10 ng/mL	>25 nmol/L	>20 ng/mL
Heart				
Initiation	19–25 nmol/L	15–20 ng/mL		
Maintenance	6–12 nmol/L	5–10 ng/mL		

(*continued*)

TABLE 3

TOXICOLOGY AND THERAPEUTIC DRUG MONITORING (*CONTINUED*)

	THERAPEUTIC RANGE		TOXIC LEVEL	
DRUG	**SI UNITS**	**CONVENTIONAL UNITS**	**SI UNITS**	**CONVENTIONAL UNITS**
Theophylline	56–111 µg/mL	10–20 µg/mL	>168 µg/mL	>30 µg/mL
Thiocyanate				
After nitroprusside infusion	103–499 µmol/L	6–29 µg/mL	860 µmol/L	>50 µg/mL
Nonsmoker	17–69 µmol/L	1–4 µg/mL		
Smoker	52–206 µmol/L	3–12 µg/mL		
Tobramycin				
Peak	11–22 µg/L	5–10 µg/mL	>26 µg/L	>12 µg/mL
Trough	0–4.3 µg/L	0–2 µg/mL	>4.3 µg/L	>2 µg/mL
Valproic acid	346–693 µmol/L	50–100 µg/mL	>693 µmol/L	>100 µg/mL
Vancomycin				
Peak	14–28 µmol/L	20–40 µg/mL	>55 µmol/L	>80 µg/mL
Trough	3.5–10.4 µmol/L	5–15 µg/mL	>14 µmol/L	>20 µg/mL

TABLE 4

VITAMINS AND SELECTED TRACE MINERALS

		REFERENCE RANGE	
SPECIMEN	**ANALYTE**	**SI UNITS**	**CONVENTIONAL UNITS**
Aluminum	S	<0.2 µmol/L	<5.41 µg/L
Arsenic	WB	0.03–0.31 µmol/L	2–23 µg/L
Cadmium	WB	<44.5 nmol/L	<5.0 µg/L
Coenzyme Q10 (ubiquinone)	P	433–1532 µg/L	433–1532 µg/L
β-Carotene	S	0.07–1.43 µmol/L	4–77 µg/dL
Copper	S	11–22 µmol/L	70–140 µg/dL
Folic acid	RC	340–1020 nmol/L cells	150–450 ng/mL cells
Folic acid	S	12.2–40.8 nmol/L	5.4–18.0 ng/mL
Lead (adult)	S	<0.5 µmol/L	<10 µg/dL
Mercury	WB	3.0–294 nmol/L	0.6–59 µg/L
Selenium	S	0.8–2.0 umol/L	63–160 µg/L
Vitamin A	S	0.7–3.5 µmol/L	20–100 µg/dL
Vitamin B_1 (thiamine)	S	0–75 nmol/L	0–2 µg/dL
Vitamin B_2 (riboflavin)	S	106–638 nmol/L	4–24 µg/dL
Vitamin B_6	P	20–121 nmol/L	5–30 ng/mL
Vitamin B_{12}	S	206–735 pmol/L	279–996 pg/mL
Vitamin C (ascorbic acid)	S	23–57 µmol/L	0.4–1.0 mg/dL
Vitamin D_3,1,25-dihydroxy, total	S, P	36–180 pmol/L	15–75 pg/mL
Vitamin D_3, 25-hydroxy, total	P	75–250 nmol/L	30–100 ng/mL
Vitamin E	S	12–42 µmol/L	5–18 µg/mL
Vitamin K	S	0.29–2.64 nmol/L	0.13–1.19 ng/mL
Zinc	S	11.5–18.4 µmol/L	75–120 µg/dL

Abbreviations: P, plasma; RC, red cells; S, serum; WB, whole blood.

TABLE 5

CLASSIFICATION OF LDL, TOTAL, AND HDL CHOLESTEROL

LDL Cholesterol	
<70 mg/dL	Therapeutic option for very high risk patients
<100 mg/dL	Optimal
100–129 mg/dL	Near optimal/above optimal
130–159 mg/dL	Borderline high
160–189 mg/dL	High
≥190 mg/dL	Very high
Total Cholesterol	
<200 mg/dL	Desirable
200–239 mg/dL	Borderline high
≥240 mg/dL	High
HDL Cholesterol	
<40 mg/dL	Low
≥60 mg/dL	High

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Source: Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001;285:2486–97. SM Grundy et al for the Coordinating Committee of the National Cholesterol Education Program: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation* 2004; 110:227.

TABLE 6

URINE ANALYSIS AND RENAL FUNCTION TESTS

	REFERENCE RANGE	
	SI UNITS	**CONVENTIONAL UNITS**
Acidity, titratable	20–40 mmol/d	20–40 meq/d
Aldosterone	Normal diet: 6–25 µg/d Low-salt diet: 17–44 µg/d High-salt diet: 0–6 µg/d	Normal diet: 6–25 µg/d Low-salt diet: 17–44 µg/d High-salt diet: 0–6 µg/d
Aluminum	0.19–1.11 µmol/L	5–30 µg/L
Ammonia	30–50 mmol/d	30–50 meq/d
Amylase		4–400 U/L
Amylase/creatinine clearance ratio $[(Cl_{am}/Cl_{cr}) \times 100]$	1–5	1–5
Arsenic	0.07–0.67 µmol/d	5–50 µg/d
Bence Jones protein, urine, qualitative	Not applicable	None detected
Bence Jones protein, urine, quantitative		
Free kappa	1.4–24.2 mg/L	0.14–2.42 mg/dL
Free lambda	0.2–6.7 mg/L	0.02–0.67 mg/dL
K/L ratio	2.04–10.37	2.04–10.37
Calcium (10 meq/d or 200 mg/d dietary calcium)	<7.5 mmol/d	<300 mg/d
Chloride	140–250 mmol/d	140–250 mmol/d
Citrate	320–1240 mg/d	320–1240 mg/d

(*continued*)

TABLE 6

URINE ANALYSIS AND RENAL FUNCTION TESTS (*CONTINUED*)

	REFERENCE RANGE	
	SI UNITS	**CONVENTIONAL UNITS**
Copper	<0.95 µmol/d	<60 µg/d
Coproporphyrins (types I and III)	0–20 µmol/mol creatinine	0–20 µmol/mol creatinine
Cortisol, free	55–193 nmol/d	20–70 µg/d
Creatine, as creatinine		
Female	<760 µmol/d	<100 mg/d
Male	<380 µmol/d	<50 mg/d
Creatinine	8.8–14 mmol/d	1.0–1.6 g/d
Dopamine	392–2876 nmol/d	60–440 µg/d
Eosinophils	<100 eosinophils/mL	<100 eosinophils/mL
Epinephrine	0–109 nmol/d	0–20 µg/d
Glomerular filtration rate	>60 mL/min/1.73 m^2 For African Americans multiply the result by 1.21	>60 mL/min/1.73 m^2 For African Americans multiply the result by 1.21
Glucose (glucose oxidase method)	0.3–1.7 mmol/d	50–300 mg/d
5-Hydroindoleacetic acid [5-HIAA]	0–78.8 µmol/d	0–15 mg/d
Hydroxyproline	53–328 µmol/d	53–328 µmol/d
Iodine, spot urine		
WHO classification of iodine deficiency:		
Not iodine deficient	>100 µg/L	>100 µg/L
Mild iodine deficiency	50–100 µg/L	50–100 µg/L
Moderate iodine deficiency	20–49 µg/L	20–49 µg/L
Severe iodine deficiency	<20 µg/L	<20 µg/L
Ketone (acetone)	Negative	Negative
17 Ketosteroids	3–12 mg/d	3–12 mg/d
Metanephrines		
Metanephrine	30–350 µg/d	30–350 µg/d
Normetanephrine	50–650 µg/d	50–650 µg/d
Microalbumin		
Normal	0.0–0.03 g/d	0–30 mg/d
Microalbuminuria	0.03–0.30 g/d	30–300 mg/d
Clinical albuminuria	>0.3 g/d	>300 mg/d
Microalbumin/creatinine ratio		
Normal	0–3.4 g/mol creatinine	0–30 µg/mg creatinine
Microalbuminuria	3.4–34 g/mol creatinine	30–300 µg/mg creatinine
Clinical albuminuria	>34 g/mol creatinine	>300 µg/mg creatinine
β_2-Microglobulin	0–160 µg/L	0–160 µg/L
Norepinephrine	89–473 nmol/d	15–80 µg/d
N-telopeptide (cross-linked), NTx		
Female, premenopausal	17–94 nmol BCE/mmol creatinine	17–94 nmol BCE/mmol creatinine
Female, postmenopausal	26–124 nmol BCE/mmol creatinine	26–124 nmol BCE/mmol creatinine
Male	21–83 nmol BCE/mmol creatinine	21–83 nmol BCE/mmol creatinine
BCE = bone collagen equivalent		
Osmolality	100–800 mosm/kg	100–800 mosm/kg
Oxalate		
Male	80–500 µmol/d	7–44 mg/d
Female	45–350 µmol/d	4–31 mg/d
pH	5.0–9.0	5.0–9.0

(*continued*)

TABLE 6

URINE ANALYSIS AND RENAL FUNCTION TESTS (*CONTINUED*)

	REFERENCE RANGE	
	SI UNITS	**CONVENTIONAL UNITS**
Phosphate (phosphorus) (varies with intake)	12.9–42.0 mmol/d	400–1300 mg/d
Porphobilinogen	None	None
Potassium (varies with intake)	25–100 mmol/d	25–100 meq/d
Protein	<0.15 g/d	<150 mg/d
Protein/creatinine ratio	Male: 15–68 mg/g Female: 10–107 mg/g	Male: 15–68 mg/g Female: 10–107 mg/g
Sediment		
Red blood cells	0–2/high-power field	
White blood cells	0–2/high-power field	
Bacteria	None	
Crystals	None	
Bladder cells	None	
Squamous cells	None	
Tubular cells	None	
Broad casts	None	
Epithelial cell casts	None	
Granular casts	None	
Hyaline casts	0–5/low-power field	
Red blood cell casts	None	
Waxy casts	None	
White cell casts	None	
Sodium (varies with intake)	100–260 mmol/d	100–260 meq/d
Specific gravity:		
After 12-h fluid restriction	>1.025	>1.025
After 12-h deliberate water intake	≤1.003	≤1.003
Tubular reabsorption, phosphorus	0.79–0.94 of filtered load	79–94% of filtered load
Urea nitrogen	214–607 mmol/d	6–17 g/d
Uric acid (normal diet)	1.49–4.76 mmol/d	250–800 mg/d
Vanillylmandelic acid (VMA)	<30 μmol/d	<6 mg/d

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REVIEW AND SELF-ASSESSMENT[a]

Charles Wiener ■ Cynthia D. Brown ■ Anna R. Hemnes

QUESTIONS

DIRECTIONS: Choose the **one best** response to each question.

1. Which of the following is a potential etiology for ischemic acute renal failure?

A. Apoptosis and necrosis of tubular cells
B. Decreased glomerular vasodilation in response to nitric oxide
C. Increased glomerular vasoconstriction in response to elevated endothelin levels
D. Increased leukocyte adhesion within the glomerulus
E. All of the above

2. A 47-year-old man with a history of diabetes mellitus, hyperlipidemia, tobacco abuse, and coronary artery disease undergoes emergency appendectomy. Which of the following conditions predisposes this patient to postoperative acute kidney injury?

A. Abdominal procedure, emergency surgery, and hyperlipidemia
B. Age greater than 40, abdominal procedure, and emergency surgery
C. Age greater than 40, emergency surgery, and diabetes mellitus
D. Coronary artery disease, tobacco abuse, and abdominal procedure
E. Diabetes mellitus and emergency procedure

3. A 57-year-old man with a history of diabetes mellitus and chronic kidney disease with a baseline creatinine of 1.8 mg/dL undergoes cardiac catheterization for acute myocardial infarction. He is subsequently diagnosed with acute kidney injury related to iodinated contrast. All of the following statements are true regarding his kidney injury EXCEPT:

A. Fractional excretion of sodium will be low.
B. His creatinine is likely to peak within 3–5 days.
C. His diabetes mellitus predisposed him to develop contrast nephropathy.

3. (*Continued*)
D. Transient tubule obstruction with precipitated iodinated contrast contributed to the development of his acute kidney injury.
E. White blood cell casts are likely on microscopic examination of urinary sediment.

4. Which of the following acute kidney injury patients is most likely to have evidence of hydronephrosis on ultrasound evaluation of the kidneys?

A. A 19-year-old man with purpura fulminans associated with gonococcal sepsis
B. A 37-year-old woman undergoing chemotherapy and radiation for advanced cervical cancer
C. A 53-year-old man with *E. coli* 0157:H7–associated thrombotic thrombocytopenic purpura
D. An 85-year-old nursing home resident with pyelonephritis and sepsis
E. None of the above

5. In evaluation for acute kidney injury in a patient who has recently undergone cardiopulmonary bypass during mitral valve replacement, which of the following findings on urine microscopy is most suggestive of cholesterol emboli as the source of renal failure?

A. Calcium oxalate crystals
B. Eosinophiluria
C. Granular casts
D. Normal sediment
E. White blood cell casts

6. A 54-year-old man is admitted to the medical intensive care unit with sepsis associated with pneumococcal pneumonia. He requires mechanical ventilation as well as norepinephrine to maintain a mean arterial pressure greater than 60 mmHg. Invasive hemodynamics show adequate left-heart filling pressures, and he is not known to have left ventricular dysfunction. On the third hospital day, his urine output drops and his creatinine increases to 3.4 mg/dL. Acute tubular

[a]Questions and answers were taken from Wiener C et al (eds): *Harrison's Principles of Internal Medicine Self-Assessment and Board Review*, 18th ed. New York: McGraw-Hill, 2012.

6. (*Continued*)
injury is diagnosed. Which of the following agents has been shown to improve outcomes associated with his acute tubular injury?

A. Furosemide
B. Bosentan
C. Low-dose dopamine
D. Insulin-like growth factor
E. None of the above

7. It is hospital day 5 for a 65-year-old patient with prerenal azotemia secondary to dehydration. His creatinine was initially 3.6 mg/dL on admission, but it has improved today to 2.1 mg/dL. He complains of mild lower back pain, and you prescribe naproxen to be taken intermittently. By what mechanism might this drug further impair his renal function?

A. Afferent arteriolar vasoconstriction
B. Afferent arteriolar vasodilatation
C. Efferent arteriolar vasoconstriction
D. Proximal tubular toxicity
E. Ureteral obstruction

8. Preoperative assessment of a 55-year-old male patient for coronary angiography shows an estimated glomerular filtration rate of 33 mL/min per 1.73 m^2 and poorly controlled diabetes. He is currently on no nephrotoxic medications, and the nephrologist assures you that he does not currently have acute renal failure. The surgery is due to begin in 4 hours, and you would like to prevent contrast nephropathy. Which agent will definitely reduce the risk of contrast nephropathy?

A. Dopamine
B. Fenoldopam
C. Indomethacin
D. *N*-acetylcysteine
E. Sodium bicarbonate

9. In stage 5 chronic kidney disease the glomerular filtration rate is below:

A. 50 mL/min per 1.73 m^2
B. 25 mL/min per 1.73 m^2
C. 15 mL/min per 1.73 m^2
D. 5 mL/min per 1.73 m^2
E. 0 mL/min per 1.73 m^2 (anuria)

10. What is the leading cause of death in patients with chronic kidney disease?

A. Cardiovascular disease
B. Hyperkalemia

10. (*Continued*)
C. Infection
D. Malignancy
E. Uremia

11. All of the following statements regarding the use of exogenous erythropoietin in patients with chronic kidney disease are true EXCEPT:

A. Exogenous erythropoietin should be administered with a target hemoglobin concentration of 100–115 g/L.
B. The use of exogenous erythropoietin is associated with improved cardiovascular outcomes.
C. The use of exogenous erythropoietin is associated with increased risk of stroke in patients with concomitant Type 2 diabetes mellitus.
D. The use of exogenous erythropoietin may be associated with faster progression to the need for dialysis.
E. The use of exogenous erythropoietin is associated with an increased incidence of thromboembolic events.

12. A patient is followed closely by her nephrologist for stage IV chronic kidney disease associated with focal segmental glomerulosclerosis. Which of the following is an indication for initiation of maintenance hemodialysis?

A. Acidosis controlled with daily bicarbonate administration
B. Bleeding diathesis
C. BUN greater than 110 mg/dL without symptoms
D. Creatinine greater than 5 mg/dL without symptoms
E. Hyperkalemia controlled with sodium polystyrene

13. A 27-year-old woman with chronic kidney disease is undergoing hemodialysis and is found to be hypotensive during her treatment. Which of the following are potential mechanisms for hypotension during hemodialysis?

A. Antihypertensive agents
B. Excessive ultrafiltration
C. Impaired autonomic responses
D. Osmolar shifts
E. All of the above

14. A 35-year-old woman with hypertensive kidney disease progresses to end-stage renal disease. She was initiated on peritoneal dialysis 1 year ago and has done well with relief of her uremic symptoms. She is brought to the emergency department with fever, altered mental status, diffuse abdominal pain, and cloudy dialysate. Her peritoneal fluid is withdrawn through her catheter and sent to the laboratory for analysis. The fluid white blood cell count is 125/mm^3

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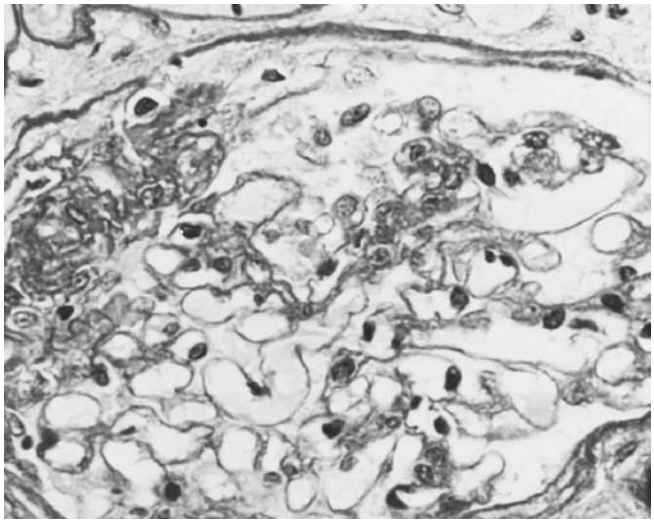

FIGURE 21

22. Which of the following is an extrarenal manifestation of autosomal dominant polycystic kidney disease?

A. Aortic regurgitation
B. Aortic root dilation
C. Colonic diverticulae
D. Intracranial aneurysm
E. All of the above

23. A 21-year-old male college student is evaluated for profound fatigue that has been present for several years but has recently become debilitating. He also reports several foot spasms and cramps, and occasional sustained muscle contractions that are uncontrollable. He is otherwise healthy, takes no medications, and denies tobacco or alcohol use. On examination he is well developed with normal vital signs including blood pressure. The remainder of the examination is normal. Laboratory evaluation shows a sodium of 138 meq/L, potassium of 2.8 meq/L, chloride of 90 meq/L, and bicarbonate of 30 mmol/L. Magnesium level is normal. Urine screen for diuretics is negative, and urine chloride is elevated. Which of the following is the most likely diagnosis?

A. Bulimia nervosa
B. Diuretic abuse
C. Gitelman's syndrome
D. Liddle's syndrome
E. Type 1 pseudohypoaldosteronism

24. A 28-year-old woman was recently diagnosed with autosomal dominant polycystic kidney disease after an episode of hematuria. She is concerned about her intracranial aneurysm risk. Which of the following statements is true regarding this risk?

24. (*Continued*)
A. Family history of ruptured intracranial aneurysms does not increase risk of rupture.
B. Prior intracranial hemorrhage does not increase risk of subsequent hemorrhage.
C. The size of the aneurysm does not correlate with its risk of spontaneous rupture.
D. There is no increased risk of intracranial aneurysm in this condition.
E. Uncontrolled hypertension augments the risk of spontaneous rupture.

25. A patient with a history of Sjögren's syndrome has the following laboratory findings: plasma sodium 139 meq/L, chloride 112 meq/L, bicarbonate 15 meq/L, and potassium 3.0 meq/L; urine studies show a pH of 6.0, sodium of 15 meq/L, potassium of 10 meq/L, and chloride of 12 meq/L. The most likely diagnosis is:

A. Type I renal tubular acidosis (RTA)
B. Type II RTA
C. Type III RTA
D. Type IV RTA
E. Chronic diarrhea

26. A 16-year-old female star gymnast presents to your office complaining of fatigue, diffuse weakness, and muscle cramps. She has no previous medical history and denies tobacco, alcohol, or illicit drug use. There is no significant family history. Examination shows a thin female with normal blood pressure. Body mass index (BMI) is 18 kg/m^2. Oral examination shows poor dentition. Muscle tone is normal, and neurologic examination is normal. Laboratory studies show hematocrit of 38.5%, creatinine of 0.6 mg/dL, serum bicarbonate of 30 meq/L, and potassium of 2.7 meq/L. Further evaluation should include which of the following?

A. Urinalysis and urine culture
B. Plasma renin and aldosterone levels
C. Urine toxicology screen for opiates
D. Urine toxicology screen for diuretics
E. Serum magnesium level

27. In which of the following cases would treatment for biopsy-proven interstitial nephritis with corticosteroids be most likely to impact long-term renal recovery?

A. A 37-year-old woman with sarcoidosis
B. A 48-year-old man with slowly progressing interstitial nephritis over 2 months with fibrosis found on biopsy
C. A 54-year-old man with diabetes mellitus and recent salmonella infection

27. (*Continued*)

D. A 63-year-old man with allergic interstitial nephritis after cephalosporin antibiotic use
E. None of the above

28. A 58-year-old woman undergoes a hysterectomy and postoperatively develops acute respiratory distress syndrome. She is treated with mechanical ventilation and broad-spectrum antibiotics. Aside from hypothyroidism, she has no underlying medical conditions. On day 5 of her hospitalization her urine output is noted to fall and her serum creatinine rises from 1.2 mg/dL to 2.5 mg/dL. Allergic interstitial nephritis from cephalosporin antibiotics is suspected. Which of the following findings will confirm this diagnosis?

A. Hematuria
B. Peripheral blood eosinophilia
C. Urinary eosinophils on urine microscopy
D. White blood cell casts on urine microscopy
E. None of the above

29. A 44-year-old obese woman undergoes elective cholecystectomy for cholelithiasis. Postoperatively she does well and is discharged after 3 days. Two days after discharge she develops altered mental status and fever, and is brought to the emergency department by her family. She takes an antidepressant, but is otherwise healthy. Her temperature is 103°F, pulse is 127 beats/min, blood pressure is 110/78 mmHg, and respiratory rate and oxygen saturation are normal. Examination is notable for confusion and a well-healed surgical incision. Routine chemistries are drawn and show normal electrolytes, BUN of 80 mg/dL, creatinine of 2.5 mg/dL, white blood cell count of 17.3 thousand/μL, hematocrit of 30%, and platelet count of 25 thousand/μL. A peripheral blood smear shows schistocytes and confirms low platelets without clumping. Which of the following statements regarding her condition is true?

A. Low activity of the metalloprotease ADAMTS13 is likely present in her peripheral blood.
B. Plasma exchange is unlikely to be helpful.
C. This was likely caused by an occult *E. coli* 0157:H7 infection.
D. This condition is more common in men than women.
E. Untreated mortality from this condition is low.

30. A 35-year-old female presents with complaints of bilateral lower extremity edema, polyuria, and moderate left-sided flank pain that began approximately 2 weeks ago. There is no past medical history. She is taking no medications and denies tobacco, alcohol, or illicit drug use. Examination shows normal vital signs,

30. (*Continued*)

including normal blood pressure. There is 2+ edema in the bilateral lower extremities. The 24-hour urine collection is significant for 3.5 g of protein. Urinalysis is bland except for the proteinuria. Serum creatinine is 0.7 mg/dL, and ultrasound examination shows the left kidney measuring 13 cm and the right kidney measuring 11.5 cm. You are concerned about renal vein thrombosis. What test do you choose for the evaluation?

A. Computed tomography of the renal veins
B. Contrast venography
C. Magnetic resonance venography
D. 99Tc-labeled pentetic acid (DPTA) imaging
E. Ultrasound with Doppler evaluation of the renal veins

31. A 48-year-old man with diabetes mellitus and hyperlipidemia presents to the emergency department for evaluation of right flank pain and groin pain that has been severe and present for approximately 3 hours. He is diagnosed with a kidney stone. Which of the following is most likely to be found as the constituent of his stone?

A. Calcium
B. Cysteine
C. Oxalic acid
D. Struvite
E. Uric acid

32. A 54-year-old woman with a history of colon cancer treated with resection 2 years prior and chemotherapy is admitted to the hospital after routine lab work at her primary care physician's office showed a BUN of 65 mg/dL and a creatinine of 4.5 mg/dL. She reports mild fatigue and recent lower back pain, but otherwise feels well. She does admit to recent NSAID use, but has not taken more than the recommended quantity. Aside from stopping NSAIDs and avoiding nephrotoxins, which of the following studies should be ordered first?

A. CT of the abdomen/pelvis with oral contrast
B. Post-void residual volume of bladder
C. Retrograde urography
D. Ultrasound of the abdomen/kidney
E. Urinary fractional excretion of sodium

33. A 67-year-old man presents to the emergency department with severe abdominal distention and pain. He is found to have a palpable bladder, and after Foley catheter placement 1.5 L of urine passes. His prostate-specific antigen (PSA) is not elevated, but he does report that he has had difficulty passing his urine for

33. (*Continued*)
several weeks, culminating in no urination for 2 days. His BUN is 89 mg/dL and creatinine is 6.4 mg/dL. Over the next 4 days of hospitalization, his BUN and Cr fall, but his urine output is found to be rising. He is not receiving intravenous fluids. He passes 6 L of urine on the third and fourth hospital days. Which is the most likely explanation for the increased urine output?

A. Cerebral salt wasting
B. Decreased medullary osmolarity
C. Increased activation of the renin-angiotensin-aldosterone system
D. Increased tubule pressure
E. Postobstructive diuresis

34. The patient in question 33 is at risk for which of the following complications?

A. Erythrocytosis
B. Hyperchloremic metabolic acidosis
C. Hyperkalemia
D. Prerenal azotemia
E. Systemic hypertension

35. The pain associated with acute urinary tract obstruction is a result of which of the following?

A. Compensatory natriuresis
B. Decreased medullary blood flow
C. Increased renal blood flow
D. Vasodilatory prostaglandins

36. You are evaluating a 28-year-old man from Peru with abdominal pain. As part of the diagnostic workup, an abdominal ultrasound shows bilateral hydronephrosis and hydroureters. Which of the following conditions is least likely in this patient?

A. Lymphoma
B. Meatal stenosis
C. Phimosis
D. Retroperitoneal fibrosis

37. During the first 2 weeks after solid organ transplantation, which family of infection is most common?

A. Cytomegalovirus and Epstein-Barr virus reactivation
B. Humoral immunodeficiency–associated infections (e.g., meningococcemia, invasive *Streptococcus pneumoniae* infection)
C. Neutropenia-associated infection (e.g., aspergillosis, candidemia)
D. T-cell deficiency–associated infections (e.g., *Pneumocystis jiroveci*, nocardiosis, cryptococcosis)

37. (*Continued*)
E. Typical hospital-acquired infections (e.g., central line infection, hospital-acquired pneumonia, urinary tract infection)

38. A 22-year-old woman underwent cadaveric renal transplantation 3 months ago for congenital obstructive uropathy. After a demanding college examination schedule during which she forgot to take some of her medications, she is admitted to the hospital with a temperature of 102°F, arthralgias, lymphopenia, and a rise in creatinine from her baseline of 1.2 mg/dL to 2.4 mg/dL. Which of the following medications did she most likely forget?

A. Acyclovir
B. Isoniazid
C. Itraconazole
D. Trimethoprim–sulfamethoxazole
E. Valganciclovir

39. A 63-year-old man complains of notable pink-tinged urine for the past month. At first he thought it was caused by eating beets, but it has not cleared. His medical history is notable for hypertension and cigarette smoking. He does report some worsening urinary frequency and hesitancy over the past 2 years. Physical examination is unremarkable. Urinalysis is notable for gross hematuria with no white blood cells or casts. Renal function is normal. Which of the following statements regarding this patient is true?

A. Cigarette smoking is not a risk for bladder cancer.
B. Gross hematuria makes prostate cancer more likely than bladder cancer.
C. If invasive bladder cancer with nodal involvement but no distant metastases is found, the 5-year survival is 20%.
D. If superficial bladder cancer is found, intravesicular BCG may be used as adjuvant therapy.
E. Radical cystectomy is generally recommended for invasive bladder cancer.

40. A 68-year-old man comes to his physician complaining of 2 months of increasing right flank pain with 1 month of worsening hematuria. He was treated for cystitis at a walk-in clinic 3 weeks ago with no improvement. He also reports poor appetite and 5 lb of weight loss. His physical examination is notable for a palpable mass in the right flank measuring greater than 5 cm. His renal function is normal. All of the following are true about this patient's likely diagnosis EXCEPT:

A. Anemia is more common than erythrocytosis.
B. Cigarette smoking increased his risk.

40. (*Continued*)

C. If his disease has metastasized, with best therapy 5-year survival is greater than 50%.

D. If his disease is confined to the kidney, 5-year survival is greater than 80%.

E. The most likely pathology is clear cell carcinoma.

41. In the patient described in question 40, imaging shows a 10-cm solid mass in the right kidney and multiple nodules in the lungs consistent with metastatic disease.

41. (*Continued*)

Needle biopsy of a lung lesion confirms the diagnosis of renal cell carcinoma. Which of the following is recommended therapy?

A. Gemcitabine

B. Interferon-gamma

C. Interleukin-2

D. Radical nephrectomy

E. Sunitinib

ANSWERS

1. The answer is E.

(Chap. 10) Ischemic acute renal failure has many potential etiologies. Microvascular disorders include increased vasoconstriction from endothelin and other mediators, decreased nitric oxide, prostaglandin- or bradykinin-mediated vasodilation, increased endothelial and vascular smooth muscle cell damage, and increased leukocyte adhesion. Tubular factors include cytoskeletal breakdown, loss of polarity, apoptosis and necrosis, desquamation of viable and necrotic cells, tubular obstruction, and backleak. Inflammatory and vasoactive mediators may affect both tubular and microvascular pathophysiologic mechanisms.

2. The answer is E.

(Chap. 10) The risk for acute kidney injury is less well studied for abdominal procedures compared to cardiac surgery, but appears to be relatively comparable. Abdominal procedures, however, are not thought to be of particular risk compared with other major chest or orthopedic procedures. Common risk factors for postoperative acute kidney injury include underlying chronic kidney disease, older age, diabetes mellitus, congestive heart failure, and emergency procedures. Most commonly, postoperative acute kidney injury is multifactorial.

3. The answer is E.

(Chap. 10) Iodinated contrast agents that are commonly used in cardiovascular and CT imaging are a major cause of acute kidney injury. Underlying mechanisms leading to kidney injury include transient tubular obstruction by contrast material, hypoxia in the other renal medulla due to alterations in renal microcirculation and occlusion of small vessels, and cytotoxic damage to the tubules directly or through the generation of free radicals by contrast material. Risk factors for contrast-associated nephropathy include diabetes mellitus, congestive heart failure, preexisting chronic kidney disease, and multiple myeloma–associated renal failure. Serum creatinine begins to rise at 24–48 hours and will peak at 3–5 days, usually with resolution within a week. Urinary sediment is bland, without casts. The fractional excretion of sodium is low in many cases, particularly early before tubular injury is extensive because of the microvascular source of injury.

4. The answer is B.

(Chap. 10) Postrenal obstruction is an important and potentially reversible cause of acute kidney injury. Ultrasound evaluation of the kidneys classically demonstrates bilateral hydronephrosis, as unilateral obstruction is unlikely to cause kidney injury unless a single functioning kidney is present, chronic kidney disease preexists, or rarely there is reflex vasospasm of the unobstructed kidney. Advanced cervical cancer with invasion into the urinary system or retroperitoneum is a common cause of obstructive uropathy. Thrombotic thrombocytopenic purpura (TTP), disseminated gonococcus with sepsis, and pyelonephritis are intrinsic causes of acute kidney failure and will not cause bilateral hydronephrosis.

5. The answer is B.

(Chap. 10) Cholesterol emboli are an important cause of acute kidney injury in patients who have undergone cardiac procedures that may disrupt aortic atherosclerotic disease and shower cholesterol emboli. Livedo reticularis is a common finding on physical examination, and peripheral blood eosinophilia may be present. When found, eosinophiluria is highly suggestive. The other major cause of eosinophiluria is acute interstitial nephritis. White blood cell casts suggest interstitial nephritis, pyelonephritis, glomerulonephritis, or malignant infiltration of the kidney; calcium oxalate crystals are found in ethylene glycol intoxication; and granular casts are suggestive of acute ischemic kidney injury (acute tubular necrosis), glomerulonephritis, vasculitis, or tubulointerstitial nephritis.

6. The answer is E.

(Chap. 10) Multiple studies have demonstrated that acute kidney injury is an independent poor prognostic indicator in critically ill patients with multiple medical conditions. Unfortunately, care of critically ill patients with acute kidney injury is supportive, as no specific therapy has been shown to improve outcomes. Agents that have specifically been shown to have no benefit in the treatment of acute tubular injury include atrial natriuretic peptide, low-dose dopamine, endothelin antagonists, loop diuretics, calcium channel blockers, α-adrenergic receptor blockers, prostaglandin

analogs, antioxidants, insulin-like growth factor, and antibodies against leukocyte adhesion molecules. Volume repletion is critical to ensure adequate perfusion, and diuretics are only indicated in patients with replete fluid status and low urinary flow rates.

7. The answer is A.

(Chap. 10) Nonsteroidal anti-inflammatory drugs (NSAIDs) do not alter glomerular filtration rate in normal individuals. However, in states of mild to moderate hypoperfusion (as in prerenal azotemia) or in the presence of chronic kidney disease, glomerular perfusion and filtration fraction are preserved through several compensatory mechanisms. In response to a reduction in perfusion pressures, stretch receptors in afferent arterioles trigger a cascade of events that lead to afferent arteriolar dilatation and efferent arteriolar vasoconstriction, thereby preserving glomerular filtration fraction. These mechanisms are partly mediated by the vasodilators prostaglandin E_2 and prostacyclin. NSAIDs can impair the kidney's ability to compensate for a low perfusion pressure by interfering with local prostaglandin synthesis and inhibiting these protective responses. Ureteral obstruction is not the mechanism by which NSAIDs impair renal function in this scenario. NSAIDs are not known to be proximal tubule toxins.

8. The answer is E.

(Chap. 10) Radiocontrast agents cause renal injury through intrarenal vasoconstriction and the generation of oxygen radicals, causing acute tubular necrosis. These medications cause an acute decrease in renal blood flow and glomerular filtration rate. Patients with chronic kidney disease, diabetes mellitus, heart failure, multiple myeloma, and volume depletion are at the highest risk of contrast nephropathy. It is clear that hydration with normal saline is an effective measure to prevent contrast nephropathy. Of the other measures mentioned here, only sodium bicarbonate or *N*-acetylcysteine could be recommended for clinical use to reduce the risk of contrast nephropathy. Dopamine has been proven an ineffective agent to prevent contrast nephropathy. Fenoldopam, a D_1-receptor agonist, has been tested in several clinical trials and does not appear to reduce the incidence of contrast nephropathy. Although several small clinical studies have suggested a clinical benefit to the use of *N*-acetylcysteine, a meta-analysis has been inconclusive, and the medication should be administered well in advance of the procedure. Sodium bicarbonate begun within 1 hour of the procedure has shown a significant benefit in a single-center, randomized controlled trial. Due to the time limitations, and based on the evidence, only sodium bicarbonate would be helpful in this patient.

9. The answer is C.

(Chap. 11) Chronic kidney disease is classified by glomerular filtration rate. In stage 0 patients, GFR is greater than 90 mL/min per 1.73 m^2, stage 2 GFR is 60–89 mL/min per 1.73 m^2, stage 3 GFR is 30–59 mL/min per 1.73 m^2, and stage 4 GFR is 15–29 mL/min per 1.73 m^2. Stage 5 GFR is less than 15 mL/min per 1.73 m^2.

10. The answer is A.

(Chap. 11) The leading cause of morbidity and mortality in patients with chronic kidney disease regardless of stage is cardiovascular disease. The presence of chronic kidney disease is a major risk factor for ischemic heart disease; in addition to traditional cardiovascular risk factors, patients with chronic kidney disease have additional risk factors including anemia, hyperphosphatemia, hyperparathyroidism, sleep apnea, and systemic inflammation. Left ventricular hypertrophy and dilated cardiomyopathy are also frequently present in those with chronic kidney disease and are strongly associated with cardiovascular morbidity and mortality.

11. The answer is B.

(Chap. 11) Anemia is a common consequence of chronic kidney disease and may be multifactorial, with etiologies including relative erythropoietin deficiency, iron deficiency, chronic inflammation, diminished red cell survival, and bleeding diathesis. Several trials of erythropoietin supplementation in patients with chronic kidney disease have failed to show improved cardiovascular outcomes with this therapy. Indeed, these trials have shown a higher incidence of thromboembolic events, stroke in Type 2 diabetics, and potentially faster progression to need for dialysis. Because of these concerning findings, erythropoietin use has been altered from prior recommendations, and current practice is to target a hemoglobin concentration of 100–115 g/L.

12. The answer is B.

(Chap. 12) The commonly accepted criteria for initiating patients on maintenance dialysis include the presence of uremic symptoms, the presence of hyperkalemia unresponsive to conservative management, persistent extracellular volume expansion despite diuretics, acidosis refractory to medical therapy, bleeding diathesis, or a creatinine clearance or estimated GFR below 10 mL/min per 1.73 m^2. BUN or creatinine values alone are inadequate to initiate dialysis.

13. The answer is E.

(Chap. 12) Hypotension is the most common complication of hemodialysis. There are many potential etiologies of hypotension including antihypertensive use, excessive ultrafiltration, impaired vasoactive or autonomic responses, impaired cardiac reserve, and osmolar shifts. Less common causes include dialyzer reactions and high-output heart failure related to large arteriovenous (AV) fistulae. Manipulation of buffer for dialysate, alterations of timing of ultrafiltration, and midodrine may be used to improve hemodynamic tolerance to hemodialysis. Patients with unexpected or new hypotension during stable dialysis should also be evaluated for graft infection and bacteremia.

14. The answer is E.

(Chap. 12) The major complication of peritoneal dialysis therapy is peritonitis, though other complications include catheter-associated non-peritonitis infections, weight gain, metabolic derangements, and residual uremia. Peritonitis is usually a result from a failure of sterile technique during the exchange procedure. Transvisceral infection from the bowel is much less common. Because of the high dextrose used in dialysate, the environment is conducive for the development of bacterial infection. This can be diagnosed by the presence of more than 100/mm^3 leukocytes with more than 50% polymorphonuclear cells on microscopy. Cloudy dialysate and abdominal pain are the most common symptoms. The most commonly isolated bacteria are skin flora such as *Staphylococcus*. Gram-negative organisms, fungi, and mycobacteria have also been described. A recent Cochrane review (Wiggins KJ et al: Treatment for peritoneal dialysis-associated peritonitis. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD005284. DOI: 10.1002/14651858.CD005284.pub2) concluded that intraperitoneal administration of antibiotics was more effective than intravenous administration, and that adjunctive treatment with urokinase or peritoneal lavage offers no advantage. Intraperitoneal vancomycin is common initial empiric therapy.

15. The answer is C.

(Chap. 12) The most common cause of mortality in patients with end-stage renal disease is cardiovascular disease (stroke and myocardial infarction). Although the underlying mechanisms driving this association are under active investigation, the shared risk factors of diabetes, hypertension, and dyslipidemia in addition to specific risks such as increased inflammation, hyperhomocysteinemia, anemia, and altered vascular function are thought to play an important role. Inefficient or inadequate dialysis is a risk for patients with difficult vascular access or poor adherence to therapy. Patients receiving hemodialysis are at risk and often develop neurologic, hematologic, and infectious complications. Nevertheless, the biggest risk to survival in these patients is also the most common cause of death in the general population.

16. The answer is B.

(Chap. 12) Although the dose is currently defined as a derivation of the fractional urea clearance, factors that are also important include patient size, residual kidney function, dietary protein intake, comorbid conditions, and the degree of anabolism/catabolism. The efficiency of dialysis depends on the counter-current flow rate of the dialysate. The number of hours/sessions prescribed for a patient is derived from the dialysis dose and is individualized.

17. The answer is A.

(Chap. 12) The potassium concentration of dialysate is usually 2.5 meq/L but may be varied depending on the predialysis serum potassium. This patient may need a lower dialysate potassium concentration. Sodium modeling is an adjustment of the dialysate sodium that may lessen the incidence of hypotension at the end of a dialysis session. Aldosterone defects, if present, are not likely to play a role in this patient since his kidneys are not being perfused. Therefore, nephrectomy is not likely to control his potassium. Similarly, since the patient is likely anuric, there is no efficacy in utilizing loop diuretics to effect kaluresis. This patient has no approved indications for implantation of a defibrillator.

18. The answer is D.

(Chap. 13) Both deceased and living donor kidney transplantations are highly successful. When compared to hemodialysis there are substantial cost-benefit advantages to individuals and society related to decreased morbidity, subsequent hospitalizations, and mortality. When first-degree relatives are donors, the graft survival rates are higher than those of deceased donors by 5–7% at 1 year. This difference persists for up to 10 years. There are few reported complications for donors, particularly in the absence of hypertension or diabetes mellitus. For deceased donors, older age, the presence of preexisting renal damage, or prolonged ischemia decreases the longevity of the graft.

19. The answer is B.

(Chap. 15) There are a wide variety of diseases that can cause glomerular injury to the kidney, ranging from genetic conditions such as TRPC6 mutation causing cation channel dysfunction and associated focal segmental glomerulosclerosis to glomerular stress from systemic hypertension and/or diabetes mellitus. Inflammatory disease such as lupus nephritis, Wegener's granulomatosis, and poststreptococcal glomerulonephritis may also cause glomerular disease. Fanconi's syndrome is a classic disease of tubular dysfunction with associated aminoaciduria, type 2 renal tubular acidosis, and rickets, not glomerular disease.

20. The answer is C.

(Chap. 15) The hallmark of glomerular renal disease is microscopic hematuria and proteinuria. IgA nephropathy and sickle cell disease are the exception to this when gross hematuria may be present. Proteinuria may be heavy (>3 g/24 hours) or lower quantity with microalbuminuria (30–300 mg/24 hours) depending on the underlying disease or site of the immune lesion. Patients with poststreptococcal glomerulonephritis often have pyuria, but cultures are not expected to be positive as the infection is usually skin or mucosal, and it is the immune reaction that drives the renal lesion.

21. The answer is B.

(Chap. 15) The characteristic pattern of focal (not all glomeruli) and segmental (not the entire glomerulus) glomerular

scarring is shown. The history and laboratory features are also consistent with this lesion: some associated hypertension, diminution in creatinine clearance, and a relatively inactive urine sediment. The "nephropathy of obesity" may be associated with this lesion secondary to hyperfiltration; this condition may be more likely to occur in obese patients with hypoxemia, obstructive sleep apnea, and right-sided heart failure. Hypertensive nephrosclerosis exhibits more prominent vascular changes and patchy, ischemic, totally sclerosed glomeruli. In addition, nephrosclerosis seldom is associated with nephrotic-range proteinuria. Minimal-change disease usually is associated with symptomatic edema and normal-appearing glomeruli, as demonstrated on light microscopy. This patient's presentation is consistent with that of membranous nephropathy, but the biopsy is not. With membranous glomerular nephritis all glomeruli are uniformly involved with subepithelial dense deposits. There are no features of crescentic glomerulonephritis present.

22. The answer is E.

(Chap. 16) Autosomal polycystic kidney disease is a common genetic disorder accounting for up to 4% of end-stage renal disease cases in the United States. Although the most common manifestations of this condition are renal cysts, hematuria, urinary tract infection, and occasionally nephrolithiasis, there are several common extrarenal manifestations including intracranial aneurysm, aortic root and annulus dilatation, valvular heart disease including aortic regurgitation and mitral valve prolapse, hepatic cysts, hernias, and colonic diverticulae with a high propensity to perforate.

23. The answer is C.

(Chap. 16) The patient presents with hypokalemia and hypochloremic metabolic alkalosis in the absence of hypertension. This is most commonly due to surreptitious vomiting or diuretic abuse, but in this case the urine diuretic screen was negative. In patients with surreptitious vomiting, urine chloride levels are low to preserve intravascular volume and this was not present in this patient. Those with Bartter's syndrome and Gitelman's syndrome have hypokalemia and hypochloremic metabolic alkalosis with inappropriately elevated urine chloride levels. Gitelman's syndrome is less severe and presents later in life than Bartter's, which is commonly found in childhood due to failure to thrive. Additionally, those with Gitelman's syndrome have more prominent fatigue and muscle cramping. Most forms of Bartter's syndrome also include associated hypomagnesemia and hypocalciuria. Those with type 1 pseudohypoaldosteronism have severe renal salt wasting and hyperkalemia. Liddle's syndrome presents with apparent aldosterone excess with severe hypertension, hypokalemia, and metabolic alkalosis.

24. The answer is E.

(Chap. 16) Patients with autosomal dominant polycystic kidney disease have a two- to fourfold increased risk of subarachnoid or cerebral hemorrhage compared to the general population. Hemorrhage tends to occur before age 50 in patients with a family history of intracranial hemorrhage, patients with a personal history of intracranial hemorrhage, aneurysms larger than 10 mm, or patients with uncontrolled hypertension.

25. The answer is A.

(Chap. 16) This patient has a normal anion gap metabolic acidosis (anion gap = 12). The calculated urine anion gap ($Na^+ + K^+ - Cl^-$) is +3; thus the acidosis is unlikely to be due to gastrointestinal bicarbonate loss. In this patient the diagnosis is type I renal tubular acidosis, or distal RTA. This is a disorder in which the distal nephron does not lower pH normally. It is associated with a urine pH greater than 5.5, hypokalemia, and lack of bicarbonaturia. This condition may be associated with calcium phosphate stones and nephrocalcinosis. Type II RTA, or proximal RTA, includes a pH less than 5.5, hypokalemia, a positive urine anion gap, bicarbonaturia, hypophosphatemia, and hypercalciuria. This condition results from the defective resorption of bicarbonate. Type III RTA is rare and most commonly is seen in children. Type IV RTA is also referred to as hyperkalemic distal RTA. Hyporeninemic hypoaldosteronism is the most common cause of type IV RTA and is usually associated with diabetic nephropathy.

26. The answer is D.

(Chap. 16) In any patient with hypokalemia the use of diuretics must be excluded. This patient has multiple warning signs for the use of agents to alter her weight, including her age, gender, and participation in competitive sports. Her BMI is low, and the oral examination may suggest chronic vomiting. Chronic vomiting may be associated with a low urine chloride level. Once diuretic use and vomiting are excluded, the differential diagnosis of hypokalemia and metabolic alkalosis includes magnesium deficiency, Liddle's syndrome, Bartter's syndrome, and Gitelman's syndrome. Liddle's syndrome is associated with hypertension and undetectable aldosterone and renin levels. It is a rare autosomal dominant disorder. Classic Bartter's syndrome has a presentation similar to that of this patient. It may also include polyuria and nocturia because of hypokalemia-induced diabetes insipidus. Gitelman's syndrome can be distinguished from Bartter's syndrome by hypomagnesemia and hypocalciuria.

27. The answer is A.

(Chap. 17) Acute interstitial nephritis is a common cause of both acute and chronic kidney dysfunction. Many causes of interstitial nephritis are successfully treated with glucocorticoids with improved rates of long-term renal recovery including Sjögren's syndrome, sarcoidosis, systemic lupus erythematosus, adults with tubulointerstitial nephritis with uveitis, and idiopathic or other granulomatous interstitial nephritis. In patients with gradually progressive disease or

fibrosis on biopsy, the benefit is less clear. Additionally, allergic interstitial nephritis recovery may be accelerated with glucocorticoid therapy, but long-term renal recovery has not been proven to improve. Postinfectious interstitial nephritis has been associated with many bacterial and viral pathogens, but generally resolves with treatment of the underlying condition.

28. The answer is E.

(Chap. 17) Allergic interstitial nephritis is a common cause of unexplained acute renal failure. This is generally a clinical diagnosis with acute renal failure in the context of exposure to a potential offending agent (often NSAIDs, antibiotics, anticonvulsants, or proton pump inhibitors) and improvement in renal function with withdrawal of the agent. Peripheral blood eosinophilia supports the diagnosis, but is rarely found. Urine microscopy often shows white blood cell casts and hematuria, but these are not specific findings. Urine eosinophils are neither sensitive nor specific for allergic interstitial nephritis. A renal biopsy is generally not required but may show extensive tubulointerstitial infiltration of white cells including eosinophils.

29. The answer is A.

(Chap. 18) The patient presents with the classic pentad for thrombotic thrombocytopenic purpura (TTP), including fever, neurologic findings, renal failure, hemolytic anemia, and thrombocytopenia. This condition is more common in women than men, and in black than white patients, and may be triggered by a number of factors including pregnancy, infection, surgery, and pancreatitis. Several drugs have been implicated in the pathogenesis of TTP such as immunosuppressive agents, chemotherapeutic agents, and antiplatelet drugs. TTP may be differentiated from hemolytic uremic syndrome (HUS) by the demographics, with HUS typically affecting young children and TTP being more common in middle-aged persons. Additionally, HUS is generally triggered by a diarrheal illness, which is much less common in TTP. On a molecular level, the metalloprotease ADAMTS13 specific for von Willebrand factor (vWF) is generally low if not absent in activity in TTP. The development of HUS is likely driven by bacterial toxins such as shiga toxin or shiga-like toxin, often from *E. coli* 0157:H7. Because TTP is associated with low protein levels that may be driven by autoantibodies, plasma exchange serves the dual purpose of removing the aberrant antibody and repleting protein levels. With appropriate therapy, 1-month mortality is approximately 20%. Untreated mortality nears 90%, primarily from microvascular thrombosis and multiorgan failure.

30. The answer is C.

(Chap. 18) Renal vein thrombosis occurs in 10–15% of patients with nephrotic syndrome accompanying membranous glomerulopathy and oncologic disease. The clinical manifestations can be variable but may be characterized by fever, lumbar tenderness, leukocytosis, and hematuria. Magnetic resonance venography is the most sensitive and specific noninvasive form of imaging to make the diagnosis of renal vein thrombosis. Ultrasound with Doppler is operator dependent and therefore may be less sensitive. Contrast venography is the gold standard for diagnosis, but it exposes the patient to a more invasive procedure and contrast load. Nuclear medicine screening is not performed to make this diagnosis.

31. The answer is A.

(Chap. 9) Calcium stones account for 75–85% of all kidney stones. Although they are most commonly caused by idiopathic hypercalciuria, hypocitraturia, hyperuricosuria, and primary hyperparathyroidism are also causes. Uric acid stones are the next most common stone, followed by cysteine and struvite. Oxalic acid does not form stones without complexing with a positive cation, such as calcium. Struvite stones are precipitated by bacterial infections, such as *Proteus*, that promote conversion of urea to ammonium and raise urinary pH. General management for calcium stones includes increasing consumption of water, low protein, and low calcium. If this is ineffective, thiazide diuretics may be used.

32. The answer is D.

(Chap. 21) Urinary tract obstruction is an important and potentially reversible cause of kidney failure. This patient is at risk for urinary obstruction based on her history of colon cancer. Although recent NSAID use may be contributing to the rapidity of her kidney damage, routine dosing is less likely to cause acute kidney injury in the absence of preexisting renal dysfunction. Ultrasound of the kidneys is the best screening test for obstruction. Hydroureter and/or hydronephrosis may be found and suggest the presence of obstruction. Although obstruction may be unilateral, it rarely causes clinically significant renal failure in the absence of underlying renal disease. CT of the abdomen is useful after ultrasound to evaluate the site and etiology of obstruction. Post-void residual is useful if functional causes of obstruction are suspected, such as urinary retention. After the obstruction site is located, retrograde urography with stent placement may be indicated, but only after defining the presence or absence of obstruction.

33 and 34. The answers are E and D, respectively.

(Chap. 21) The patient has relief of recent urinary obstruction and is now making an inappropriately large amount of urine. This is likely due to postobstructive diuresis, which results from release of obstruction, increase in GFR over the course of days, decreased tubule pressure, and increased solute load per nephron, resulting in increased urine output. Decreased medullary osmolarity is a feature of chronic obstruction and persistent obstruction. The patient has not had recent head trauma or neurosurgical procedure and is unlikely to have cerebral salt wasting. Increased activation

of the renin-angiotensin-aldosterone system is associated with chronic, unrelieved obstruction. Patients with postobstructive diuresis are at risk for volume depletion with possible development of prerenal azotemia and resultant acute kidney injury, as well as electrolyte imbalance, particularly due to losses of Na, K, PO_4, Mg, and free water. Erythrocytosis may be seen in patients with obstruction, but is a rare feature and is not associated with postobstructive diuresis. Systemic hypotension is more common than hypertension due to volume depletion.

35. The answer is C.

(Chap. 21) In acute urinary tract obstruction, pain is due to distention of the collecting system or renal capsule. Acutely, there is a compensatory increase in renal blood flow when kidney function is impaired by obstruction, which further exacerbates capsular stretch. Eventually, vasodilatory prostaglandins act to preserve renal function when glomerular filtration rate has decreased. Medullary blood flow decreases as the pressure of the obstruction further inhibits the renal parenchyma from perfusing; however, the ensuing chronic renal destruction may occur without substantial pain. When an obstruction has been relieved, there is a postobstructive diuresis that is mediated by relief of tubular pressure, increased solute load (per nephron), and natriuretic factors. There can be an extreme amount of diuresis, but this is not painful.

36. The answer is D.

(Chap. 21) The level of obstruction is important when considering urinary tract obstruction. Bilateral hydronephrosis and hydroureter suggest either a systemic process or mechanical obstruction at or below the level of the ureterovesical junctions. While retroperitoneal fibrosis can cause such a picture, it is most common among middle-aged men. In patients of reproductive age, genital tract infections can cause meatal stenosis if left untreated or if infections are recurrent. Retroperitoneal lymphomas can cause bilateral hydroureter, as can more distal obstructions like phimosis. In the developing world, one may also consider schistosomiasis and genitourinary tuberculosis.

37. The answer is E.

(Chap. 14) Ultimately, solid organ transplant patients are at highest risk for infection because of T-cell immunodeficiency from antirejection medicines. As a result, they are also at risk for reactivation of many of the viruses from the herpes virus family, most notably cytomegalovirus, varicella-zoster virus, and Epstein-Barr virus. However, immediately after transplant, these deficits have not yet developed in full. Neutropenia is not common after solid organ transplantation as in bone marrow transplantation. In fact, patients are most at risk of infections typical for all hospitalized patients, including wound infections, urinary tract infection, pneumonia, *Clostridium difficile* infection, and line-associated infection. Therefore, a standard evaluation of a febrile patient in the first weeks after a solid organ transplant should include a detailed physical examination, blood and urine cultures, urinalysis, chest radiography, and *C. difficile* stool antigen or toxin studies if warranted, in addition to a transplant-specific evaluation.

38. The answer is E.

(Chap. 14) The patient presents with symptoms suggestive of infection in the middle period after transplantation (1–4 months). In patients with prior cytomegalovirus (CMV) exposure or receipt of CMV-positive organ transplant, this is a period of time when CMV infection is most common. The patient presented here has classic signs of CMV disease with generalized symptoms in addition to dysfunction of her transplanted organ (kidney). Often bone marrow suppression is present, demonstrated here by lymphopenia. Because CMV infection is linked with graft dysfunction and rejection, prophylaxis is frequently used, including valganciclovir. Trimethoprim–sulfamethoxazole is used for *Pneumocystis jiroveci* prophylaxis, acyclovir generally is used for varicella-zoster virus prophylaxis, itraconazole may be considered in patients considered at risk for histoplasmosis reactivation, and isoniazid is used for individuals with recent purified protein derivative conversion or positive chest imaging and no prior treatment.

39. The answer is D.

(Chap. 22) Bladder cancer is the fourth most common cancer in men and the thirteenth most common cancer in women. Cigarette smoking has a strong association with bladder cancer, particularly in men. The increased risk persists for at least 10 years after quitting. Bladder cancer is an infrequent cause of cancer deaths because most detected cases are superficial with an excellent prognosis. Most cases of bladder cancer come to medical attention by the presence of gross hematuria emanating from exophytic lesions. Microscopic hematuria is more likely caused by prostate cancer than bladder cancer. Cystoscopy under anesthesia is indicated to evaluate for bladder cancer. In cases of superficial disease, bacille Calmette-Guérin (BCG) is an effective adjuvant to decrease recurrence or treat unresectable superficial disease. In the United States, cystectomy is generally recommended for invasive disease. Even invasive cancer with nodal involvement has a greater than 40% 10-year survival after surgery and adjuvant therapy.

40 and 41. The answers are C and E, respectively.

(Chap. 22) The incidence of renal cell carcinoma continues to rise and is now nearly 58,000 cases annually in the United States, resulting in 13,000 deaths. The male-to-female ratio is 2 to 1. Incidence peaks between the ages of 50 and 70 years, although this malignancy may be diagnosed at any age. Many environmental factors have been investigated as possible contributing causes; the strongest association is with cigarette smoking. Risk is also increased for patients who have acquired cystic disease of the kidney

associated with end-stage renal disease and for those with tuberous sclerosis. Most renal cell carcinomas are clear cell tumors (60%) with papillary and chromophobic tumors being less common. Clear cell tumors account for more than 80% of patients who develop metastases. The classic triad of hematuria, flank pain, and a palpable mass is only present in 10% to 20% of patients initially. Most cases currently are found as incidental findings on computed tomography or ultrasonography done for different reasons. The increasing number of incidentally discovered low-stage tumors has contributed to an improved 5-year survival. The paraneoplastic phenomenon of erythrocytosis caused by increased production of erythropoietin is only found in 3% of cases; anemia caused by advanced disease is far more common. Stage 1 and 2 tumors are confined to the kidney and have a greater than 80% survival after radical nephrectomy. Stage 4 tumors with distant metastases have a 50-year survival of 10%. Renal cell carcinoma is notably resistant to traditional chemotherapeutic agents. Cytokine therapy with interleukin-2 or interferon-gamma produces regression in 10% to 20% of patients with metastatic disease. Recently, the advent of antiangiogenic medications has changed the treatment of advanced renal cell carcinoma. Sunitinib was demonstrated to be superior to interferon-gamma, and it (or sorafenib) is now first-line therapy for patients with advanced metastatic disease.

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