Nephrology and Hypertension

BOARD REVIEW

SECOND EDITION

Phuong-Chi T. Pham
Phuong-Thu T. Pham

Wolters Kluwer

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Preface

A practicing nephrologist is expected to have a firm grasp on a wide scope of potentially life-threatening electrolyte and acid–base disturbances; acquired and inherited kidney diseases; acute kidney injuries; complex chronic kidney disease–related metabolic, endocrinologic, skeletal/mineral, and cardiovascular complications; difficult-to-treat hypertension, kidney stones, all forms of kidney replacement modalities including hemodialysis, peritoneal dialysis, continuous renal replacement therapy, and kidney transplant, among many other topics. Mastering this broad spectrum of diseases can be a difficult task for the practicing nephrologists, particularly for those working in hectic private settings.

We aimed to write this book as an abbreviated review for renal fellows and general nephrologists who have limited time to study for the nephrology board certifying examination or who simply wish to review and update their nephrology knowledge. The book content closely reflects the American Board of Internal Medicine blueprint outlined for the nephrology certifying examination.

In this second edition, we have updated the latest guidelines and included more tables and figures to better illustrate difficult concepts, simplify differential diagnoses, and consolidate management strategies and options for commonly encountered conditions.

We herein also include foreword by Dr. Norimoto Yanagawa, Professor Emeritus of Medicine, David Geffen School of Medicine at the University of California, Los Angeles, to give us a glimpse into the exciting future of nephrology.

Abbreviations

[HCO_3^-]: serum bicarbonate concentration
Ab–Ag: antibody–antigen
ABMR: antibody-mediated rejection
ACC/AHA: American College of Cardiology/American Heart Association
ACEI: angiotensin-converting enzyme inhibitor
ACKD: acquired cystic kidney disease
ACR: acute cellular rejection
ACR: albumin-to-creatinine ratio
ACR: American College of Radiology
ACS: abdominal compartment syndrome
ACTH: adrenocorticotropic hormone
AD: autosomal dominant
ADAMTS13: *a d*isintegrin *a*nd *m*etalloproteinase with a *t*hrombospondin type 1 motif, member *13*
ADH: antidiuretic hormone
ADHF: acute decompensated heart failure
AE-1: anion exchanger 1
AER: albumin excretion rate
AFLP: acute fatty liver of pregnancy
AG: anion gap
AGE: advanced glycation end
AGE:RAGE: AGE and AGE-receptor interaction
aHUS: atypical hemolytic uremic syndrome
AII: angiotensin II
AKI: acute kidney injury
AKIN: Acute Kidney Injury Network
ALT: alanine aminotransferase
AME: apparent mineralocorticoid excess
ANCA: antineutrophil cytoplasmic antibody
ANP: atrial natriuretic peptide
APP: abdominal perfusion pressure
APS: antiphospholipid syndrome
AQP: aquaporin
AR: autosomal recessive
ARB: angiotensin-receptor blocker
ARDS: acute respiratory distress syndrome
ARR: aldosterone-to-renin ratio
AST: aspartate aminotransferase

ATIN: acute tubulointerstitial nephritis
ATN: acute tubular necrosis
ATP: adenosine triphosphate
AV: arteriovenous
AVF: arteriovenous fistula
AVG: arteriovenous graft
AVN: avascular necrosis
AVP: vasopressin
AVR: vasopressin receptor
AVS: adrenal venous sampling
AZA: azathioprine
BKN: BK nephropathy
BMI: body mass index
BP: blood pressure
BUN: blood urea nitrogen
C_{OSM}: osmolar clearance
CA: cancer antigen
CABG: coronary artery bypass grafting
CAD: coronary artery disease
CA II: carbonic anhydrase II
CA IV: carbonic anhydrase IV
CAPD: continuous ambulatory peritoneal dialysis
CaSR: calcium-sensing receptor
CCB: calcium channel blocker
CCT: cortical collecting tubule
CDC: complement-dependent cytotoxicity
cDI: central diabetes insipidus
CHF: congestive heart failure
CI-AKI: contrast-induced acute kidney injury
CKD: chronic kidney disease
CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration
CMV: cytomegalovirus
CNI: calcineurin inhibitor
CNS: central nervous system
CO: cardiac output
COPD: chronic obstructive pulmonary disease
CPK: creatine phosphokinase
cPRA: calculated panel reactive antibody
CR: complete remission
CrCl: creatinine clearance
CRRT: continuous renal replacement therapy
CRS: cardiorenal syndrome
CSA: cyclosporine
CSW: cerebral salt wasting

CT: computed tomography
CTG: chronic transplant glomerulopathy
CTIN: chronic tubulointerstitial nephritis
CTLA-4: cytotoxic T-lymphocyte–associated antigen-4
CVD: cardiovascular disease
CVP: central venous pressure
CVVH or CAVH: continuous venovenous (or arteriovenous) hemofiltration
CVVHDF: continuous venovenous hemodiafiltration
CYC: cyclophosphamide
D5: 5% dextrose
DBP: diastolic blood pressure
DCT: distal convoluted tubule
DDAVP: desmopressin
DDD: dense-deposit disease
DEXA: dual-energy X-ray absorptiometry
DGF: delayed graft function
DHP: dihydropyridine
DI: diabetes insipidus
DIC: disseminated intravascular coagulation
DKD: diabetic kidney disease
DM: diabetes mellitus
DOPPS: Dialysis Outcomes and Practice Patterns Study
DR: diabetic retinopathy
dRTA: distal renal tubular acidosis
DSA: donor-specific antibody
DVT: deep vein thrombosis
EBV: Epstein–Barr virus
ECG: electrocardiogram
EF: ejection fraction
EFWC: electrolyte-free water clearance
EGF: epithelial growth factor
eGFR: estimated glomerular filtration rate
eKt/V: equilibrated Kt/V
EM: electron microscopy
ENaC: sodium epithelial channel
EPO: erythropoietin
ESA: erythropoiesis-stimulating agent
ESRD: end-stage renal disease
ESWL: extracorporeal shock-wave lithotripsy
ET: endothelin
EVAR: endovascular aortic aneurysm repair
FBS: fasting blood sugar
$FeHCO_3$: fractional excretion of bicarbonate
FeMg: fractional excretion of magnesium

FeNa: fractional excretion of sodium
$FePO_4$: fractional excretion of phosphate
FeUrea: fractional excretion of urea
FGF-23: fibroblast growth factor 23
FHH: familial hyperkalemic hypertension (Gordon) or familial hypocalciuric hypercalcemia
FiO_2: fraction of inspired oxygen
FLC: free light chain
FMD: fibromuscular dysplasia
FSGS: focal segmental glomerulosclerosis
FWC: free water clearance
GBM: glomerular basement membrane
GFR: glomerular filtration rate
GI: gastrointestinal
GN: glomerulonephropathy
GRA: glucocorticoid-remediable aldosteronism
GU: genitourologic
HAART: highly active antiretroviral therapy
hANP: human atrial natriuretic peptide
Hb: hemoglobin
HbA1C: hemoglobin A1C
HBV: hepatitis B virus
HCTZ: hydrochlorothiazide
HCV: hepatitis C virus
HD: hemodialysis
HDL: high-density lipoprotein
HELLP: *h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelets
HF: heart failure
HIT: heparin-induced thrombocytopenia and/or thrombosis
HIV: human immunodeficiency virus
HLA: human leukocyte antigen
HMG-CoA: hydroxymethylglutaryl-CoA
HPF: high-power field
hPTH: hyperparathyroidism
HR: hazard ratio
HRS: hepatorenal syndrome
HSP: Henoch–Schönlein purpura
HSS: hypertonic saline solution
HTN: hypertension
HUS: hemolytic uremic syndrome
IAH: intra-abdominal hypertension
IAP: intra-abdominal pressure
IC: immune complex
ICP: intracranial pressure
ICU: intensive care unit

IDH: isolated diastolic hypertension
IDH: isolated dominant hypomagnesemia
IDWG: interdialytic weight gain
IF: immunofluorescent microscopy
IgAN: IgA nephropathy
IGIV: intravenous immunoglobulin
iMGN: idiopathic membranous glomerulonephropathy
INR: international normalized ratio
IRRT: intermittent renal replacement therapy
ISH: isolated systolic hypertension
IV: intravenous
IVC: inferior vena cava
KDIGO: Kidney Disease: Improving Global Outcomes
KDOQI: Kidney Disease Outcomes Quality Initiative
LDH: lactate dehydrogenase
LDL: low-density lipoprotein
LM: light microscopy
LN: lupus nephritis
LVEDA: left ventricular end-diastolic area
MAG3: mercaptoacetyltriglycine (used in nuclear renal scanning)
MAHA: microangiopathy and hemolytic anemia
MAP: mean arterial pressure
MARS: molecular adsorbent recirculating system
MBD: mineral bone disease
MCD: minimal change disease
MDRD: Modification of Diet in Renal Disease
MELD: model for end-stage liver disease
MFI: mean fluorescence intensity
MGN: membranous glomerulonephropathy
MHC: major histocompatibility complex
MM: multiple myeloma
MMF: mycophenolate mofetil
MPA: mycophenolic acid
MPGN: membranoproliferative glomerulonephritis/
MPGN: membranoproliferative glomerulonephropathy
MPO: myeloperoxidase
MRA: mineralocorticoid receptor antagonist
MRI: magnetic resonance imaging
mTOR: mammalian target of rapamycin
Na^+_e; K^+_e: exchangeable Na^+; exchangeable K^+
NBC: sodium bicarbonate cotransporter
NCC: sodium chloride cotransporter
nDI: nephrogenic diabetes insipidus
NE: norepinephrine

NFAT: nuclear factor of activated T cells
NHE3: sodium–hydrogen exchanger-3
NODAT: New-Onset Diabetes Mellitus After Transplant
NOS: not otherwise specified
NPT: sodium–phosphate transporter
NS: normal saline
NSAIDs: nonsteroidal anti-inflammatory drugs
NSF: nephrogenic systemic fibrosis
NSIAD: nephrogenic syndrome of inappropriate antidiuresis
NT-proBNP: N-terminal of the prohormone brain natriuretic peptide
ODS: osmotic demyelination syndrome
OGTT: oral glucose tolerance test
OPTN/UNOS: Organ Procurement and Transplantation Network/United Network of Organ Sharing
P[K^+]: plasma potassium concentration
P[Na^+]: plasma sodium concentration
PA: pulmonary artery
PAI-1: plasminogen activator–inhibiting factor 1
PAN: polyarteritis nodosa
PaO_2: arterial partial pressure
PAoP: pulmonary artery occlusion pressure
PCR: polymerase chain reaction
PCR: protein-to-creatinine ratio
PD: peritoneal dialysis
PDG: phosphate-dependent glutaminase
PEEP: positive end-expiratory pressure
PEPCK: phosphoenolpyruvate carboxykinase
PGL: paraganglioma
PGNMID: proliferative glomerulonephritis with monoclonal immunoglobulin deposits
PH: primary hyperoxaluria
PHA: pseudohypoaldosteronism
PHEO: pheochromocytoma
PMN: polymorphonuclear leukocyte
POSEIDON trial: Prevention of Contrast Renal Injury with Different Hydration Strategies trial
PPAR: peroxisome proliferator–activated receptor
PPV: pulse pressure variation
PR: partial remission
PR3: proteinase 3
PRA: panel–reactive antibody
PRA: plasma renin activity
PRCA: pure red cell aplasia
PRES: posterior reversible encephalopathy syndrome
pRTA: proximal renal tubular acidosis
PTF: pentoxifylline
PTH: parathyroid hormone

PTHrp: parathyroid hormone–related peptide
PTLD: posttransplantation lymphoproliferative disorder
PTRA: percutaneous transluminal renal angioplasty
PTT: partial thromboplastin time
PVR: peripheral vascular resistance
RAAS: renin–angiotensin–aldosterone system
RBC: red blood cell
RCC: renal cell carcinoma
ROMK: renal outer medullary potassium channel
RRT: renal replacement therapy
RTA: renal tubular acidosis
RUA: routine urinalysis
S[K^+]: serum potassium concentration
S[Na^+]: serum sodium concentration
S_{OSM}: serum osmolality
S(PO_4): serum phosphate concentration
SAG: serum anion gap
SBP: systolic blood pressure
$S_{CV}O_2$: oxygen saturation in central vein
SCa: total serum calcium
SCD: sickle cell disease
SCr: serum creatinine
SCUF: slow continuous ultrafiltration
sFLt1: soluble fms-like tyrosine kinase 1
SGLT2: sodium–glucose cotransporter 2
SIADH: syndrome of inappropriate secretion of antidiuretic hormone
SLE: systemic lupus erythematosus
SLEDD: sustained low-efficiency daily dialysis
SNAT3: sodium-dependent amino acid transporter 3
SNS: sympathetic nervous system
S_{OG}: serum osmolality gap
SPEP: serum protein electrophoresis
SRC: scleroderma renal crisis
SSRI: selective serotonin reuptake inhibitor
SV: stroke volume
SVR: systemic vascular resistance
SVV: stroke volume variation
t½: half-life
TAC: tacrolimus
TB: tuberculosis
TBM: tubular basement membrane
TBMN: thin basement membrane nephropathy
TEB: thoracic electrical bioimpedance
TG: triglycerides

TGF: transforming growth factor
TIPS: transjugular intrahepatic portosystemic shunt
TLS: tumor lysis syndrome
TMP: transmembrane pressure
TRALI: transfusion-related acute lung injury
TRIM: transfusion-related immunomodulation
TRPV5: transient receptor potential V5 channel
TSAT: serum transferrin saturation
TTP: thrombotic thrombocytopenic purpura
TZD: thiazolidinedione
U[K^+]: urine potassium concentration
U[Na^+]: urine sodium concentration
$U_{GLUCOSE}$: urine glucose concentration
U_{OSM}: urine osmolality
U_{PO4}: urine phosphate concentration
U_{UREA}: urine urea concentration
U_{Cr}: urine creatinine concentration
UF: ultrafiltration
uPCR: urine protein-to-creatinine ratio
UPEP: urine protein electrophoresis
URR: urea reduction ratio
UT: urea transporter
V_d: volume of distribution
VDRA: vitamin D receptor agonist
VEGF: vascular endothelial growth factor
VZV: varicella zoster virus
WBC: white blood cell
WCH: white coat hypertension
WNK: with-no-lysine kinase
WRN: warfarin-related nephropathy
XO: xanthine oxidase

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We thank our late parents for their guidance, endless sacrifices, and unconditional love and support.

In honor and memory of our most loving and supportive parents, We direct all proceeds from this book to the Pham Family Patient Assistance Fund, Created in September 2015, To help financially challenged patients with basic fees while seeking medical care.

Foreword

The Future of Building a Kidney

Norimoto Yanagawa

Nearly 75 years after Dr. Willem Kolff successfully treated his first uremic patient with dialysis in 1945, dialysis remains the only viable long-term extracorporeal organ replacement therapy, which, as we know, is associated with complications and poor quality of life. On the other hand, while kidney transplantation currently offers the best option for patients with end-stage kidney disease (ESKD), it is also limited by the scarcity of donor organs and the need for immunosuppression. Therefore, the idea that a human kidney might be created de novo in a laboratory is not only inspiring for nephrologists and renal scientists but also provides hope for ESKD patients. The capability of creating a patient-specific custom-made kidney will not only eliminate the need for dialysis but also solve the donor shortage problem and avoid the need for life-long immunosuppression.

A major milestone that brought this dream closer to reality was the report by a group of researchers in Japan led by Yamanaka in 2006, showing that somatic cells can be reprogrammed to become embryonic stem cell–like cells, that is, induced pluripotent stem cells (iPSCs).[1] Subsequent studies showed that the iPSCs derived from human somatic cells, such as fibroblasts, could be differentiated into different cell types from all three germ layers in vitro. These advances opened an avenue for a whole new era of regenerative medicine and spurred an avalanche of attempts to generate new organs in the laboratory, including kidneys. Since then, protocols have been developed to convert iPSCs into kidney-specific lineages, and various approaches have been taken aiming to create new kidneys using iPSC-derived kidney

progenitor cells.

One such approach is decellularization/recellularization. Native kidney extracellular matrix (ECM) has been reported to provide a scaffold for cell seeding and a niche for stem cells to differentiate into adult kidney cells. Decellularized scaffolds can be prepared by continuous rinsing of the whole kidney with detergent, such as sodium dodecyl sulfate (SDS), through the renal artery until all cells are removed. Recellularization of the kidney scaffold is then made by the anterograde infusion of cells through the vasculature, together with retrograde infusion of cells through the ureter under negative pressure.[2] For clinical applications, kidney scaffolds could be obtained from porcine or discarded human kidneys. However, the major challenges of this approach lie in the difficulty of reintroducing all the required cell types into the complex narrow channels of the nephrons within the scaffolds. It is also unclear whether the ECM alone can induce the differentiation of iPSCs to become more than two dozen different types of adult kidney cells at each specific location. Clearly, there is a long way to go to recreate an organ of this scale in this way.

Another approach that was proposed is 3D bioprinting, which is a technology that can accurately deposit living cells or cell aggregates together with hydrogel-based supporting biomaterials, that is, bio-ink, into precise geometries to build organ-like structures in three dimensions. In recent years, 3D proximal tubule channels have been printed on microfluidic chips, providing an in vitro model for studying proximal tubule function and toxicology.[3] However, despite the great potential of this technology in the field of tissue engineering, it is obvious that the spatial resolution of current bioprinting technology remains insufficient to recapitulate the hierarchical structure of a complex organ like the adult kidney that consists of up to a million nephrons, with each nephron containing more than two dozen different type of cells at different locations.

In order to circumvent such an insurmountable hurdle imposed by the complex structure of the adult human kidney, alternative approaches have also been attempted. One such approach is xenotransplantation. Owing to the rapid progress of genome editing technology, attempts have been made to

generate genetically engineered pigs that possess organs transplantable to humans by, for example, eliminating the histocompatibility complexes responsible for rejection upon xenotransplantation and inactivating porcine endogenous retrovirus to prevent possible infection of human recipients. Along this line of approach is a strategy called blastocyst complementation, which is a method aimed at generating organs in vivo by injecting iPSCs into blastocyst-stage embryos of a recipient host animal that is genetically manipulated to carry DNA mutations that prevent the development of a target organ. The injection of donor-derived iPSCs would therefore developmentally compensate for the defect and contribute to the generation of the missing organ that consists of cells derived from the injected iPSCs. This strategy has been used for the reconstitution of iPSC-derived mouse kidney in *Sall1*-targeted anephric rats.[4] However, besides issues related to the xenogenic barriers that remain to be solved, complete compensation of all renal lineages, including vascular and nervous systems in the kidney, requires multiple mutations in a host animal strain that lacks all these lineages. In addition, the ethical concern of generating interspecific chimeras containing brain derived from the injected iPSCs requires additional genetic modifications to prevent such possibility.

Another approach to sidestep the obstacle of the complex structure of the adult kidney is to focus on the structurally relatively simple embryonic kidney. Mammalian adult kidney is developed from an embryonic primordium called metanephros. Metanephros is formed from three populations of kidney precursor cells, that is, metanephric mesenchymal (MM) cells, ureteric bud (UB) cells, and stromal (SM) cells. Through their mutual interactions, MM cells induce branching of UB cells from Wolffian duct to form the collecting tubules and urinary drainage tract, while UB cells induce mesenchymal–epithelial transition (MET) of MM cells to form the remaining tubular structures. The SM cells differentiate to become mesangial cells and also contribute to the development of vasculature and interstitium in the kidney.

It was shown that when metanephroi harvested from mouse embryos were implanted into another recipient animal, they induced minimal immune

response and survived to develop normal architecture identical to the native kidney. They were also vascularized to achieve glomerular filtration and produced renin, erythropoietin, and 1,25-dihydroxyvitamin D3. These observations have raised hope that structurally relatively simple embryonic kidneys may be generated and implanted in vitro to develop into adult kidneys in vivo, that is, the developmental engineering approach.

Resembling embryonic kidneys are kidney organoids developed from iPSC-derived kidney progenitor cells.[5] The term “organoids” refers to suspensions of human pluripotent stem cells that self-organize in culture to form small organs and tissue arrangements. Therefore, a kidney organoid is a miniaturized and simplified version of a kidney produced in vitro that shows a realistic renal microanatomy. When iPSC-derived kidney precursor cells are aggregated and placed in organ culture, impressive morphogenesis proceeds in three dimensions to form nephron-like structures, including glomeruli, proximal tubules, loop of Henle, distal tubules, and collecting tubules, as shown by the expression of the respective marker proteins. Kidney organoids can thus serve as a useful tool for not only studying human kidney development but also the generation of patient-specific organoids, which can also serve as a useful platform for disease modeling and drug screening. However, the kidney organoids that have been reported so far are immature in terms of their developmental stage. They are also limited in their growth, with only up to 100 nephrons, as compared to a million in the adult human kidney. These organoids also do not develop cortex/medulla patterning, which is required for urine concentration. Furthermore, there is no congruent collecting system, including renal pelvis and ureter, and so when these kidney organoids are implanted, the urine generated cannot be drained into the urinary bladder, which results in hydronephrosis. Therefore, although kidney organoid may be sufficient for drug screening or disease modeling, it cannot represent a tissue capable of renal replacement, at least at its current state.

In conclusion, despite the significant progress made, reconstruction of a complete functional kidney remains difficult, and many problems remain unsolved. However, with the accelerating advances in stem cell biology and bioengineering, the possibility of creating a patient-specific custom-made

kidney is no longer science fiction. It will open the door to new therapeutic strategies for kidney regeneration and provide hope to ESKD patients.

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Contents

CHAPTER 1

Sodium/Water

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HYPONATREMIA

Background

Definition

- Hyponatremia is clinically defined as a serum sodium concentration (S[Na^+]) <136 mmol/l. plasma sodium concentration (p[na^+]) refers to sodium concentration [na^+] in the plasma in vivo or in the plasma of anticoagulated blood ex vivo. s[na^+] refers to [na+] measured in the serum extracted from coagulated blood ex vivo. p[na+] and s[na+] may herein be used interchangeably.

Determinants of body tonicity and S[Na^+]

- Thirst
- Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH):
  - AVP or ADH is synthesized in the paraventricular neurons of the hypothalamus as pre-pro-AVP and proteolytically cleaved into ***vasopressin*** + neurophysin II + ***copeptin*** (**Fig. 1.1**).

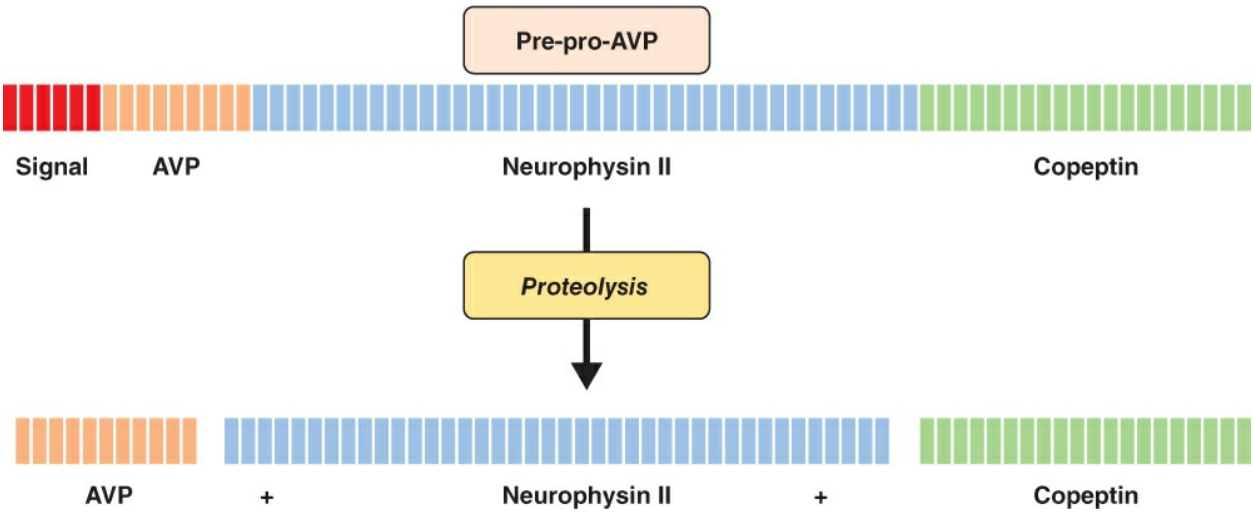

FIGURE 1.1 Proteolysis of pre-pro-AVP. Abbreviation: AVP, vasopressin.

- These molecules are stored in secretory granules in the posterior pituitary and released upon osmotic (e.g., hyperosmolality) and nonosmotic stimuli (e.g., stress, drug induced, nausea, and pain).
- ADH may be seen as a "pituitary bright spot" or hyperintense T1 signal within the posterior pituitary on brain MRI. The loss of this "pituitary bright spot" suggests the lack of ADH, and thus the diagnosis of central diabetes insipidus (cDI). However, one-third of patients with cDI may have normal brain MRI. Thickening or enlargement of the pituitary stalk may also be seen in cDI.
- **Copeptin** as a surrogate for ADH:
  - Copeptin is the C-terminal segment of pro-AVP that is released in equivalent amounts as AVP.
  - Blood level of copeptin is more easily measured than that of ADH (greater stability than ADH) and has been suggested to be a good ADH surrogate.
  - The osmotic threshold for both ADH and copeptin release is 282 ± 4.3 mOsm/kg.
  - Copeptin levels parallel ADH levels in various clinical settings:
    - Increased levels in heart failure (HF), syndrome of inappropriate ADH secretion (SIADH), sepsis
    - Reduced levels in cDI
  - Copeptin level has been shown to increase earlier than troponin in

acute myocardial infarction and has been suggested to be used as an early marker for its diagnosis.

- Na^+ and K^+: both Na^+ and K^+ are effective exchangeable solutes.
  - The early Edelman equation predicts $P[Na^+]$ is directly proportional to $(Na^+_e + K^+_e)$ as follows:

$$P[Na^+] = 1.11 \times (Na^+_e + K^+_e)/(\text{total body water}) - 25.6$$

    where $(Na^+_e + K^+_e)$ represents the sum of total body *exchangeable* Na^+ and K^+ and the *constant 25.6* represents the pool of *osmotically inactive* Na^+ and K^+ (*e.g., "inexchangeable" Na^+ and K^+ sequestered in bones, nonfluid phase*).

  - Over the years, modifications to the Edelman equation have been derived, partly because the complete equivalence of Na^+ and K^+ have been questioned. Although newer equations may be more factually accurate, older equations are sufficiently accurate in predicting $P[Na^+]$ in the clinical setting.
  - Key point to remember from Edelman equation for routine clinical purposes:

    Equimolar amounts of exchangeable Na^+ and K^+ have similar effect on raising $P[Na^+]$. That is, giving a patient 50 mmol of Na^+ increases $P[Na^+]$ similarly as giving the same patient 50 mmol of K^+.

    Figure 1.2 illustrates plausible mechanisms on how administering K^+ can increase $P[Na^+]$.

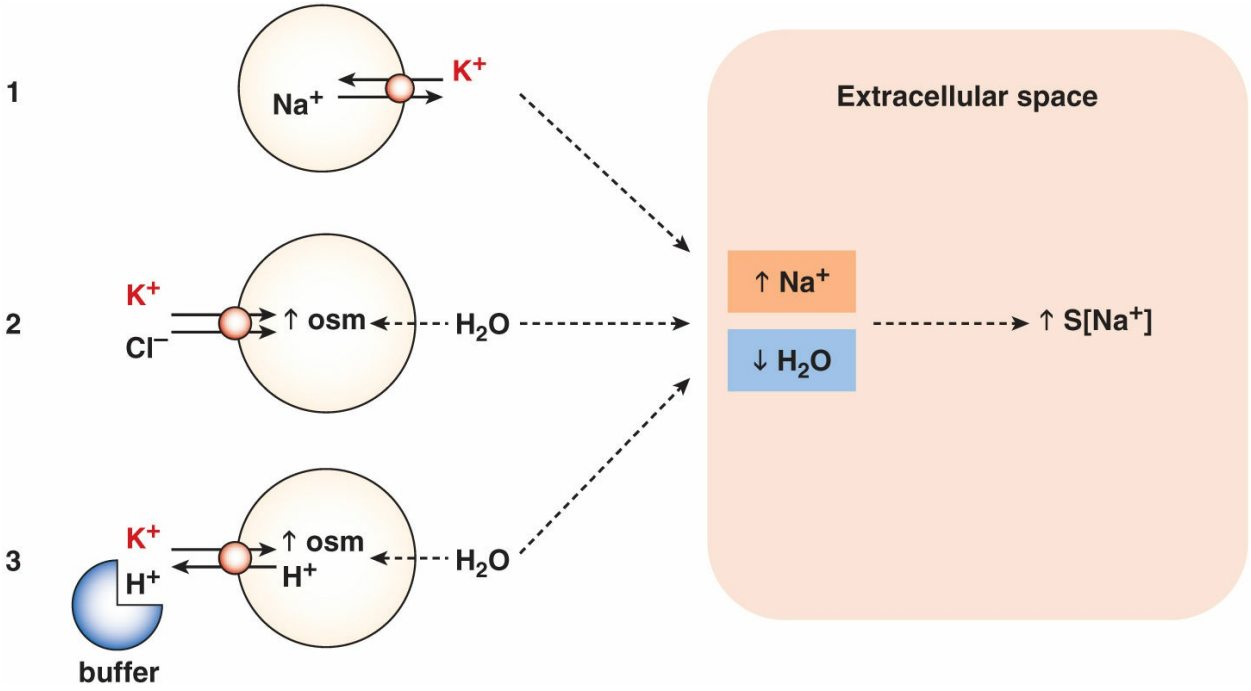

FIGURE 1.2 Mechanisms whereby potassium administration can increase serum sodium concentration ($S[Na^+]$). **(1)** Potassium enters cells in exchange for sodium, which increases $S[Na^+]$; **(2)** potassium enters cells along with chloride to maintain electrical neutrality, which leads to increased intracellular osmolality and subsequent intracellular water shift. The reduced extracellular water volume leads to increased $S[Na^+]$; or **(3)** potassium enters cells in exchange for a proton. While potassium entry increases intracellular osmolality, therefore intracellular water shift and subsequent increase in $S[Na^+]$, the extracellular proton shift is taken up by the extracellular buffer system and does not affect extracellular osmolality. Abbreviations: osm, osmolality; $S[Na^+]$, serum sodium concentration.

Clinical Significance and Manifestations of Hyponatremia

- Clinical significance:
  - Increased all-cause mortality reported in various settings (e.g., ambulatory setting, emergency department, intensive care unit, geriatric patients, patients with HF or ST-elevation myocardial infarction, patients with cirrhosis, patients receiving kidney replacement therapies)
  - Increased postoperative morbidities (major coronary events, wound infections, pneumonia, acute kidney injury [AKI] requiring dialysis, length of hospital stay)
  - Predictor of hepatorenal syndrome (HRS), hepatic encephalopathy in patients with liver disease
  - Increased risks for osteoporosis, gait instability, fall, and fracture
- Clinical manifestations:

- Risk and severity of neurologic effects depend on the rate of change of S[Na^+]. In acute and severe hyponatremia, free water shifts into brain cells and potentially causes brain edema. Severe neurologic complications and death can follow due to the confinement of the brain within the skull.
- Mild: S[Na^+] ≥125 mmol/L: usually asymptomatic to minimally symptomatic
- Moderate: impaired attention, poor mentation, lethargy, headaches, nausea/vomiting, disorientation, muscle cramps, reduced reflexes
- Severe: hyponatremic encephalopathy, seizures, coma, respiratory arrest, brain stem herniation, death. Hospitalized premenstrual women are thought to be at increased risk for hyponatremic encephalopathy compared to men and postmenopausal women.

Broad Categorization of Hyponatremia

- **Pseudohyponatremia:**
  - Refers to falsely low S[Na^+]. Flame photometric assay is an old method used to detect sodium content *via* intensity of flame color divided by serum volume. In patients with falsely elevated serum volume due to space-occupying paraproteins or lipids, the S[Na^+], defined as sodium content divided by the serum volume, will be falsely low. Newer methods of measuring S[Na^+] are now widely used to avoid pseudohyponatremia:
    - Ion-specific electrodes that measure [Na^+] directly from the serum
    - Supracentrifugation of serum to remove paraproteins/lipids prior to measuring S[Na^+]
  - Conditions with falsely high plasma volume leading to "pseudohyponatremia":
    - Severe hyperlipidemia
    - Hyperparaproteinemia (multiple myeloma, Waldenstrom macroglobulinemia)
- **Extracellular H_2O shift:** transient hyponatremia due to extracellular free H_2O shift in the presence of osmotically active agents in the extracellular

space

- Hyperglycemia
- Hypertonic mannitol
- Sucrose, maltose (mixed in intravenous immunoglobulin G [IgG] solutions)

- **True hyponatremia:** truly low Na^+ content per unit water volume, due to increased free water retention, excessive Na^+ loss, or both leading to a hypoosmolar state

Differential Diagnoses of True Hyponatremia

Hypovolemic hyponatremia (Fig. 1.3)

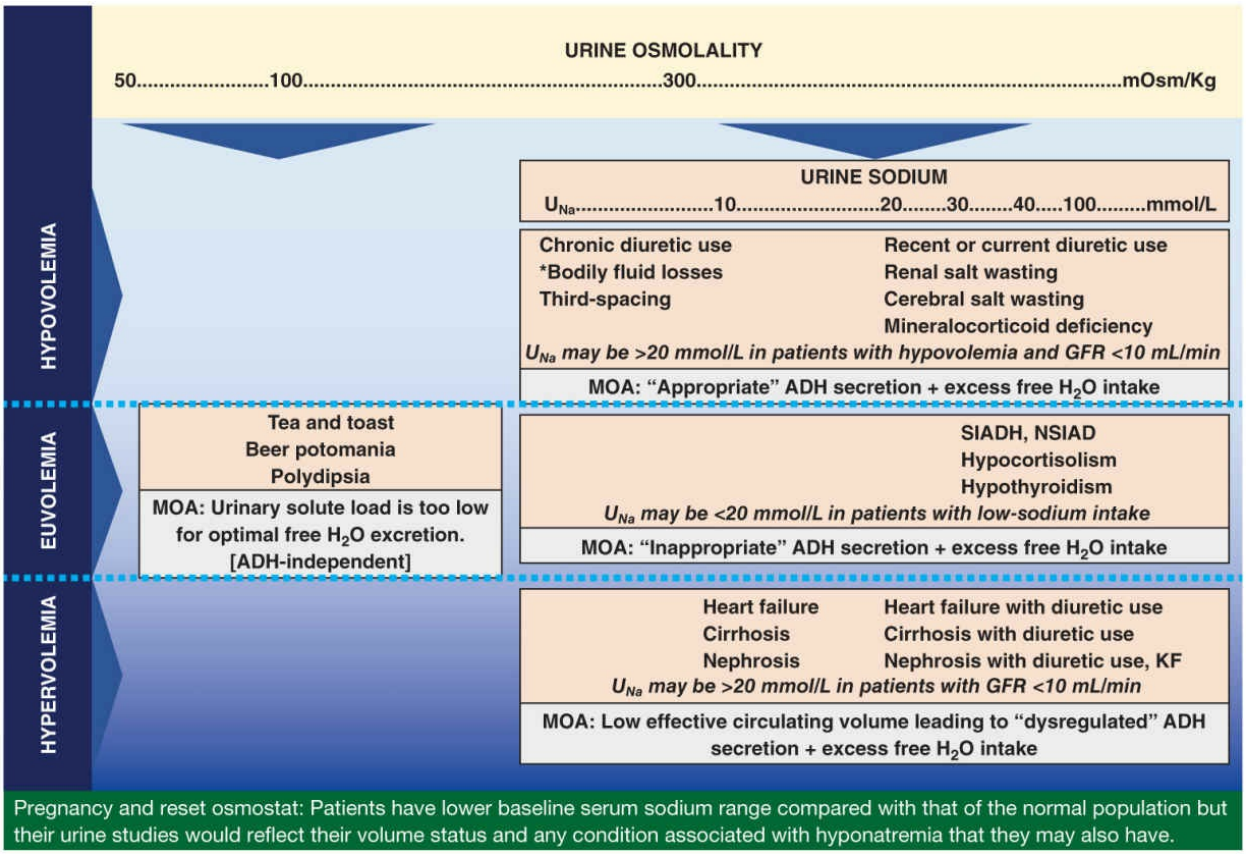

FIGURE 1.3 Differential diagnoses and clinical evaluation of hyponatremia. Abbreviations: ADH, antidiuretic hormone; GFR, glomerular filtration rate; KF, kidney failure; MOA, mechanism of action; NSIAD, nephrogenic syndrome of inappropriate antidiuresis; SIADH, syndrome of inappropriate antidiuretic hormone secretion; U_{Na}, urine sodium concentration. *Blood loss, diarrhea, vomitus, sweats.

- Mechanism of hypovolemic hyponatremia: appropriate increase in ADH

secretion due to volume depletion + H_2O intake

- Conditions associated with hypovolemic hyponatremia:
  - Bodily fluid loss, chronic diuretics (thiazides), third-spacing
    - Typical presentation: hypovolemia; urine Na^+ concentration (U_{Na}) < 20 mmol/l, urine osmolality (u_{osm}) typically >300 mOsm/kg.
  - Renal salt wasting: acute or recent diuretic use, tubulointerstial diseases, mineralocorticoid insufficiency (typically with adrenal insufficiency), cerebral salt wasting (CSW)
    - Typical presentation: hypovolemia, U_{Na} > 20 to 30 mmol/L, U_{OSM} typically >300 mOsm/kg
- In patients with any cause of hypovolemic hyponatremia *and* advanced kidney failure, tubular reabsorption of sodium and concentrating capacity may be reduced, in which case U_{Na} may be >20 mmol/L and U_{OSM} may not be concentrated to above 300 to 400 mOsm/kg.

Euvolemic hyponatremia

This may be driven by either the inappropriate secretion of ADH or mechanisms independent of ADH.

Euvolemic hyponatremia: ADH dependent

- Mechanism of ADH-dependent euvolemic hyponatremia: ADH secretion is inappropriate (i.e., ADH is NOT secreted in response to volume loss or hyperosmolar state) + H_2O intake.
- Conditions associated with “inappropriate” ADH euvolemic hyponatremia:
  - SIADH: central nervous system (CNS) or pulmonary pathology, drugs affecting the CNS, antipsychotics, antiepileptics, antidepressants, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclophosphamide, acute pain, nausea/vomiting, hypoglycemia, symptomatic HIV
    - Laboratory criteria for SIADH: U_{OSM} > 150 mOsm/kg, U_{Na} > 20 to 30 mmol/L
    - Note that these laboratory criteria are not valid for the diagnosis of SIADH among patients with advanced chronic kidney disease (CKD) or very low sodium intake. Patients with advanced CKD may have U_{OSM} > 150 because of poor diluting capacity and not necessarily

relating to a high ADH state.

NOTE Patients with advanced CKD have poor diluting as well as concentrating capacity. For this reason, they cannot optimally dilute their urine in the event of hyponatremia or optimally concentrate their urine in the event of hypernatremia.

- Severe hypothyroidism (myxedema coma or thyroid-stimulating hormone > 50 mIU/mL): mechanisms unclear, thought to be due to both ADH-dependent and possibly ADH-independent mechanisms. ADH-dependent mechanism is thought to reflect reduced cardiac output and hypoperfusion of the kidneys.
- Hypocortisolism leads to increased synthesis of corticotropin-releasing hormone, which is coexpressed with ADH and, thus, increased ADH level.
- Pregnancy: reduced threshold for ADH secretion + increased thirst

- Typical presentation for conditions associated with "inappropriate" ADH secretion:
  - Clinical criteria: euvolemia, $U[Na^+]$ > 20 to 30 mmol/L (on normal dietary water and sodium intake), U_{OSM} > 150 mOsm/kg, and low serum uric acid

NOTE In the presence of hyponatremia, the kidneys are expected to maximally dilute the urine to <100 mosm/kg. any urine osmolality >150 mOsm/kg in the presence of hyponatremia indicates either suboptimal diluting capacity by the kidneys or presence of ADH, whether it be appropriate, inappropriate, or dysregulated. Suboptimal diluting capacity by the kidneys may be seen in patients of older age or with poor kidney function.

  - In addition to the clinical criteria above, hypothyroidism, hypocortisolism, diuretic use (particularly thiazides), and reduced kidney function must also be ruled out prior to making the diagnosis of SIADH.
  - Other tests that may be considered in the diagnosis of SIADH:
    - Fractional excretion of uric acid: A level >12% has been suggested to provide a positive predictive value of 100% for the diagnosis of SIADH, whereas a value of <8% excludes the diagnosis.
    - Water loading test: In equivocal cases of SIADH, a water loading test

may be considered. This test may only be performed in patients with mild hyponatremia (*not* in those with moderate or severe hyponatremia). In this test, normal individuals will dilute the urine to U_{OSM} < 100 mosm/kg and appropriately excrete >90% of a free water load (given at 20 mL/kg body weight) within 4 hours, whereas patients with SIADH will inappropriately hold on to the free water load. See **Appendix A** for protocol.

Euvolemic hyponatremia: ADH independent

- Reset osmostat
  - Mechanism of disease: lower osmotic threshold for ADH release
  - Conditions associated with reset osmostat: normal variant, hypothalamic injury, malnutrition
  - Laboratory findings: U_{Na} and U_{OSM} vary according to volume status and S_{OSM}
- Primary polydipsia
  - Mechanism for hyponatremia: water load exceeds the capacity of the kidneys to excrete free water ingestion
  - Conditions associated with primary polydipsia: psychiatric patients ± phenothiazines with associated dry mouth, hypothalamic infiltrative disease such as sarcoidosis affecting thirst center, use of mouth-drying medications (e.g., anticholinergic agents, decongestants)
- Tea and toast syndrome, beer potomania:
  - Mechanism of hyponatremia: insufficient solute intake to provide the necessary solute load required by the kidneys to excrete water. Kidneys cannot excrete pure free water. Kidneys need a minimum of 50 to 100 mOsm of solute to excrete every 1 L of water. The “maximal diluting capacity” of healthy kidneys is typically 50 to 100 mOsm/kg. Patients with poor kidney function have reduced “maximal diluting capacity”; therefore, U_{OSM} may be on the higher range of 100 to 150 mOsm/kg.
- Increased H_2O reabsorption from the use of irrigation fluids with various genitourinary procedures (e.g., transurethral resection, hysteroscopy, nephrolithotomy) may lead to hyponatremia for the following reasons:
  - 1.5% glycine solution:

        - Solution is hypotonic: osmolality = 200 mOsm/kg
        - Glycine may also directly stimulate ADH secretion.
    - 3% sorbitol:
        - Solution is hypotonic: osmolality = 165 mOsm/kg. Additionally, sorbitol is metabolized to glucose + fructose in liver, then to CO_2 and H_2O.
        - Fructose is also known to stimulate ADH synthesis.

NOTE 5% mannitol solution usually does not cause hyponatremia because it is isotonic to plasma, osmolality = 275 mOsm/kg.

- Typical presentation for all ADH-independent conditions above: euvolemia, U[Na^+] is variable depending on sodium intake; U_{OSM} < 100 to 150 mosm/kg (kidneys appropriately dilute urine to excrete free h_2o).
- Nephrogenic syndrome of inappropriate antidiuresis (NSIAD)
    - Mechanism of disease: X-linked gain-of-function mutation of vasopressin 2 receptor (AVP2R); these receptors are constitutively activated in the absence of ADH.
    - Typical presentation:
        - Hyponatremia (female carriers may be asymptomatic with mild hyponatremia), decreased thirst, infrequent voiding (due to increased tubular H_2O reabsorption)
        - Laboratory findings are similar to those seen with SIADH, but ADH level is undetectable (in contrast to SIADH where ADH levels are high).
        - Similar to patients with SIADH, those with NSIAD also have abnormal response to water loading test.
    - Definitive diagnosis requires sequencing of the *AVP2R* gene.

Hypervolemic hyponatremia

- ADH dependent: dysregulated continuing ADH secretion due to conditions associated with reduced effective circulating volume (e.g., HF, cirrhosis, nephrotic syndrome)
- ADH independent: advanced kidney failure, oliguria/anuria—kidneys have

reduced capacity to excrete free water load.

Hyponatremia with variable volume status

- Exercise-induced hyponatremia (e.g., marathon runner hyponatremia):
  - Volume status is variable.
  - Mechanisms of hyponatremia: (1) excess free water ingestion relative to salt and water loss from sweating and (2) concurrent increased ADH level associated with muscle injury during heavy exercise
  - To avoid exercise-induced hyponatremia, heavy exercisers should be advised to only drink per thirst.

Drugs Associated With Hyponatremia

- Drugs affecting both sodium and H_2O homeostasis: diuretics (thiazides, indapamide, amiloride, furosemide)
- Drugs affecting H_2O homeostasis:
  - Increase hypothalamic ADH production: antidepressants (amitriptyline, protriptyline, desipramine, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors), antipsychotics (thioridazine, trifluoperazine, haloperidol), antiepileptics (carbamazepine, oxcarbazepine, sodium valproate), chemotherapeutic agents (vincristine, vinblastine, IV cyclophosphamide, melphalan, ifosfamide, methotrexate, interferon α and γ, levamisole, pentostatin, monoclonal antibodies), opiates
  - Potentiate ADH effect: antiepileptics (carbamazepine, lamotrigine), antidiabetics (chlorpropamide, tolbutamide), anticancer agents (IV cyclophosphamide), NSAIDs
  - Desmopressin (DDAVP): Hyponatremia may easily occur in patients with excessive free water intake while receiving DDAVP for various reasons (e.g., enuresis, cDI, or von Willebrand disease). Patients must be instructed to only drink water with thirst, adjust DDAVP dose per urine volume, and recognize signs and symptoms of hyponatremia.
- Drugs that reset osmostat: antidepressants (venlafaxine), antiepileptics (carbamazepine)

Other Noteworthy Causes of Drug-Induced Hyponatremia

- Angiotensin-converting enzyme inhibitors (ACEI): ACEI inhibits the conversion of angiotensin I (AI) to II (AII) in peripheral tissue, but not in brain. In the brain, AI continues to be converted to AII, which can stimulate thirst and ADH release. Use of ACEI increases AI levels, hence increased brain AII. ACEI may also induce increased ADH secretion by delaying bradykinin degradation.
- Intravenous immune globulins (IV Ig) mixed in maltose or sucrose: Hyponatremia may occur *via* (1) pseudohyponatremia, if measured by flame photometric assay due to large amount of space-occupying globulins; (2) dilutional hyponatremia, due to extracellular free water shift with accumulation of maltose or sucrose (important if poor kidney function and reduced excretion of maltose or sucrose)
- Amphetamines: 3,4-methylenedioxymethylamphetamine (i.e., "**ecstasy**"): increase hypothalamic ADH secretion and excessive water intake due to associated hyperthermia and thirst
- Less common causes: nicotine patch, colchicine poisoning, dopaminergic agents, unfractionated heparin, hydroxyurea, azithromycin, clonidine, glipizide, tacrolimus, cotrimoxazole, theophylline, proton pump inhibitors

Management of Hyponatremia

General considerations

- Provide adequate *oxygenation*, mechanical ventilation support if necessary. Hypoxemia may exacerbate hyponatremic encephalopathy.
- *Potassium and sodium are equivalent effective exchangeable* osmoles. Any K^+ given during the treatment of hyponatremia will correct S[Na^+] *exactly* as if the same amount of Na^+ was given. See **Figure 1.2** for mechanisms.

  Example: If a patient needs 200 mmol of Na^+ to raise his or her hyponatremia to goal, but also needs 75 mmol K^+ for concurrent hypokalemia, the clinician should give:

125 mmol of Na^+ + 75 mmol of K^+ = 200 mmol total of Na^+ + K^+ *instead of* 200 mmol of Na^+ + 75 mmol K^+
= 275 mmol total of Na^+ + K^+. The latter

combination would overshoot the goal S[Na^+].

- *Monitor urine output:* Hypotonic polyuria can easily overcorrect hyponatremia if not recognized. Hypotonic polyuria may be seen during the treatment of hyponatremia with the following conditions: postpituitary infarction, glucocorticoid replacement in patient with cortisol insufficiency, discontinuation of DDAVP in patients with chronic use (e.g., for cDI), recovery from acute respiratory failure, withdrawal of thiazides, water deprivation in primary polydipsia, rapid volume expansion with boluses of intravenous saline. (Normal saline [NS] boluses should be reserved for hemodynamically unstable patients.)
- Cases of osmotic demyelination syndrome (ODS) have been reported in patients with concurrent hypokalemia, hypomagnesemia, hypophosphatemia, thiamine deficiencies, or any combination of these deficiencies *independent* of the rate of Na^+ correction. It is important to monitor and correct these deficiencies during the management of hyponatremia.

Rate of correction

- A 5% increase in S[Na^+] should substantially reduce cerebral edema.
- Rapid correction can lead to ODS, previously known as central pontine myelinolysis (CPM), due to insufficient time allowed for brain synthesis of organic osmolytes or "idiogenic osmoles" to counteract the acute rise in extracellular osmolality. Major brain organic osmolytes include glutamine, glutamate, taurine, myo-inositol, among others.
  - *High risks for ODS:* S[Na^+] < 105 mmol/l, alcoholism, malnutrition, advanced liver disease, hypokalemia
  - Clinical manifestations of ODS:
    - 1 to 2 days: generalized encephalopathy
    - 2 to 3 days: behavioral changes, cranial nerve palsies, progressive weakness, quadriplegia, "locked-in" syndrome; death is possible.
    - Diagnosis: presence of nonenhancing and hyperintense pontine and extrapontine lesions on T2-weighted MRI. A time lag of up to 2

weeks for the presence of MRI abnormalities is possible.
    - ODS may be reversible, even in some cases with severe symptoms at presentation.
  - Reversal of overcorrection with hypotonic fluids and DDAVP has been shown to be beneficial in rats and human case reports.
- Correction rate for acute symptomatic hyponatremia (known duration < 24 to 48 hours):
  - Urgent correction by 4 to 6 mmol/L to prevent brain herniation and cerebral ischemia
  - No need to restrict correction rate if truly acute
  - For severe symptoms (e.g., seizures, coma): infuse 100 mL of 3% NaCl over 10 minutes × 3 as needed
  - For mild to moderate symptoms: infuse 3% NaCl at 0.5 to 2 mL/kg/h. *Must* monitor change in S[Na^+] closely and specify duration of treatment to avoid overcorrection.
- Correction rate for hyponatremia with associated seizures or coma, presence of intracranial pathology, or increased intracranial pressure *and* unknown duration:
  - Urgent correction by 4 to 6 mmol/L
    - After urgent correction above, treat based on total daily correction rate limits used for chronic hyponatremia mentioned below.
  - Correction rate for chronic hyponatremia (lasting ≥48 hours):
    - 4 to 8 mmol/L/d
    - Use lower correction rate for high-risk ODS patients (4 to 6 mmol/L/d)
    - Normal risk for ODS: may correct 10 to 12 mmol/L in any 24-hour period, but not to exceed 18 mmol/L in any 48-hour period

Specific Treatment Options (Table 1.1)

Table 1.1 Treatment options in the management of hyponatremia

Treatment Categories	Specific Options	Indications and Comments
	Sodium chloride	Stable euvolemic SIADH (e.g., patients with end-stage conditions

	tablets	such as malignancy with associated SIADH)
Salt supplement	Normal saline	Volume depletion; avoid boluses unless patients are hemodynamically unstable.
	3% saline	Severe neurologic complications, severe salt wasting (e.g., renal or cerebral salt wasting), severe SIADH with urine osmolality >> 300 mOsm/kg + severe hyponatremia and unclear volume status
	Potassium salt	Patients with concurrent hypokalemia. Note that potassium supplement increases $S[Na^+]$ exactly as if the same amount of sodium is given.
Free H_2O restriction	Reduce free water intake to 500 mL below urine output	Therapy failure predictors: baseline urine output < 1,500 ml/d; $(u_{na} + u_k)/s_{na} > 1$; $U_{OSM} > 500$ mOsm/kg
	Loop diuretic	Volume overload (e.g., heart failure, cirrhosis, nephrotic syndrome)
Increase free H_2O excretion	Vaptans	SIADH, heart failure (not suggested in patients with cirrhosis or those with severe neurologic complications); concurrent use with loop diuretic not recommended
	Demeclocycline	SIADH (contraindicated during pregnancy and children due to interference with bone development, nephrotoxicity, photosensitivity)
	Increase solute load (e.g., protein drinks, urea)	Poor solute intake or malnutrition. Consider nutrition consult.
General measures	Maintain adequate oxygenation/airway if altered mental status; follow serum magnesium, phosphorus, potassium levels, and replete as needed.	

Abbreviation: SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Fluid restriction

- Fluid restriction may be considered for euvolemic or hypervolemic patients.
- "Fluid" implies all fluid consumed by drinking and food source, not just water.
- Restriction volume should be aimed at 500 mL below the patient's average daily urine volume.
- However, fluid restriction is often ineffective, particularly in patients with severe SIADH.
- Predictors of likely failure with fluid restriction alone:
  - High $U_{OSM} > 500$ mOsm/kg
  - $\frac{U[Na^+] + U[K^+]}{S[Na^+]} > 1$

- Baseline urine volume < 1,500 ml/d
- Minimal increase in S[Na^+] (i.e., less than 2 mmol/L/d increase over 24-48 h) on a strict fluid restriction of < 1 l/d

Salt supplement

- NS or salt-balanced solution: recommended for hypovolemic patients. Avoid boluses unless hemodynamically unstable. Rapid volume expansion can lead to high-volume aquaresis, and therefore rapid overcorrection of hyponatremia.
- Hypertonic saline:
  - Indicated for patients who are severely symptomatic (e.g., seizures, severely depressed mental status): 100 mL 3% bolus every 10 minutes as needed to break seizures or up to a total of three boluses, whichever comes first
  - May also be considered at low infusion rates for:
    - Patients with severe SIADH + severe hyponatremia whose U_{OSM} >> 300 mOsm/kg

NOTE NS can worsen hyponatremia in SIADH patients with U_{OSM} >> 300 mOsm/kg. This is due to a process called "*desalination*" (**Fig. 1.4**).

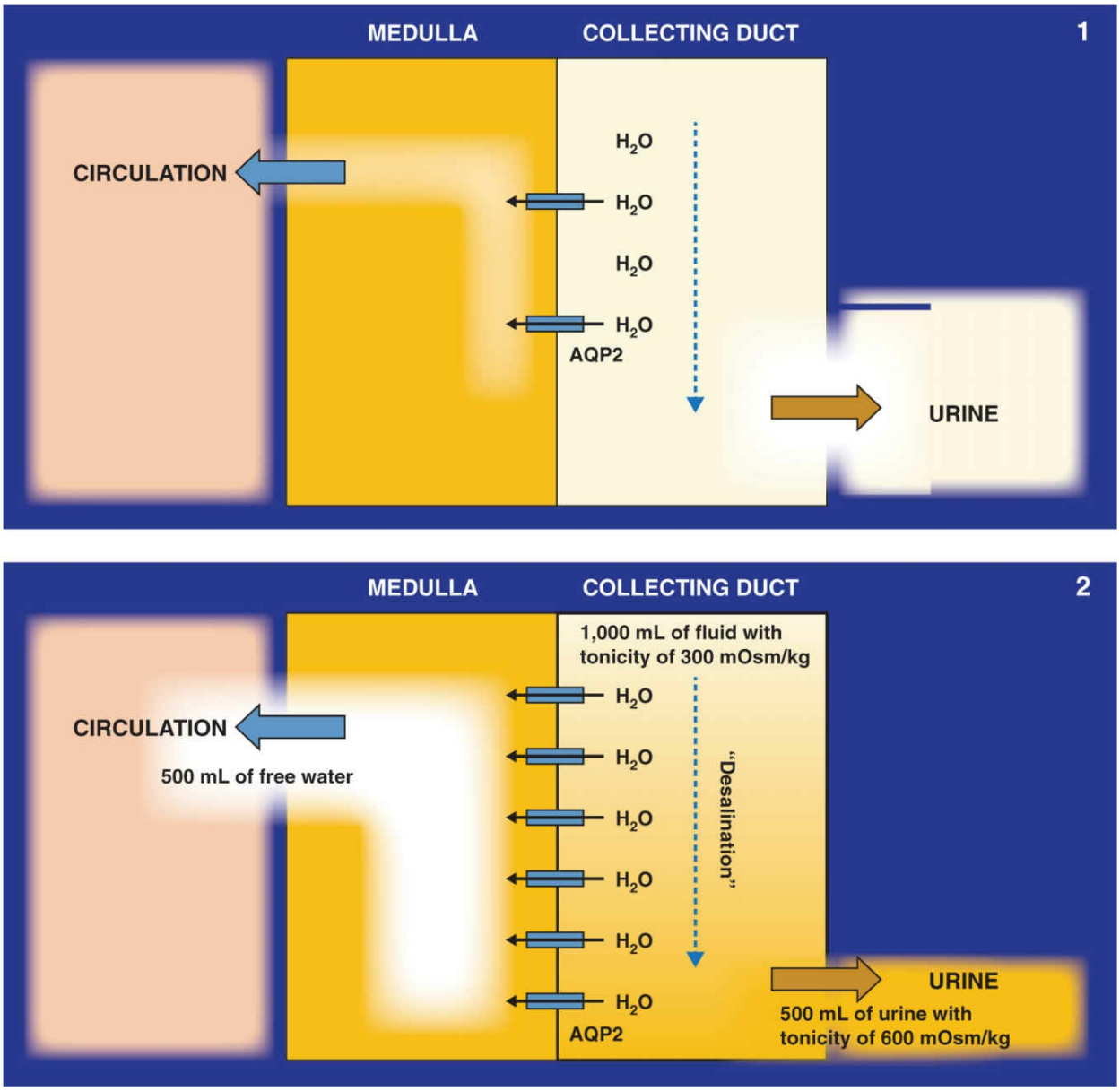

FIGURE 1.4 Desalination with syndrome of inappropriate secretion of antidiuretic hormone (ADH). **Panel 1.** Patient with low level of ADH: there is low level of aquaporin 2 (AQP2) expression, thus minimal free water reabsorption. Urine volume and tonicity remain relatively high and dilute, respectively. **Panel 2.** Patient with syndrome of inappropriate secretion of antidiuretic hormone (SIADH): There is increased aquaporin 2 expression that allows for avid water reabsorption. Imagine a patient with known SIADH who can concentrate urine up to 600 mOsm/kg. If this patient is given 1,000 mL of NS with approximate tonicity of 300 mOsm/kg, the kidneys will reabsorb 500 mL of free water and excrete 500 mL of urine with tonicity of 600 mOsm/kg. The high volume of free water reabsorbed results in worsening of existing hyponatremia and the excretion of a highly concentrated urine (desalination of the administered fluid).

Example: Imagine a patient with severe SIADH, whose kidneys **always** concentrate the urine to an osmolality of ~600 mOsm/kg.

Conceptually, this is essentially equivalent to 600 mOsm/1 L of urine.

- If this patient receives 1 L of NS, he or she receives a solution consisting of 308 mOsm of solutes (154 mmol Na + 154 mmol Cl) + 1 L of free water, which is approximately 300 mOsm of solutes + 1 L of free water.
- Kidneys would see 1 L of NS as:: 300 mOsm of solutes + 1 L of free water
- Kidneys' task: excrete urine with an osmolality of 600 mOsm/kg ~600 mOsm/L
- Kidneys will use up all 300 mOsm of solutes, but only 500 mL of water from the fluid administered to make urine with osmolality 600 mOsm/kg.
- This means that the remaining 500 mL of water gets reabsorbed into the patient. This leads to worsening of the patient's existing hyponatremia.
- In effect, the kidneys "desalinate" or remove all NaCl from the NS to make urine with the high osmolality dictated by the patient's degree of SIADH. The "leftover" water gets reabsorbed into the patient.
- By the same reasoning, imagine another patient with moderate SIADH with a typical U_{OSM} of 300 mOsm/kg. The use of NS would never correct the patient's hyponatremia because this patient's kidneys typically excrete urine with the same osmolality as NS. Since there is no salt gained or lost from the NS infusion, there will be no change in the existing hyponatremia.

Bottom line: Any saline solution used in a patient with SIADH for the sole purpose of increasing $S[Na^+]$ must have higher osmolality than that of urine.

- May be used in patients with severe salt wasting (e.g., patients with severe CSW or renal wasting associated with cisplatin)

- Salt tablets: may be preferred over strict fluid restriction in stable euvolemic patients with SIADH and terminal conditions (i.e., metastatic

malignancy for better quality of life—authors' opinion)

Increase H_2O excretion by the kidneys

- Increase solute load if poor nutrition: parenteral feeding, encourage high oral solute intake (salt and protein)
- Urea (0.5 to 1.0 g/kg/d or higher as needed) may also be used as an osmotic diuretic agent to increase free water excretion in patients with chronic hyponatremia due to SIADH.
- Vasopressin (ADH) antagonists:
  - Demeclocycline: inhibits ADH by inhibiting adenylyl cyclase activation
    - Contraindicated in children and during pregnancy due to interference with bone development, teeth discoloration
    - Should not be used in liver patients; hepatitis and liver failure may occur with demeclocycline
    - Other complications: photosensitive rash, nephrotoxicity
  - Vasopressin receptor antagonists (i.e., vaptans, aquaretics): for euvolemic and hypervolemic hyponatremic patients with dysregulated ADH or SIADH.
    - FDA-approved agents:
      - Conivaptan: intravenous formulation only; combined V1a and V2 receptor antagonist; limit use to 4 days due to significant drug interactions with other agents metabolized by CYP3A4.
      - Tolvaptan: oral formulation; V2 receptor antagonist
      - Both agents improve free water excretion and improve S[Na^+] without altering 24-hour sodium excretion.
      - Vaptans have not been shown to improve long-term outcome in the treatment of hyponatremia.
    - Use of vaptans is not recommended immediately following cessation of other treatments of hyponatremia, particularly 3% saline.
    - Vaptans are ineffective in patients with reduced kidney function (i.e., SCr > 3 mg/dL)
    - Major side effects and risks: thirst, transaminitis, gastrointestinal bleed

- Overly rapid correction leading to ODS is possible particularly if used concurrently with diuretics or in patients without access to free water (e.g., patients who are mechanically ventilated or debilitated, bed bound). Relowering of $S[Na^+]$ should be considered in cases with overly rapid corrections.
- Data are lacking to recommend use of vaptans in severe asymptomatic hyponatremia—that is, $S[Na^+] < 120$ mmol/l.
- Vaptans should not be used in patients with symptomatic acute hyponatremia, particularly in those with neurologic symptoms due to its delayed onset of action. Hypertonic 3% saline infusion is the treatment of choice in such cases.

- Loop diuretic (e.g., furosemide): may be used in patients with hypervolemia. Concurrent use with vaptan is not recommended due to the risk of rapid free H_2O excretion and overly rapid correction of hyponatremia.

Management considerations for NSIAD

- Conservative therapy: water restriction, increase in salt intake combined with loop diuretic, oral urea (if available)
- The use of vaptan is ineffective in all cases with Arg137Cys (arginine to cysteine substitution at amino acid 137) mutation but effective in F229V (phenylalanine to valine substitution at amino acid 229) mutation. The ineffectiveness of vaptans in specific NSIAD mutations is thought to be due to the inability of vaptans to deactivate the constitutively activated AVP receptor.

Calculations for the correction of hyponatremia

- Commonly used equations to calculate expected $S[Na^+]$ (Na_2), given initial $S[Na^+]$ (Na_1), total body water volume, input and output volumes (Vol_{input}/Vol_{inf}, Vol_{out}) and their respective sodium and potassium concentrations $(Na + K)_{out}$, $(Na + K)_{in}$, and net volume change ΔVol ($Vol_{input} - Vol_{out}$)

Adrogue–Madias equation:

$$Na_2 = \frac{(Na_1 \times TBW) + [Vol_{inf} \times (Na + K)_{inf}]}{TBW + Vol_{inf}},$$

Barsoum–Levine equation:

$$Na_2 = \frac{(TBW \times Na_1) + [Vol_{input} \times (Na + K)_{input} - Vol_{out} \times (Na + K)_{out}]}{TBW + Vol},$$

Nguyen–Kurtz equation:

$$Na_2 = \frac{[(Na_1 + 23.8) \times TBW] + [1.03 \times [(Na + K)_{input} - (Na + K)_{out}]]}{TBW + Vol} - 23.8.$$

For calculations involving multiple sources of input and output and estimates for both fluid tonicity and rate administration, see Curbside Consultant App (available 2021).

- Correction of hyponatremia in the dialysis patient:
  - Uremic patients are thought to be relatively protected from ODS with rapid correction of hyponatremia during hemodialysis. Although the mechanism is not known, it has been speculated that the simultaneous removal of uremic solutes offsets the rapid rise in S[Na+]. Nonetheless, it must be cautioned that ODS has been reported in hemodialysis patients.
  - Correction rates should therefore follow the same guidelines for nonuremic patients.
    - Calculations of blood flow to correct hyponatremia with intermittent hemodialysis (IHD): See **Appendix A**.
    - Calculations for hyponatremia correction using continuous renal replacement therapy (CRRT): See Chapter 12.

Management of overly rapid correction of hyponatremia

- For acute water intoxication, relowering of sodium is not necessary.
- For patients with presenting S[Na^+] < 120 mmol/l, relowering of s[na^+] should be considered (particularly in patients with high risks for ods):
  - Replace water losses with intravenous 5% dextrose water or oral water

to achieve desired goal—For adult patients with hyperglycemia who cannot tolerate high dose of dextrose and cannot drink water (e.g., patients with high serum glucose), 2.5% dextrose water may be used.

- Administer DDAVP 2 to 4 µg intravenously q8h as needed (per Hyponatremia Expert Panel). In our experience, 2 µg DDAVP q12h to q24h is typically sufficient.

NOTE Do NOT give large volume of water replacement while patient receives DDAVP. Rapid and excessive relowering of S[Na^+] can easily occur.

- If patient was given vaptan, hold the next dose if correction exceeds 8 mmol/L/24 h. In case of unsafe overcorrection, administer free water and DDAVP as above.
- Monitor S[Na^+] closely.
- Consider administration of high-dose glucocorticoids to reduce ODS risk in case of severe overcorrection (e.g., dexamethasone 4 mg q6h for 24 to 48 hours).

Special notes about therapy

- Treat underlying condition that causes SIADH.
- Hyponatremia in patients with HF:
  - For mild to moderate symptoms:
    - Begin with fluid restriction 1 L/d. Add loop diuretic as needed for volume overload.
    - Tolvaptan may be considered, but must be closely monitored to assess long-term need. Combined loop diuretic and vaptan should be avoided to prevent rapid and excessive overcorrection.
  - For severely symptomatic patients with severe hyponatremia, consider the administration of 3% NaCl plus loop diuretics. Close monitoring is required.
- For primary polydipsia:
  - Consider behavioral therapy.
  - Avoid anticholinergic agents, antihistamines, decongestants.
  - Consider atypical antipsychotics in patients with psychogenic polydipsia

(limited data): clozapine, olanzapine, risperidone.

- Discontinue thirst- or hyponatremia-inducing drugs. See Other Noteworthy Causes of Hyponatremia above.

FLUID MANAGEMENT

Basic Concepts and Formulas

Osmolar clearance (C_{OSM})

$$C_{OSM} = \frac{U_{OSM} \times V}{P_{OSM}}$$

where U_{OSM} is urine osmolality,

V is urine volume, and

P_{OSM} is plasma osmolality (serum osmolality, S_{OSM})

- A typical osmolar clearance is <3 l/d.
- C_{OSM} > 3 L/d generally indicates the presence of a solute diuresis.

Urine output (V)

$$V = C_{OSM} + C_{H_2O}$$

Alternatively, $C_{H_2O} = V - C_{OSM}$

where C_{H_2O} is the free water clearance (FWC)

Free water clearance (Fig. 1.5)

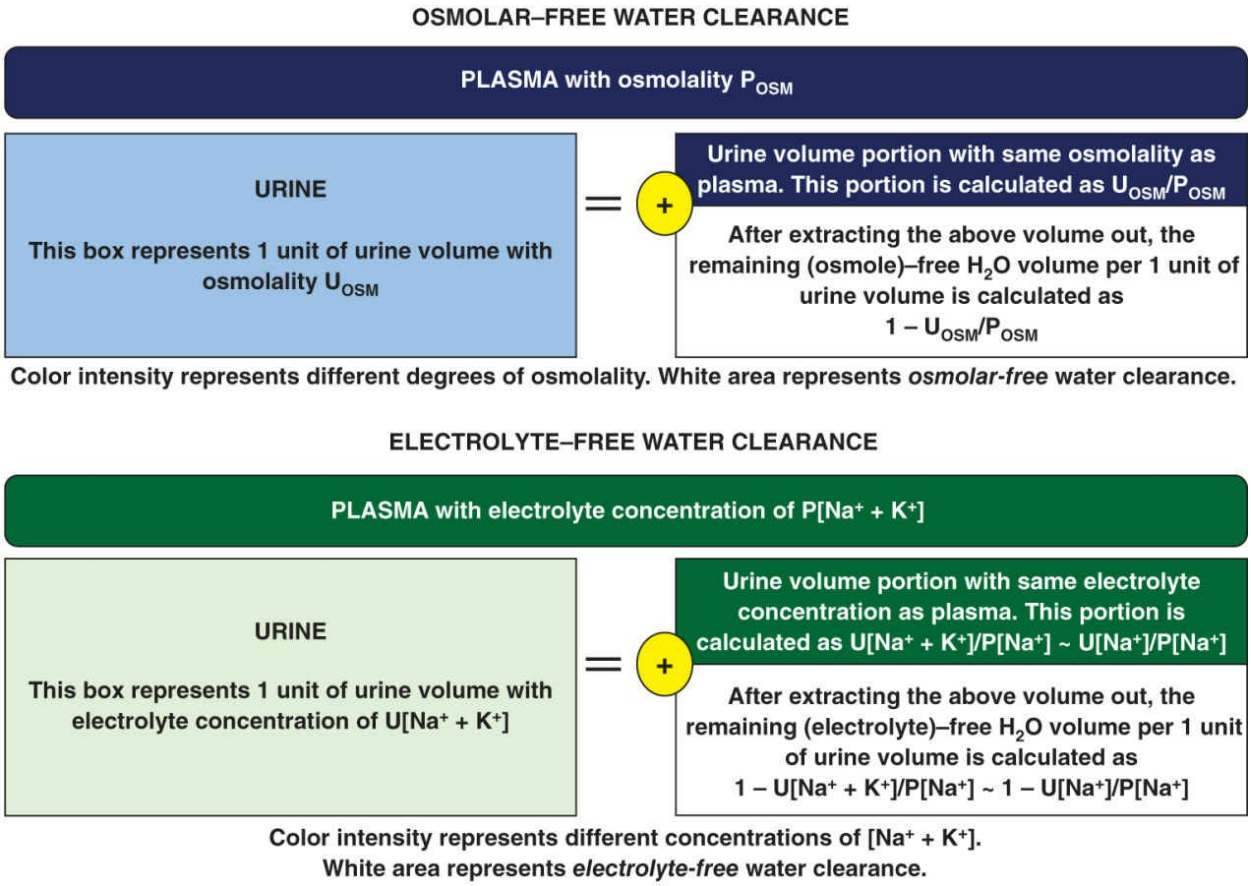

FIGURE 1.5 Osmolar– and electrolyte–free water clearance.

- FWC or C_{H_2O} may be calculated as:

$$FWC = \text{urine volume} \times (1 - U_{OSM}/S_{OSM})$$

  Conceptually, FWC is the urine volume with osmolality of zero that remains after the portion of urine normalized to serum osmolality has been extracted/removed from the initial total urine volume. Depending on the urine and serum osmolalities, FWC may be positive or negative.

- A positive FWC indicates that a patient makes urine that is hypoosmolar to the plasma, thereby losing free water and increasing plasma osmolality, whereas a negative FWC indicates that a patient makes urine that is hyperosmolar to the plasma, thereby gaining free water and lowering plasma osmolality. The change in plasma osmolality does not necessarily imply a similar change in $S[Na^+]$. Any change in $S[Na^+]$ depends on the actual amount of salt loss or gain per unit of urine volume relative to that of the plasma.

This leads to the concept of electrolyte–free water clearance (EFWC).

Electrolyte–free water clearance (Fig. 1.5)

- EFWC may be calculated as:

$$EFWC = \text{urine volume} \times (1 - U[Na^+ + K^+]/S[Na^+ + K^+])$$

Because $S[K^+]$ is << $s[na^+]$, efwc is typically simplified to:

$$EFWC = \text{urine volume} \times (1 - U[Na^+ + K^+]/S[Na^+])$$

Essentially, EFWC is the electrolyte–free urine volume that remains after the portion of urine normalized to $P[Na^+]$ has been extracted/removed from the initial total volume. Depending on the urine and serum ($Na^+ + K^+$), EFWC may be positive or negative.

A positive EFWC indicates electrolyte–free water loss that predicts an increase in $S[Na^+]$, whereas a negative EFWC implies electrolyte–free water retention and predicts a fall in $S[Na^+]$.

PROBLEMS

1. How would the $S[Na^+]$ change (increase or decrease) in a patient with current $S[Na^+]$ 132 mmol/L and making 4 L of urine with $U[Na^+]$ 38 mmol/L and $U[K^+]$ 13 mmol/L while receiving 7 L of 5% dextrose half NS (77 mmol/L of NaCl)?
   - EFWC of urine = $4 \times (1 - [38 + 13]/132) = 2.45$ L
   - EFWC of fluid = $7 \times (1 - 77/132) = 2.92$ L
   - There will be a net gain of 0.47 L of electrolyte–free H_2O so $S[Na^+]$ would decrease.
2. A patient is undergoing postobstructive diuresis with current $S[Na^+]$ 135 mmol/L, P_{OSM} 297 mmol/L, and urine rate of 300 mL/h with U_{OSM} 450 mOsm, $U[Na^+]$ 73 mmol/L, $U[K^+]$ 20 mmol/L. Would the patient's $S[Na^+]$ increase or decrease with time if he or she continues current urine output?
   - EFWC of urine = $0.3 \times (1 - [73 + 20]/135) = 0.93$ L or 93 mL/h.
   - The positive EFWC indicates that at the current rate of electrolyte–free water loss, the patient's $S[Na^+]$ will be expected to increase with time.

3. Can a patient with a urine osmolality greater than serum osmolality develop hypernatremia?
   - Yes, as long as the EFWC is positive.
   - Example: patient with U_{OSM} of 500 mOsm/kg, U[Na^+] of 15 mmol/L, U[K^+] of 17 mmol/L, S[Na^+] of 140 mmol/L
   - EFWC = (1 – [15 + 17]/140) = 0.77; for every liter of urine lost, 77% of the volume is free of Na^+ and K^+. This *electrolyte–free water loss* (EFWC) would be expected to lead to hypernatremia.
4. A patient with congestive HF is on continuous bumetanide infusion with S[Na^+] 148 mmol/L and urine output of 125 mL/h with urine [K^+] 15 mmol/L and U[Na^+] 75 mmol/L. Which one of the following fluids will not worsen the fluid overload state *and* not increase current S[Na^+]? Which one of the fluids will not worsen the fluid overload *and* could decrease S[Na^+]? Which one of the fluids will increase S[Na]?
   - 125 mL/h of NS per hour
   - 125 mL/h of half NS per hour
   - 50 mL/h of 5% dextrose (D5) water per hour
   - 75 mL/h of D5 water per hour
   - 125 mL/h of D5 ¼ NS per hour

   Hint: The amount of free H_2O loss in the urine is 125 × (1 – [15 + 75]/148) = 50 mL/h. Calculate the rate of electrolyte–free water for each of the solutions above.
5. Can a patient with a relatively dilute urine (e.g., U_{OSM} 150 mOsm/kg and P_{OSM} 277 mmol/kg) have a solute diuresis?
   - Yes. Example: same urine and serum osmolalities above, but patient makes 10 L of urine daily. The total solute load in the urine would be 150 mOsm/kg × 10 L = 1,500 mOsm. An average American diet intake would give a typical urine solute load of ~800 mOsm; 1,500 mOsm is in great excess of 800 mOsm. This patient has both solute and water diuresis.
   - Alternatively, $C_{OSM} = U_{OSM}\ V/P_{OSM} = 150 \times 10/277 = 5.4$ L, which is much greater than the typical <3 l/d for an average person on an average diet.

HYPERNATREMIA AND HYPEROSMOLALITY

Background

- Hypernatremia is defined as having S[Na^+] > 145 mmol/L.
- Hypernatremia may be due to one or more of the following factors:
  - Inadequate free H_2O intake (e.g., limited access to free H_2O or defective thirst sensation)
  - Excessive free H_2O loss
  - Excessive sodium intake/retention
  - Transient intracellular free water uptake

NOTE Hypernatremia typically does not develop unless patients (even in those with diabetes insipidus [DI]) have limited access to free water (e.g., debility, status post major surgery with inability to ingest water) or thirst defect.

Clinical Manifestations of Hypernatremia

- Lethargy, weakness, irritability, seizures, intracerebral and subarachnoid hemorrhages due to rupture of cerebral veins with marked decrease in brain volume, coma, death

Differential Diagnosis of Hypernatremia (Table 1.2)

Table 1.2 Evaluation of hypernatremia

Urine osmolality (mOsm/kg)	Hypovolemia	Euvolemia	Hypervolemia
<300	Complete central or nephrogenic diabetes insipidus Volume status depends on access to free water.		
300–600	Partial central or nephrogenic diabetes insipidus Volume status depends on access to free water. Osmotic diuresis (intrinsic, e.g., hyperglycemia) Volume status depends on access to free water.		
>600	Inability to access free water High insensible fluid loss Primary hypodipsia	Sodium, osmotic overload (iatrogenic, e.g., large volume of hypertonic saline infusion or large volume parenteral feeding): volume status depends on the kidneys' ability to excrete excess solute and water load.	
Variable urine osmolality	Intracellular free water shift (e.g., rhabdomyolysis, seizures): volume status depends on access to free water. Adipsic central diabetes insipidus: urine osmolality can increase with fluid restriction.		
		Reset osmostat	Primary mineralocorticoid excess

Water loss/inadequate water intake

- Inadequate intake, poor water access
- Increased insensible loss: skin, respiratory
- Hypothalamic disorders:
  - Primary hypodipsia
  - Adipsic DI, previously known as "essential hypernatremia" (**Fig. 1.6)**:
    - Combined defects in osmoreceptor function *and* thirst. Osmolality-driven ADH secretion is defective, but volume-regulated ADH secretion is intact. That is, the patient with *adipsic* DI cannot stimulate ADH secretion in response to hyperosmolar state. However, ADH secretion can be stimulated if the patient is hypovolemic. In contrast, the patient with cDI cannot stimulate ADH release with either hyperosmolar or hypovolemic state.

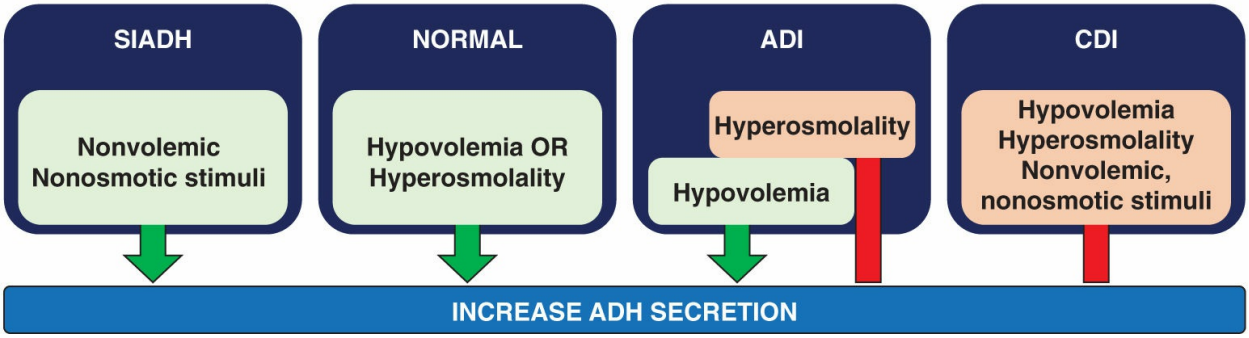

FIGURE 1.6 Conditions with dysregulated secretion of ADH. In SIADH, ADH secretion can be stimulated by conditions other than hypovolemia and hyperosmolality; in normal individuals, ADH secretion can be stimulated by either hypovolemia or hyperosmolality; in adipsic diabetes insipidus, ADH secretion is stimulated by hypovolemia but not hyperosmolality; in cDI, ADH secretion cannot be stimulated by anything. Abbreviations: ADH, antidiuretic hormone; ADI, adipsic diabetes insipidus; cDI, central diabetes insipidus; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

- Clinical manifestations of adipsic DI:
  - Typically asymptomatic due to chronicity of condition
  - Hypernatremia can be severe. S[Na^+] ~155 to 190 mmol/L.
  - Patient may be hypovolemic with associated high renin/aldosterone state and hypokalemic metabolic alkalosis.
  - Adipsic DI is associated with obesity, sleep apnea, venous thrombosis during episodes of hypernatremia, thermoregulatory dysfunction, seizures, and increased mortality.
- Causes of adipsic DI: congenital or acquired CNS lesions, for example, postclipping of anterior communicating artery (ACA) aneurysms following subarachnoid hemorrhage (osmoreceptors in the hypothalamus derive their vascular supply from small perforating branches of the ACA), postsurgeries for large craniopharyngiomas or suprasellar tumors, neurosarcoidosis, CNS tuberculous infection. Recovery of thirst is uncommon.

- Classic clinical scenario of adipsic DI:
  - Hypernatremia does not correct with free water administration during the euvolemic state because osmolality-dependent ADH secretion is defective. The lack of ADH impairs tubular free water reabsorption to correct the hypernatremia.
  - However, hypernatremia can be corrected with free water administration during the hypovolemic state. Volume-regulated

ADH secretion is intact. The presence of ADH promotes optimal free water reabsorption.
    - Unlike the patient with cDI, the patient with adipsic DI is able to concentrate urine overnight (i.e., increased U_{OSM} in the morning) due to increase ADH secretion with relative volume depletion from being nil per os (NPO) while sleeping.
    - Treatment of adipsic DI is DDAVP.
  - cDI (also see **Polyuria** section):
    - Primary/familial cDI
    - Secondary cDI: craniopharyngioma, nonfunctioning adenoma, autoimmune or infiltrative diseases, tumors, prolactinoma, vascular abnormalities, tuberculosis, Rathke cyst, apoplexy
- Nephrogenic causes:
  - Hereditary nephrogenic diabetes insipidus (nDI): mutation of aquaporin 2 (AQP2) or AVP V2R (vasopressin receptors)
    - AVP V2R mutations are X-linked and account for 90% of congenital nDI.
    - AQP2 mutations are typically autosomal recessive and less commonly autosomal dominant.
  - Secondary nDI: hypercalcemia, hypokalemia, pregnancy, lithium, demeclocycline, methoxyflurane, foscarnet, aminoglycosides, amphotericin B, cidofovir, vaptans
  - Lithium-induced nDI:
    - Lithium-induced tubular toxicity and nDI is thought to arise from lithium entry into tubular cells via the epithelial sodium channel (ENaC).
    - Mechanisms leading to nDI include downregulation of AQP2 and reduced urinary concentration.

Free water in excess of sodium loss (hypotonic fluid loss)

- Extrarenal loss: skin (burns, excessive sweating), gastrointestinal tract (nasogastric suction, viral gastroenteritis, nonelectrolyte osmotic diarrhea [e.g., lactulose, vomiting])

- Renal loss: loop diuretics, osmotic diuresis (hyperglycemia, mannitol, high-protein diet, tissue hypercatabolism, urea), postobstructive diuresis, postacute tubular necrosis diuresis

Water shifting into cells

- Transient, typically with only mild hypernatremia
- May occur with seizures or rigorous exercise, rhabdomyolysis (the associated increase in intracellular metabolism leads to an increase in intracellular breakdown of larger molecules into many smaller molecules, which then leads to increased intracellular osmolality and subsequent intracellular free H_2O shift).

Excess sodium load

- Administration of hypertonic saline or $NaHCO_3$ (e.g., excessive $NaHCO_3$ administration during a code or inadvertent mixing of 2 to 3 ampules of $NaHCO_3$ in NS instead of 5% dextrose water. Note that 1 ampule [50 mL] of 7.5% $NaHCO_3$ contains 45 mmol/L of Na^+; 1 ampule of 8.4% $NaHCO_3$ contains 50 mmol/L of Na^+).
- Acute salt poisoning (e.g., accidental salt feeding in babies [salt instead of sugar or baby formula]—1 teaspoon of sodium chloride contains 104 mmol Na^+); intrauterine instillation of hypertonic saline for abortion; saltwater ingestion
- Primary mineralocorticoid excess:
  - Hypernatremia may be due to:
    - Increased sodium uptake via ENaC
    - Chronic sodium retention/volume expansion causing mild chronic ADH suppression
  - Presenting S[Na+] is mild ~143 to 147 mmol/L
  - The use of diuretics (i.e., aldosterone antagonists or ENaC inhibitors) corrects the volume expansion and releases the chronic suppression of ADH. Once ADH is synthesized and released, free water reabsorption can occur to correct the chronic hypernatremia.

Diagnosis of hypernatremia

- Obtain full medical history.
- Diagnosis of hypernatremia relies on the assessment of volume status and evaluation of urine osmolality (Table 1.2).

Management of Hypernatremia

Estimating water deficit

- Water deficit = Total body volume × (S[Na^+]/140 − 1)
  where total body volume = 0.4 to 0.5 × current body weight

  Note: 0.4 to 0.5 × body weight may be used to calculate total body volume in patients with volume depletion; 0.5 to 0.6 × body weight is typically used for euvolemic patients.

Correction rates

- Acute onset (minutes to hours), for example, acute salt poisoning: rapid infusion of 5% dextrose water (or 2.5% dextrose water if hyperglycemia is a problem in adult patients) to rapidly lower sodium level; may consider emergent hemodialysis in case of acute and severe hypernatremia
- 1 to 2 days onset: Correct S[Na^+] by 2 mmol/L/h until normalization
- 2 or more days or unknown duration: decrease S[Na^+] by 10 mmol/L/d

Fluid selection

- Fluid selection depends on hemodynamic stability and degree of salt loss.
- For hemodynamically unstable, hypotensive patients: use NS for rapid intravascular expansion.
- For hemodynamically stable patients with:
  - Recent or ongoing salt loss: use 2.5% or 5% dextrose ¼ NS or ½ NS.
  - Pure water loss or salt poisoning: use 2.5% or 5% dextrose water.
  - Volume overload (e.g., decompensated HF and hypernatremia): use loop diuretic *plus* 2.5% or 5% dextrose water, *never* use furosemide alone as furosemide produces hypotonic urine and can worsen hypernatremia.

Special treatment considerations (also see Table 1.9)

- For any reversible cause, treat underlying disease/condition.
- Perform dialysis if concurrent kidney failure, anuria. (Calculations are

similar to those given for the treatment of hyponatremia.)

- cDI: DDAVP (oral, nasal spray, subcutaneous, or intravenous). In the case of nasal mucosal inflammation or mechanical ventilation, avoid nasal spray.
- nDI:
  - Thiazides
    - Thiazide induces volume depletion, thus enhancing proximal sodium and water reabsorption, thereby reducing fluid delivery to distal nephron for excretion.
    - Thiazide is also thought to inhibit carbonic anhydrase in the proximal tubule, resulting in increased fluid delivery to the macula densa and thus decreased glomerular filtration via tubuloglomerular feedback.
  - Prostaglandin (PG) inhibitors (indomethacin, 2 mg/kg/d): PG inhibitors are thought to reduce free water excretion by (1) increasing AQP2 expression via the release of PGE2 inhibition on adenylyl cyclase activity, thus downstream cyclic adenosine monophosphate (cAMP) effect on AQP2; (2) increasing medullary solute reabsorption thus medullary tonicity to enhance free water reabsorption.
- Lithium-induced nDI (via downregulation of AQP2 expression):
  - Amiloride may be used to reduce renal uptake of Li *via* principal cells in collecting duct.
  - Acetazolamide has also been shown to reduce polyuria in Li-induced nDI. Mechanism is likely via tubuloglomerular feedback response.
- DI in general: Reduce solute load with low salt and/or protein intake to increase free water reabsorption (nutrition consult recommended to avoid malnutrition). In contrast, for patients with malnutrition and polyuria due to poor medullary concentration, increased protein intake is necessary to rebuild the medullary concentration gradient.
- Kidney failure, anuric: dialysis
- Adipsic DI: DDAVP
- Primary mineralocorticoid excess: low-dose diuretic (aldosterone antagonist or ENaC inhibitor)

SALT EXCESS (EDEMATOUS STATES)

Regulation of Fluid Exchange Between Plasma and Interstitium

Starling Law: Net filtration = LpS × (Δhydraulic pressure − Δoncotic pressure)

$$= LpS \times ([P_{CAP} - P_{IF}] - s[\pi_{CAP} - \pi_{IF}])$$

where Lp is the permeability or porosity of the capillary wall, S is the surface area available for filtration, P_{CAP} is the capillary hydraulic pressure, P_{IF} is the interstitial hydraulic pressure, π_{CAP} is the capillary oncotic pressure, π_{IF} is the interstitial oncotic pressure, and s is the reflection coefficient of proteins across the capillary wall (with values ranging from 0, if completely permeable, to 1, if completely impermeable).

- Normally, there is a small mean gradient of ~0.3 mm Hg favoring fluid filtration out of the vascular space. The extravasated fluid is returned systemically via lymphatics, thereby avoiding interstitial fluid accumulation and clinical edema.
- Edema formation occurs when there is alteration in ≥1 Starling forces
  1. ↑Capillary hydraulic pressure
  2. ↑Capillary permeability
  3. ↓Interstitial oncotic pressure
  4. ↓Plasma oncotic pressure

  or

  5. Lymphatic obstruction
  6. Excess renal sodium and water retention

Common Clinical Edematous Conditions

Heart failure

- Poor cardiac output → Decreased effective circulating volume
- Renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system (SNS), ADH are stimulated → sodium and free H_2O retention → increased plasma volume. In early HF, the increased plasma volume can enhance cardiac contractility, hence cardiac output (Frank–Starling curve).

As the underlying cardiac disease progresses, the continuing accumulation of plasma volume will reach a point where even maximum cardiac contractility can no longer improve cardiac output. The continuing Na^+ and H_2O retention only leads to severe volume expansion → decompensated HF.

Management of Acute Decompensated HF

Diuresis and ultrafiltration: Summary of major trials (Table 1.3)

Table 1.3 Diuresis and ultrafiltration in patients with acute decompensated heart failure: Summary of major trials

Trials	Aims	*N*	Findings

DOSE	Evaluate efficacy and adverse effects of various loop diuretic strategies:
	• Low dose (1 × outpatient oral dose) vs. high dose (2.5 × outpatient oral dose)
	• Bolus q12h vs. continuous infusion × 72 h
		308	• There was no statistically significant difference in global symptom relief or change in renal function at 72 h for either:
			  • q12h dosing or continuous infusion
			  • low dose or high dose
			• High intensification (2.5 × oral dose) was associated with trends toward greater improvement in symptom relief (global assessment and dyspnea), weight loss and net volume loss, proportion free from signs of congestion, and reduction in NT-proBNP.

EVEREST	Evaluate the effects of tolvaptan 30 mg daily vs. placebo	4,133	• Early benefit in dyspnea on day 1 and edema/weight on day 7, but no benefit on heart failure hospitalization or mortality.

UNLOAD	Evaluate the effectiveness of UF vs. aggressive loop diuretic
	• UF arm: UF up to 500 mL/h
	• Diuretic arm: IV diuretics at ≥2 times outpatient oral dose within 48 h of randomization
		200	• Early UF:
			  • Produces greater weight and fluid loss than intravenous diuretics, without adverse impact on kidney function.
			  • Reduces percentage of patients requiring rehospitalization for HF, number of HF rehospitalizations, days of rehospitalization for HF, emergency department and

			unscheduled office visits at 90 days. • UNLOAD suggested superiority of UF over diuretics in patients hospitalized for volume overloaded HF.
CARRESS-HF	Compare the effect of UF with that of stepped pharmacologic therapy on renal function and weight loss in patients with heart failure who have worsening renal function and persistent congestion following stepped pharmacologic therapy vs. UF	188	• The use of a stepped pharmacologic therapy algorithm was superior to a strategy of UF for the preservation of renal function at 96 h. • Similar amount of weight loss was achieved with two approaches. • UF was associated with a higher rate of adverse events. • A substudy of CARRESS-HF suggested that renal function recovery at 60 d was superior in patients with increased tubular injury markers during intensive volume removal by either modality, suggesting the benefits of decongestion may outweigh any modest or transient increases in SCr or tubular injury markers. **Note:** Compared to UNLOAD trial, the medical arm in the current study using the stepped pharmacologic therapy achieved greater fluid removal. This may have made the difference in outcome.

Abbreviations: CARRESS-HF, Cardiorenal Rescue Study in Acute Decompensated Heart Failure; DOSE, Diuretic Optimization Strategies Evaluation trial; EVEREST, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan; HF, heart failure; *N*, number of patients; NT-proBNP, N-terminal proB-type natriuretic peptide; SCr, serum creatinine; UF, ultrafiltration; UNLOAD, Ultrafiltration versus intravenous diuretics for Patients Hospitalized for ADHF.

Bottom line for fluid removal in acute decompensated HF:

- Use of diuretics:
  - Continuous furosemide infusion = bolus therapy in terms of efficacy
  - Continuous infusion has a lower risk of ototoxicity than bolus therapy.
  - Ultrafiltration is not superior to stepped pharmacologic therapy.

"Stepped pharmacologic" therapy per CARRESS-HF trial is outlined

below. The goal is to escalate therapy to achieve target urine output 3 to 5 L/d.

1. *IV loop diuretic →*
2. *Add thiazide (metolazone up to 5 mg bid) →*
3. *Add dopamine or dobutamine at 2 µg/kg/h if systolic blood pressure (SBP) <110 mm Hg and ejection fraction <40% or right ventricular systolic dysfunction OR add nitroglycerin or nesiritide if SBP > 120 mm Hg (any ejection fraction) and severe symptoms →*
4. *Add left ventricular assist device (LVAD) →*
5. *Dialysis or ultrafiltration*

Class IIa recommendation from the American College of Cardiology/American Heart Association (ACC/AHA): Ultrafiltration is reasonable for patients with refractory congestion not responding to medical therapy (Level of evidence: B).

  - Oral bumetanide or torsemide provides better bioavailability than that of furosemide.
- For diuretic resistance: Combine loop and aldosterone antagonist or thiazide
- Use of aquaretics:
  - Vaptans: Vasopressin V2 receptor antagonists
  - Improves free water excretion, reduces furosemide use and body weight
  - Early benefit in dyspnea and edema/weight, but no benefit on HF, hospitalization, or mortality (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan [EVEREST] trial)
  - Vaptans are currently *not* indicated in the treatment of cardiorenal syndrome.
- Nesiritide, a recombinant human B-type natriuretic peptide, does *not* reduce the rate of recurrent HF hospitalization or death at 30 days (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure [ASCEND-HF] trial). Its use is associated with hypotension and bradycardia. Nesiritide (Natrecor) is discontinued in the United States.

Others: Vasodilators, inotropes, vasopressors

- Vasodilators for patients with adequate end-organ perfusion (i.e., normal or elevated blood pressure): nitroglycerin or nitroprusside
- Intravenous inotropes (e.g., dobutamine or milrinone) for patients with known systolic HF (low ejection fraction) and signs of acute decompensation
- Intravenous vasopressor (phenylephrine) for patients with diastolic HF with signs of shock or hypotension. Do not give inotrope.
- Unknown cardiac status with signs of shock or hypotension: intravenous inotropes (e.g., dobutamine or milrinone), +/− vasopressor, and mechanical support

Neprilysin inhibitor

- Neprilysin is an enzyme that cleaves and inactivates vasodilators including substance P and bradykinin. A neprilysin inhibitor inhibits the breakdown of vasodilators thereby reduces blood pressure and myocardial workload.
- Neprilysin, however, also breaks down AII. The use of a neprilysin inhibitor can thus increase AII level and negate the beneficial vasodilating effect above. For this reason, neprilysin inhibitor must be used together with an agent that reduces AII levels, which could theoretically be either ACEI or ARB. However, because both neprilysin inhibitors and ACEI increase bradykinin level, and therefore angioedema risks, the use of an **AR**B with **N**eprilysin **i**nhibitors is chosen over ACEI, hence "**ARNi**."
- Sacubitril/Valsartan combination (Entresto): This ARNi combination was tested in patients with chronic HF with reduced ejection fraction (HFrEF).
- Prospective Comparison of ARNi with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM) trial:
  - Aim: compare ARNi with enalapril in patients who had HFrEF.
  - Double-blind trial: 8,442 patients with class II, III, or IV HF and an ejection fraction of 40% or less were randomized to receive either ARNi or enalapril (10 mg twice daily) in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for HF.
  - Findings:
    - 20% reduction in primary outcome of cardiovascular death or HF

hospitalization and 16% reduction in all-cause mortality
    - Symptomatic hypotension was more common with ARNi, but not associated with worse kidney function.
    - The number of angioedema was higher with ARNi compared with enalapril, but not statistically different.
  - ***Current ACC/AHA/Heart Failure Society of America (HFSA) recommendations:*** *For patients with New York Heart Association (NYHA) II or III and stable on either an ACEI or ARB, switching to ARNi (if estimated glomerular filtration rate [eGFR] > 30 mL/min/1.73 m^2) is recommended to further reduce morbidity and mortality. For those on ACEI, discontinue ACEI for ≥36 hours prior to starting ARNi.*
- See Table 1.4 for directed medical therapy for patients with HFrEF stage C. Stage C is defined as having structural heart disease with prior or current symptoms of HF.

Table 1.4 Optimizing “directed medical therapy” for patients with HFrEF stage C

ACEI/ARB β-blocker Diuretic	Consider adding thiazide (e.g., metolazone) if high dose of loop diuretic is being used (e.g., equivalent dose of furosemide 120 mg bid) Notes regarding diuresis in patients with acute decompensated heart failure: Continuous furosemide infusion is equivalent to bolus therapy in terms of efficacy Double home dose of furosemide results in faster improvement without more adverse effects Continuous infusion has a lower risk of ototoxicity than bolus therapy Outpatient bumetanide or torsemide has better bioavailability than furosemide Ultrafiltration is not superior to step-approach medical therapy For diuretic resistance: combine loop and aldosterone antagonist or thiazide Closely monitor and replete electrolytes with diuretic use (K^+, Mg^{2+})
Hydralazine + isosorbide	Add as safely tolerated in persistently symptomatic African Americans NYHA class III–IV
ARNI	For patients with NYHA II–III *and* stable on ACEI or ARB, switch to ARNI. ARNI provides a 20% reduction in primary outcome of cardiovascular death or heart failure hospitalization and 16% reduction in all-cause mortality. **Note:** 36-h washout period is required if patient is being switched from an ACEI to ARNI.
Aldosterone antagonist	Add in patients with NYHA class II–IV with eGFR ≥ 30 mL/min/1.73 m^2 and serum potassium < 5.0 mmol/L
Ivabradine	Add in patients with NYHA class II–III and resting heart rate ≥70 beats/min on maximally tolerated β-blocker dose in sinus rhythm. Ivabradine is an adjunctive medical therapy to reduce heart rate in patients with chronic HFrEF on maximally tolerated doses of β-blocker who are in sinus rhythm. It is a specific inhibitor of the I_f current involved in sinoatrial nodal activity and reduces heart rate without lowering blood pressure. Heart rate independently predicts outcomes in HFrEF.

Note: Stage C is defined as structural heart disease with prior or current symptoms of heart failure.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; bid, twice daily; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; NYHA class, New York Heart Association functional classification.

Based on the Yancy CW, Januzzi JL Jr, Allen LA, et al. 2017 ACC Expert Consensus Decision Pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction. A report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2018;71(2):201–230.

- Of note, neprilysin also metabolizes amyloid-**a**, a process thought to be protective against Alzheimer disease. Hence, there is a theoretical concern for an increased risk for the development or progression of existing Alzheimer dementia with ARNi. Prospective studies to evaluate cognitive function are ongoing.

Nephrotic Syndrome

Underfilling theory

- Hypoalbuminemia due to urinary loss and/or altered albumin metabolism reduces intracapillary oncotic pressure, thus arterial "underfilling." This leads to stimulation of the RAAS, SNS, and ADH systems to enhance renal sodium and water retention. This is likely not the sole mechanism of edema in nephrotic syndrome because edema may improve with kidney disease improvement prior to any rise in serum albumin.
- Overfilling theory: Edema is due to avid renal sodium retention induced by the underlying diseased kidneys independent of hypoalbuminemia. This occurs *via*:
  - Increased Na^+-K^+-ATPase and ENaC activities in cortical collecting tubules
  - Relative resistance to atrial natriuretic peptide and urodilatin
  - Enhanced proximal tubular reabsorption *via* increased sodium–hydrogen exchanger activity

Management of nephrotic syndrome

- Hypertension: Current data support a goal systolic blood pressure of 120 mm Hg in patients with glomerular disease and proteinuria >1 g/d
- Proteinuria:
  - RAAS blockade: Either ACEI or ARB but not both are typically used. The benefit of ACEI and ARB dual therapy over single therapy for severe proteinuria in patients with glomerulonephritis has not been established.
  - Aldosterone blockade may be used to reduce albuminuria. Aldosterone may cause damage to the glomerular endothelial glycocalyx and contribute to albuminuria.
  - Sodium-glucose transport protein 2 (SGLT2) inhibitors in patients with diabetes mellitus type 2: A 2019 meta-analysis demonstrated that SGLT2 inhibitors lower the risk of albuminuria development or progression and reduce the risk of progression to kidney failure compared with placebo or other antidiabetic drugs among patients with diabetes mellitus type 2.

- Diuretics:
  - Loop diuretics with or without one of the following:
    - K-sparing diuretics (e.g., amiloride to block ENaC), thiazides
      - Proteins filtered into tubular lumen may contain proteases that can cleave and activate ENaC, thereby enhancing sodium reabsorption. ENaC inhibitors may thus be considered in the management of edema associated with nephrotic syndrome.
      - Addition of salt-poor albumin: This practice has not been shown to increase urinary sodium excretion in patients with nephrotic syndrome or cirrhosis with a mean serum albumin of 3 g/dL. The benefit of albumin infusion in patients with more severe hypoalbuminemia remains unknown.

Ascites and HRS With Advanced Liver Disease, Cirrhosis

Pathogenesis of ascites and HRS

- Three major hemodynamic changes induced by advanced liver disease, hepatic cirrhosis include (**Fig. 1.7**):
  - ***Portal hypertension,**** as a result of:
    - Postsinusoidal obstruction induced by hepatic fibrosis, followed by
  - ***Splanchnic vasodilation***, due to:
    - Local release of potent vasodilators (e.g., nitric oxide, cannabinoids) thought to be driven by portal hypertension and reduced clearance of bacterial products, which in turn leads to splanchnic blood pooling, fall in systemic effective circulating volume, *and*
  - ***Reduced systemic vascular resistance***

    *Splanchnic arterial vasodilation leads to increased portal venous inflow, which further feeds into the existing portal hypertension.

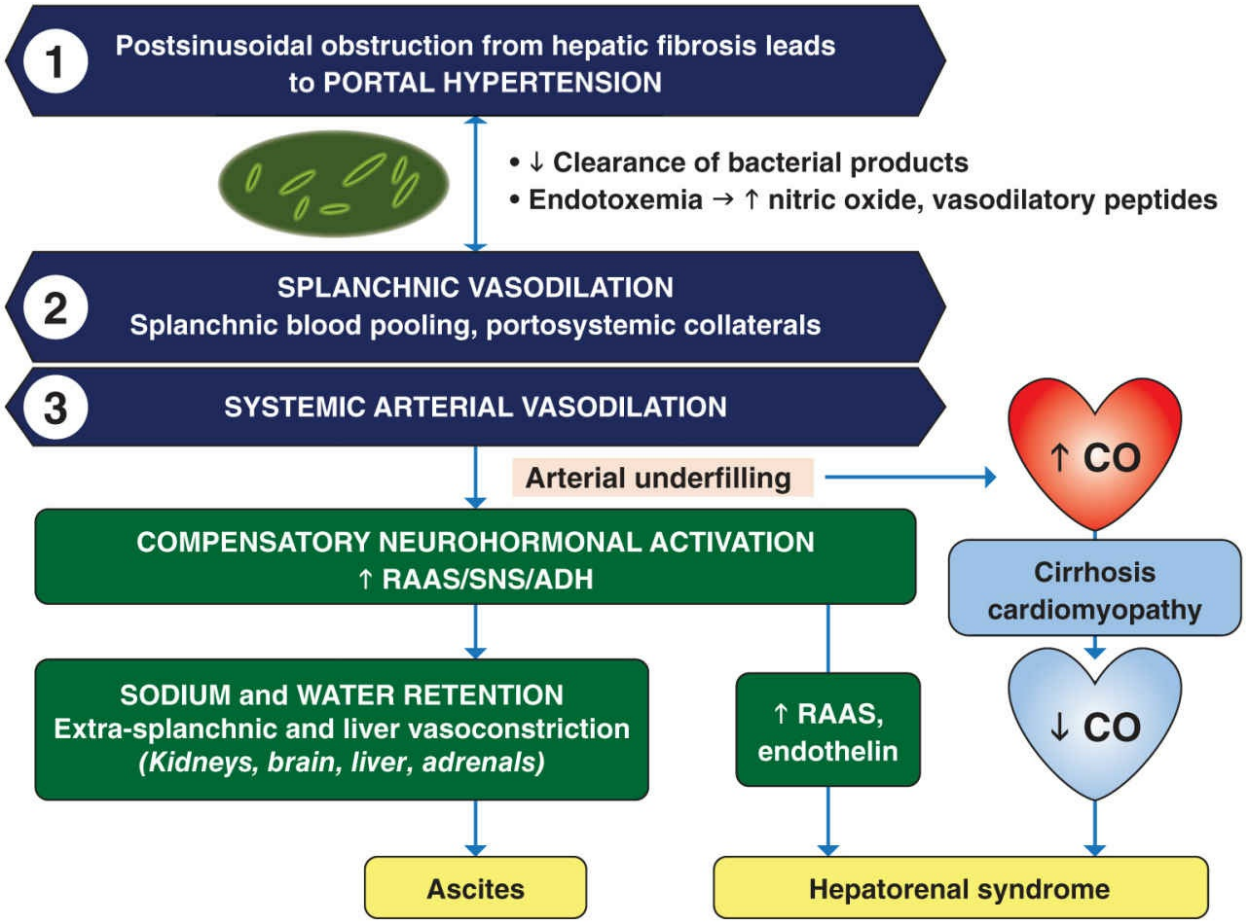

FIGURE 1.7 Mechanisms of ascites formation and hepatorenal syndrome. Abbreviations: ADH, antidiuretic hormone; CO, cardiac output; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system.

- Early compensation following hemodynamic changes above leads to *HYPERdynamic* circulation with increased cardiac output.
- With disease progression, there may be cardiac dysfunction, known as "cirrhotic cardiomyopathy":
  - Cirrhotic cardiomyopathy is characterized by reduced contractile responsiveness to hemodynamic or pharmacologic stress and diastolic dysfunction with electrophysiologic abnormalities in the absence of known cardiac disease.
    - Routine use of albumin and vasoconstrictors with HRS is thought to be beneficial for cirrhotic cardiomyopathy via anti-inflammatory and hemodynamic effects, respectively.
    - β-Blockers are likely not helpful because β-adrenergic receptors are

downregulated in cirrhosis.

- Use of cardiac inotrope (dobutamine) has been reported to reverse HRS. More data are needed.

- With cirrhotic cardiomyopathy, cardiac output cannot adequately compensate the increasing splanchnic arterial vasodilation and result in *effective arterial hypovolemia.* This is followed by activation of RAAS, SNS, and ADH systems and endothelin to promote Na^+ and H_2O retention and vasoconstriction of liver and extrasplanchnic organs (kidneys, brain, adrenals).
  - The continuing Na^+ and H_2O retention lead to edema and ascites formation.
  - The high ADH state leads to hyponatremia in the presence of excess free water relative to solute intake.
  - Severe vasoconstriction in the brain is thought to partially contribute to hepatic encephalopathy.
  - The severe renal vasoconstriction leads to a precipitous fall in glomerular filtration rate (GFR). This state of *functional* renal dysfunction is referred to as HRS and may be reversed with a liver transplant.
- See Table 1.5 for the diagnostic criteria for HRS.

Table 1.5 Diagnostic Criteria for Hepatorenal Syndrome (Ascites International Club)

1. Diagnosis of cirrhosis with ascites	
2. AKI	AKI as defined per AKIN/KDOQI: • Increase in serum creatinine by ≥0.3 mg/dL from stable baseline in <48 h, *or* • ≥50% increase in stable baseline serum creatinine within the prior 3 m
3. No improvement in serum creatinine after at least 2 d with diuretic withdrawal and volume expansion with albumin	Recommended albumin dose: 1 g/kg of body weight per day up to a maximum of 100 g/d
4. Absence of shock	
5. No current or recent treatment with nephrotoxic drugs	E.g., no recent use of antibiotic or nonsteroidal anti-inflammatory drugs

6. Absence of parenchymal kidney disease	Absence of proteinuria >500 mg/d, microhematuria >50 red blood cells per high power field, and/or abnormal kidney ultrasonography

Abbreviations: AKI, acute kidney injury; AKIN/KDOQI, Acute Kidney Injury Network and the Kidney Disease Outcomes Quality Initiative.

- See Table 11.4 for the management of HRS.

Drug-Induced Edema Due to Sodium Retention

- Vasodilators: minoxidil (pericardial effusion and tamponade have been reported), diazoxide

- Thiazolindinediones (thought to be due to (1) increase in sodium reabsorption by ENaC and proximal tubules, (2) vascular vasodilation via activation of peroxisome proliferator–activated receptor γ [PPARγ], subsequent fall in blood pressure and sodium retention): pioglitazone (rosiglitazone is discontinued from the market)
- Sex hormones (possibly via associated mineralocorticoid activity): estrogen, testosterone
- NSAIDs and cyclooxygenase-2 inhibitors (via reducing vasodilatory PGs in glomerular afferent arterioles, thus GFR)
- Pramipexole, dopamine agonist, used to treat Parkinson disease and restless leg syndrome (suggested to be due to lymphatic insufficiency)
- Insulin (presumably via increasing aldosterone level and renal sodium reabsorption): refeeding of individuals who fast for ≥3 days with carbohydrates may develop insulin-mediated sodium retention and edema, known as refeeding edema.
- Others: gabapentin, pregabalin, proton pump inhibitors, docetaxel

NOTE Dihydropyridine calcium channel blocker (CCB)-related peripheral edema is caused by preferential precapillary arteriolar vasodilation relative to the venous bed, which leads to the transmission of higher systemic pressure into the venous bed, resulting in an increase in hydraulic pressure within the venous bed and subsequent fluid leak into the interstitial space and edema formation. CCB-induced edema is NOT due to renal sodium retention and should not be treated with diuretics.

SALT DEPLETION

Cerebral Salt Wasting

- Typically associated with subarachnoid hemorrhage, which is thought to be associated with:
  - Impaired sympathetic neural input (SNS normally promotes proximal tubular Na^+, uric acid, and water reabsorption and renin–aldosterone release), and/or
  - Increased brain natriuretic peptide → impairs renal tubular Na^+ reabsorption and inhibits renin release
- Clinical manifestations: volume depletion, orthostatic hypotension
- Laboratory findings: hyponatremia, low serum uric acid, high urine osmolality, U[Na^+] > 40 mmol/L, low renin and aldosterone levels (similar to those seen with SIADH)

NOTE CSW patients present with volume depletion, in contrast to SIADH patients who present with euvolemia or mild hypervolemia.

- Treatment of CSW:
  - Volume repletion (NS, salt tablets once stable and tolerate oral intake). **Note:** NS may worsen hyponatremia in SIADH when urine osmolality >300 mOsm/kg but would improve hyponatremia in CSW.
  - Consider mineralocorticoids, for example, fludrocortisone 0.2 mg twice daily.
  - Typically transient condition—long-term treatment is likely not necessary.

NOTE Common features between SIADH and CSW: high ADH and natriuretic peptide levels, high U[Na^+], low renin and aldosterone levels, low uric acid levels. ADH level decreases after volume repletion in CSW but not in SIADH. Accordingly, U_{OSM} can decrease with volume repletion in CSW but not SIADH.

Mineralocorticoid Deficiency

Aldosterone deficiency

- The causes of hypoaldosteronism can be differentiated by measurements of plasma renin activity (PRA), serum aldosterone, and serum cortisol following the administration of a loop diuretic or 3 hours after being in the

upright position.

- Primary adrenal insufficiency:
  - Underlying causes: congenital adrenal hyperplasia or hypoplasia; adrenoleukodystrophy; autoimmune, infiltrative, and infectious diseases (HIV, tuberculosis); metastatic malignancy; bilateral adrenalectomy; use of pharmacologic inhibitors of aldosterone biosynthesis (e.g., inhibitors of RAAS, both unfractionated and fractionated low-molecular-weight heparin inhibit aldosterone synthesis and reduce AII level and affinity to its receptors in the zona glomerulosa)
  - Laboratory findings: Reduced Na^+ reabsorption and reduced distal K^+ secretion at aldosterone-sensitive distal nephron (i.e., late distal convoluted tubules [DCTs], connecting segment, and cortical collecting tubules) lead to varying degrees of hyponatremia, hyperkalemia, and metabolic acidosis.

NOTE Secondary adrenal insufficiency due to pituitary disorders (affecting adrenocorticotropic hormone secretion) and tertiary adrenal insufficiency due to hypothalamic disorders (affecting corticotropin release hormone secretion) only present with hypocortisolism, *not* mineralocorticoid insufficiency. For this reason, both secondary and tertiary forms of adrenal insufficiency are not associated with hyperkalemia.

- Treatment of primary adrenal insufficiency:
  - Glucocorticoid (hydrocortisone or prednisone) to correct cortisol deficiency
  - Fludrocortisone (0.05 to 0.2 mg/d) *and* adequate sodium intake (i.e., $U[Na^+] > 20$ to 40 mmol/L to indicate adequate Na^+ delivery to cortical tubules)
  - **Note:**
    - Hydrocortisone 20 mg and prednisone 50 mg provide a mineralocorticoid effect equivalent to ~0.1 mg of fludrocortisone. The addition of fludrocortisone may not be necessary.
    - Fludrocortisone requires tubular sodium delivery to the cortical collecting tubules to work. Salt-depleted patients cannot deliver adequate sodium to the cortical collecting tubules, rendering

fludrocortisone ineffective or suboptimally effective. That is, if a patient does not adequately respond to fludrocortisone (i.e., persistent hyperkalemia ± hypotension), make sure patient has adequate sodium intake or U[Na^+] > 20 mmol/L before increasing fludrocortisone dose.

- In patients with volume expansion and/or preexisting hypertension, consider adding low-dose loop or thiazide diuretics. This will not only reduce Na^+ retention but also enhance distal Na^+ delivery for optimal fludrocortisone activity.

- Isolated aldosterone synthase deficiency (ASD)
  - Rare autosomal recessive condition with loss-of-function mutation in the gene *CYP11B2* coding aldosterone synthase. This enzyme catalyzes the final three steps in aldosterone biosynthesis. Mutations involving CYP11B2 may affect either the hydroxylation of corticosterone at 18-carbon (ASD type 1) or oxidation of 18-hydroxycorticosterone (ASD type 2). See **Figure 1.8**.

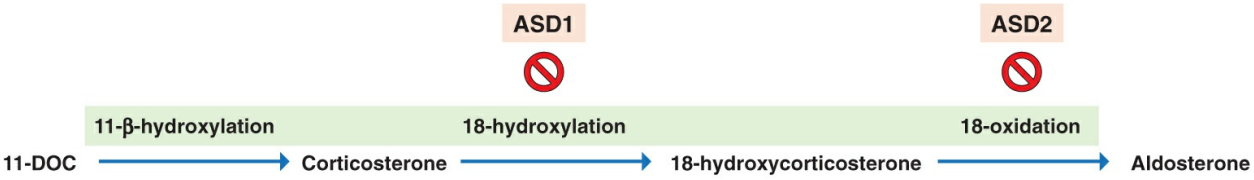

FIGURE 1.8 Aldosterone synthase deficiency. ASD1 involves a defect in the 18-hydroxylation of corticosterone to form 18-hydroxycorticosterone, which results in low levels of 18-hydroxycorticosterone. ASD2 involves a defect in the 18-oxidation of 18-hydroxycorticosterone to form aldosterone, which results in markedly elevated level of 18-hydroxycorticosterone. Both ASD1 and ASD2 result in low levels of aldosterone and elevated plasma renin activity levels. Abbreviations: ASD, aldosterone synthase deficiency; DOC, deoxycorticosterone.

  - This condition is characterized by severe dehydration, vomiting, failure to thrive, hyperkalemia, and hyponatremia in infancy.
  - Laboratory findings: hyperkalemia, hyponatremia, metabolic acidosis, increased PRA, low aldosterone
  - Treatment: salt replacement, fludrocortisone (0.05 to 0.2 mg/d)

Aldosterone resistance

- This category consists of a rare group of disorders characterized by resistance to aldosterone action, known as pseudohypoaldosteronism type

1 (PHA1).

- PHA1 is diagnosed in the neonatal period and is categorized into renal PHA1 and systemic PHA1.
  - Pseudohypoaldosteronism type 1 (PHA1)
    - Rare group of disorders characterized by resistance to aldosterone action diagnosed in the neonatal period
  - Renal type 1
    - Autosomal dominant
    - Defect: loss-of-function mutation of aldosterone receptor
    - Clinical manifestations: milder salt wasting compared to systemic type 1 (see below) improves with age
    - Treatment: High sodium supplementation ± fludrocortisone 1 to 2 mg/d or carbenoxolone (antagonizes cortisol metabolism, thereby allowing accumulation of cortisol to activate mineralocorticoid receptors)

NOTE A much higher dose is needed in PHA1 than that in primary adrenal insufficiency.

  - Systemic type 1
    - Autosomal recessive
    - Defect: loss-of-function mutation of ENaC
    - Clinical manifestations: salt wasting presentation is typically much more severe because ENaC mutation affects multiple organs. Associated complications are notable for chronic pulmonary syndrome (recurrent chronic coughs and wheezing, increased susceptibility to pulmonary infections), cholelithiasis, polyhydramnios, and characteristic skin changes (miliaria rubra-like cutaneous eruptions).
    - Treatment: high sodium supplementation; indomethacin may be considered to reduce urine output.
    - Laboratory findings common to both PHA1 types: hyperkalemia, hyponatremia, metabolic acidosis, significantly elevated renin and aldosterone levels. In systemic type 1, sweat chloride testing is also

positive for high chloride secretion >30 mmol/L.

Renal Salt Wasting

- Salt-losing nephropathy:
  - Salt wasting may be observed in patients with advanced kidney disease, tubulointerstitial diseases, or proximal renal tubular acidosis (pRTA).
  - Salt wasting in pRTA is due to obligatory Na^+ and K^+ losses associated with bicarbonaturia. Potassium loss also occurs due to volume depletion–induced increase in aldosterone.
- Renal PHA1 (see earlier)
- Drug-induced renal salt wasting:
  - Cisplatin may induce severe renal salt wasting in association with Fanconi syndrome. Prophylactic NS infusion along with cisplatin administration is key.
  - Tenofovir may also induce renal salt wasting in association with Fanconi syndrome and acute tubular necrosis.
  - Diuretics and osmotic agents

Diuretics: Loop and Thiazide Diuretics

Loop diuretics

- All loop diuretics except ethacrynic acid have a sulfa group. Furosemide and especially ethacrynic acid are highly ototoxic. Ethacrynic acid should only be used if sulfa allergic.
- See Table 1.6 for commonly used loop diuretics.

Table 1.6 Loop diuretics

Loop Diuretics	Bioavailability	Intravenous to Oral Dose Conversion	Dose Equivalent	Comments
Bumetanide	75%	1:1	1	Not as ototoxic as furosemide if administered at clinically equivalent dose (e.g., 2 mg of bumetanide is not as ototoxic as 80 mg of furosemide)
Furosemide	50%	1:2	40	Most commonly used
Torsemide	80%	1:1	20	Has longer half-life and greater

				bioavailability than bumetanide and furosemide
Ethacrynic acid	100%	1:1	50	No sulfa group compared to all other loop diuretics; highly ototoxic and should only be considered in patients with sulfa allergy

Thiazide and thiazide-like diuretics

- Thiazides:
  - Hydrochlorothiazide (HCTZ): short half-life ($t_{1/2}$) 6 to 15 hours
  - Chlorothiazide: $t_{1/2}$ 1 to 2 hours; only thiazide available in both intravenous and oral forms
- Thiazide-like diuretics (absence of benzothiadiazide ring):
  - Chlorthalidone: long $t_{1/2}$ 48 to 72 hours
  - Indapamide: $t_{1/2}$ 14 hours
  - Metolazone: $t_{1/2}$ 14 hours; Maximal diuretic effect occurs within an hour of oral intake and may persist up to 24 hours.
- General points regarding thiazides and thiazide-like diuretics:
  - Long-acting chlorthalidone and indapamide have been shown to reduce cardiovascular events in randomized trials. There are no similar data for short-acting HCTZ. The use of long-acting agents is therefore preferred over HCTZ in the treatment of hypertension.
  - Blood pressure reduction is significantly greater with chlorthalidone and indapamide compared with HCTZ.
  - Dose-dependent adverse effects for thiazides and thiazide-like diuretics: hyponatremia, hypokalemia, hyperglycemia, hyperuricemia (gout), hypomagnesemia, hyperlipidemia (transient). Hypercalcemia may occur in at-risk individuals.
  - Hypokalemia is thought to play a role in reducing pancreatic insulin secretion, thus thiazide-associated hyperglycemia. Thiazide-induced hyperglycemic effect can be minimized with the concurrent use of K-sparing agents such as inhibitors of the renin–angiotensin system (ACEIs, ARBs, or aldosterone antagonists) or potassium supplement.
  - Thiazides and thiazide-like diuretics may be added to loop diuretics to treat refractory edema. Electrolyte disturbances may be severe and must

be monitored.

- Thiazides and thiazide-like agents generally have poor efficacy as diuretics when GFR < 30 ml/min/1.73 m^2. although metolazone has been reported to work even at gfr < 20 ml/min/1.73 m^2, it may have been related to the use of a very high dose and not any intrinsic characteristic of the drug per se.

Loop Versus Thiazide Diuretic

Common features: both induce volume depletion and compensatory increase in ADH secretion.

Differences:

- Diuretic effect:
  - Loop diuretics are much more potent than thiazides.
  - Antidiuretic activity duration: short-lived (i.e., <2 weeks) with thiazides due to increased compensatory sodium reabsorption at more proximal nephron segments
- Calcium: Calcium wasting is seen with loop diuretics, whereas calcium-sparing effect is seen with thiazides.
- Hyponatremia:
  - Hyponatremia is commonly seen with thiazides but not with loop diuretics.
  - Mechanisms:
    - Loop diuretics inhibit Na^+–K^+–$2Cl^-$ cotransporter leads to:
      - Reduction in free H_2O production thus less free H_2O delivery to the collecting tubules for reabsorption.
      - Reduction in the medullary tonicity. Optimal H_2O reabsorption at the collecting tubules depends on a high medullary concentration gradient. The reduced medullary tonicity reduces the efficiency of free H_2O reabsorption.
      - The impaired free H_2O reabsorption with loop diuretics “protects” patients from developing hyponatremia despite having increased ADH.
    - Thiazide diuretics do not affect luminal free H_2O production nearly

as much as loop diuretics and do not affect the medullary concentration gradient. A compensatory increase in ADH with thiazides, therefore, will lead to avid free H_2O reabsorption in the presence of any free H_2O intake. Consequently, hyponatremia may develop within 5 to 14 days. At-risk patients include underweight and elderly women. Concurrent low-solute intake predisposes these patients to hyponatremia.

- Of note, potassium depletion (e.g., associated with diuretic use) may directly stimulate water intake *via* alterations in osmoreceptor sensitivity and increased thirst. This may play a contributory role in diuretic-induced hyponatremia.

Osmotic Diuresis (See Polyuria Section for Diagnosis) Gastrointestinal losses and third-spacing

- Clinical history
- Laboratory findings:
  - High U_{OSM}, low $U[Na^+] < 10$ to 20 mmol/l
  - Exceptions: $U[Na^+]$ may be >20 mmol/L if there is concurrent kidney failure from acute tubular necrosis or acute vomiting (see **Chapter 2**).

Table 1.7 summarizes salt-depleted conditions.

Table 1.7 Salt-depleted conditions

	Specific Conditions	Diagnostic Pearls	Management

Brain	CSW
	• Associated with acute intracranial pathology, typically subarachnoid hemorrhage
		• Laboratory findings are similar to those observed in patients with SIADH:
		  • Hyponatremia; low serum uric acid
		  • U_{OSM} > 200–300 mOsm/kg
		  • $U[Na^+]$ > 40 mmol/L
		  • Low renin and aldosterone
			• Treatment with normal saline improves hyponatremia in most CSW cases but may worsen hyponatremia in severe SIADH cases.
			• In severe CSW cases, 3% saline infusion may be necessary.
			• In contrast to patients with SIADH who are generally euvolemic, patients with CSW present with volume

		levels • High ADH level (suppressible with volume repletion)	depletion and orthostatic hypotension. Additionally, unlike SIADH, volume repletion in CSW can suppress ADH and accordingly reduce U_{OSM}.
Adrenals	Primary adrenal insufficiency (both glucocorticoid and mineralocorticoid deficiencies)	Laboratory findings: • Hyperkalemia due to aldosterone deficiency • Hyponatremia due to hypocortisolism-induced ADH secretion • Mild metabolic acidosis	• Glucocorticoid (hydrocortisone or prednisone) to correct cortisol deficiency[a] • Fludrocortisone (0.05–0.2 mg/d) *and* liberal sodium intake to maintain $U[Na^+] > 20$ mmol/L.
	Isolated aldosterone deficiency	Laboratory findings: • Hyperkalemia, hyponatremia, metabolic acidosis • High PRA, low aldosterone level	• Fludrocortisone (0.05–0.2 mg/d) *and* liberal sodium intake to maintain $U[Na^+] > 20$ mmol/L

	Aldosterone receptor mutation (pseudohypoaldosteronism type 1 [PHA1], renal PHA1)	• PHA1 typically manifests with hypovolemia, sodium wasting, and hyperkalemia in neonatal period.
		• Laboratory findings:
		  • Hyponatremia, hyperkalemia, metabolic acidosis
		  • Very high PRA and plasma and urine aldosterone
			• High-salt diet ±
			• Fludrocortisone 1–2 mg/d (or carbenoxolone)
			• Renal PHA1 improves well with salt supplementation. Systemic PHA1 requires more aggressive therapy.

Kidney	Salt-losing nephropathy	Consider in patients with advanced kidney disease, tubulointerstitial diseases, or pRTA Presence of proteinuria	Correct underlying kidney disease Na^+ and K^+ supplement as needed.

	Drug-induced kidney injury (cisplatin, tenofovir)	• Laboratory findings:
		  • Mild tubular proteinuria
		  • K^+, Mg^{2+}, PO_4^{2-}, Ca^{2+} wasting
		  • Kidney failure from acute tubular necrosis is common with tenofovir
			• Moderate to severe tubular salt wasting associated with Fanconi syndrome may be observed.
			• Preventive measure with normal saline infusion is key.

	Epithelial sodium channel mutation (systemic PHA1)	• Laboratory findings are similar to renal PHA1 above • Presentation of systemic PHA1 is typically much more severe than that seen with renal PHA1 because ENaC mutation affects multiple organs, most notable for pulmonary complications and infections.	• Treatment as in renal PHA1; much more intensive care for associated complications is typically required; indomethacin may be considered to reduce urine output. • Associated complications include chronic pulmonary syndrome, cholelithiasis, polyhydramnios, characteristic skin changes (miliaria rubra-like cutaneous eruptions).
	Diuretics, osmotic agents	Review medical history; see text and Table 1.6	
Gastrointestinal tract	Vomiting, biliary drainage, diarrhea	See **Chapter 2 Acid–Base and Potassium Disorders** (Acid–Base Disorders section)	Treat underlying conditions

Abbreviations: ADH, antidiuretic hormone; CSW, cerebral salt wasting; ENaC, epithelial sodium channel; PRA, plasma renin activity; pRTA, proximal renal tubular acidosis; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; U[Na^+], urine sodium; U_{OSM}, urine osmolality.
[a]Hydrocortisone 20 mg and prednisone 50 mg provide a mineralocorticoid effect equivalent to ~0.1 mg of fludrocortisone. Addition of fludrocortisone may not be necessary.

POLYURIA

Background

- Polyuria is typically defined as having urine volume greater than 40 mL/kg body weight/day.
- Polyuria may be due to osmotic diuresis, aquaresis, or both.
- Aquaresis is due to either failure of the kidneys to reabsorb water or excessive free water intake.

Basic Physiologic Steps Involved in Free Water Reabsorption (Fig. 1.9)

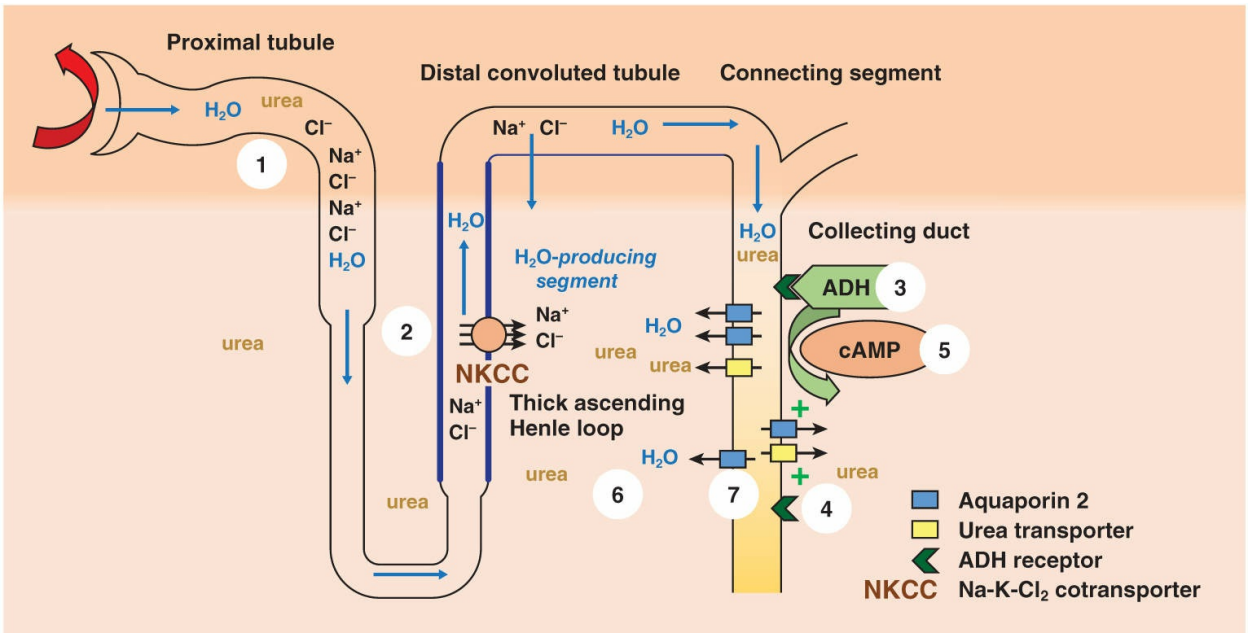

FIGURE 1.9 Water reabsorption within a nephron segment. **(1)** Sodium and water are reabsorbed at the proximal tubule. **(2)** Free water is produced within the lumen of the water-impermeable thick ascending Henle loop when sodium and water get reabsorbed via NKCC. **(3)** In the presence of ADH and **(4)** binding of ADH to its receptor, **(5)** cAMP is produced, which mediates the increase in the expression of both aquaporin 2 and urea transporters. **(6)** Increased urea transport from the lumen increases the medullary tonicity, which serves to reabsorb water from the collecting duct via aquaporin 2. **(7)** Intact aquaporin 2 is needed for free water reabsorption. Abbreviations: ADH, antidiuretic hormone; cAMP, cyclic adenosine monophosphate; NKCC, sodium potassium 2-chloride cotransporter.

- Salt and water are delivered to the thick ascending limb of loop of Henle and DCT.
- At these nephron segments where there is relative impermeability to H_2O (more so in loop of Henle than DCT), intraluminal free H_2O is "produced" when sodium is reabsorbed but not H_2O.
- Free H_2O produced is delivered to the collecting tubules where it is

reabsorbed *via* apical aquaporin 2 and basolateral aquaporins 3 and 4. The efficiency of H_2O reabsorption depends on the presence and integrity of AQP2 and high medullary concentration gradient. The latter acts as a dry sponge that soaks up any H_2O delivered to the collecting tubules: the higher the medullary concentration gradient, the more efficient the H_2O reabsorption.

- AQP2 regulation *via* ADH: ADH binds to its receptor and activates adenylyl cyclase *via* G-protein to produce cAMP. cAMP mediates the shuttling of cytoplasmic AQP2 to the apical side of principal cells along the collecting tubules where intraluminal H_2O can be reabsorbed. Prolonged ADH elevation (>24 hours) can also increase the expression of AQP2.
- ADH also stimulates the shuttling of urea transporters to cell surfaces in the inner medullary collecting ducts to increase urea reabsorption, thereby building up the inner medullary tonicity required for optimal water reabsorption.

Limitations to Effective H_2O Reabsorption (Table 1.8)

Table 1.8 Limitations for effective water reabsorption and associated conditions

Refer to Figure 1.9	Problems Leading to Suboptimal H_2O Reabsorption	Conditions
1	Proximal tubular dysfunction	Poor proximal tubular function
2	Suboptimal NKCC cotransporter	Hypokalemia, hypercalcemia
3	Reduced ADH level	Reduced ADH synthesis (central diabetes insipidus), pregnancy-associated increase in vasopressinase production
4	Abnormal ADH receptor	X-linked mutation of ADH receptor
5	Reduced cAMP production	Hypokalemia, hypercalcemia, demeclocycline, lithium
6	Reduced medullary concentration/tonicity	Sickle cell disease, malnutrition, suboptimal NKCC function, poor kidney function, hypokalemia, hypercalcemia
7	Reduced AQP2 function or expression	Autosomal dominant or recessive mutation of AQP2 Downregulation of AQP2: hypokalemia, malnutrition, lithium

Numbers 1-7 in this table corresponds to steps 1-7 in Figure 1.9.
Abbreviations: ADH, antidiuretic hormone; AQP2, aquaporin 2; cAMP, cyclic adenosine monophosphate; NKCC, sodium potassium 2-chloride cotransporter.

- Increased distal salt and water delivery seen with poor proximal tubular function
- Reduced ADH:
  - Reduced production: cDI
  - Increased destruction: Increased placental vasopressinase production associated with large placental weight, twin pregnancies, or pregnancy complicated by HELLP (hemolysis, elevated liver enzyme levels, and a low platelet count) syndrome or preeclampsia leads to the degradation of ADH and subsequent increased water excretion, known as gestational DI. This condition may be treated with DDAVP but not vasopressin (pitressin). Vasopressinase breaks down vasopressin (pitressin) and renders it inactive but not DDAVP. cDI would respond to either DDAVP or pitressin, but gestational DI due to increased vasopressinase level only responds to DDAVP. Gestational DI resolves with delivery.
- Abnormal ADH receptor: nDI (loss-of-function mutation of ADH receptor)
- Defect in cAMP production: chronic poor kidney function, hypokalemia, hypercalcemia, demeclocycline, lithium
- Problems with AQP2:
  - Mutation of AQP2 with functional defect
  - Downregulation of AQP2: chronic poor kidney function, hypokalemia, malnutrition, lithium therapy. **Of interest, lithium has** been shown to inhibit cAMP formation by the collecting duct and downregulate the expression of AQP3 and the urea transporter UT-A1. The latter reduces urea accumulation in the inner medulla, thus medullary concentration gradient required for water reabsorption. The intrinsic renal purinergic system involving adenosine triphosphate/adenosine diphosphate/uridine triphosphate (ATP/ADP/UTP) has been shown to counteract the action of AVP in the collecting duct and reduce free water reabsorption. Blockage of the purinergic system with clopidogrel reduces polyuria in animal models of lithium-induced nDI.

- Loss of medullary concentration gradient: chronic poor kidney function, hypokalemia, hypercalcemia, sickle cell disease, protein malnutrition

Causes of Polyuria

Aquaresis (water diuresis)

- Primary polydipsia:
  - Patients with psychiatric illness or anxiety disorders
  - Medications: high-dose antihistamines, decongestants, anticholinergics, urinary incontinence drugs (oxybutynin), antidepressants, psycholeptics
  - Hypothalamic lesions affecting thirst center (infiltrative diseases, sarcoidosis)
- cDI:
  - Idiopathic (autoimmune injury to ADH-producing cells)
  - Trauma, neurosurgery: although rare, a triphasic response may be observed in patients with severe hypothalamic or hypothalamic tract injury.
    1. Initial *polyuric phase* begins within 24 hours and lasts up to 4 to 5 days due to the inhibition of ADH release from hypothalamic "shock".
    2. *Antidiuretic phase* due to the slow release of stored ADH from the degenerating posterior pituitary occurs during days 6 to 11 (SIADH equivalent). Excessive free water intake during this phase can cause hyponatremia.
    3. *Permanent cDI* occurs due to the depletion of stored ADH in the posterior pituitary.
  - Pituitary surgery
  - Hypoxic/ischemic encephalopathy
  - Malignancy (metastatic disease involving hypothalamic–pituitary region, particularly lung, leukemia, lymphoma, craniopharyngioma, pinealoma)
  - Familial (rare, autosomal dominant; due to preservation of function of the normal allele, polyuria may not present until after the first year of life or even in young adulthood)

- Infiltrative diseases:
  - Langerhans cell histiocytosis or histiocytosis X: a rare histiocytic disorder commonly characterized by single or multiple osteolytic bone lesions with histiocyte infiltration; extraskeletal involvement: skin, lymph nodes, lungs, thymus, liver, spleen, bone marrow, CNS
  - Granulomatous diseases: sarcoidosis, tuberculosis, granulomatous polyangiitis
  - Autoimmune lymphocytic hypophysitis: lymphocytic infiltration and enlargement of pituitary followed by destruction of pituitary cells. More common in women, often associated with late pregnancy or postpartum.
  - IgG4-related disease
  - Post–supraventricular tachycardia: due to decreased ADH secretion, presumably due to increased left atrial and systemic pressure and subsequent activation of local baroreceptors
  - Other causes of cDI: cerebral aneurysm, anorexia nervosa, infections, Guillain–Barré syndrome
- nDI:
  - Hereditary:
    - Severe polyuria and hypernatremia typically occur during the first week of life.
    - X-linked: mutations of *AVPR2* gene encoding the vasopressin receptor V2
    - Autosomal recessive and dominant: mutations of aquaporin 2 gene
  - Acquired:
    - Drug induced: chronic lithium use, demeclocycline
    - Electrolyte disturbances: hypercalcemia, hypokalemia
    - Conditions leading to reduced medullary concentration gradient: sickle cell disease/trait, protein malnutrition
- Pregnancy: DI induced by placental production of vasopressinase. In the setting of preeclampsia, twins or triplets, or subclinical cDI, a transient DI may ensue from vasopressinase-mediated degradation of N-terminal amino acids from the vasopressin molecule. Because DDAVP is already

deaminated at the N-terminal, it is resistant to the effect of vasopressinase and may be used to treat pregnancy-associated DI. Delivery with removal of the placenta corrects the problem.

NOTE

- In adults, the onset of cDI is usually abrupt, whereas the onset of acquired nDI or primary polydipsia is typically gradual.
- New-onset nocturia may be an early sign of DI.

Solute (osmotic) diuresis

- Electrolytes: Excessive saline infusion, salt (Na^+, K^+) intake
- Nonelectrolytes: glucosuria, mannitol, total parenteral nutrition, contrast dye, urea, hemoglobin, myoglobin

Diagnosis of Polyuria (Fig. 1.10)

- Confirm polyuria by volume to rule out urinary frequency. Urine volume > 40 mL/kg/d generally defines polyuria.
- Determine water versus solute diuresis versus both
  - Solute/osmotic diuresis is likely if:
    - Total urine osmolality (24-hour urine volume × U_{OSM}) >> 800 mOsm/d (800 mOsm is the daily solute load [or 10 mOsm/kg/d] for an average American diet), or
    - C_{OSM} >> 3 L/d, or
    - U_{OSM}/S_{OSM} >> 0.7
  - Aquaresis is likely if:
    - Urine volume × (1 − U_{OSM}/S_{OSM}) >> 0 or
    - U_{OSM}/S_{OSM} << 0.7

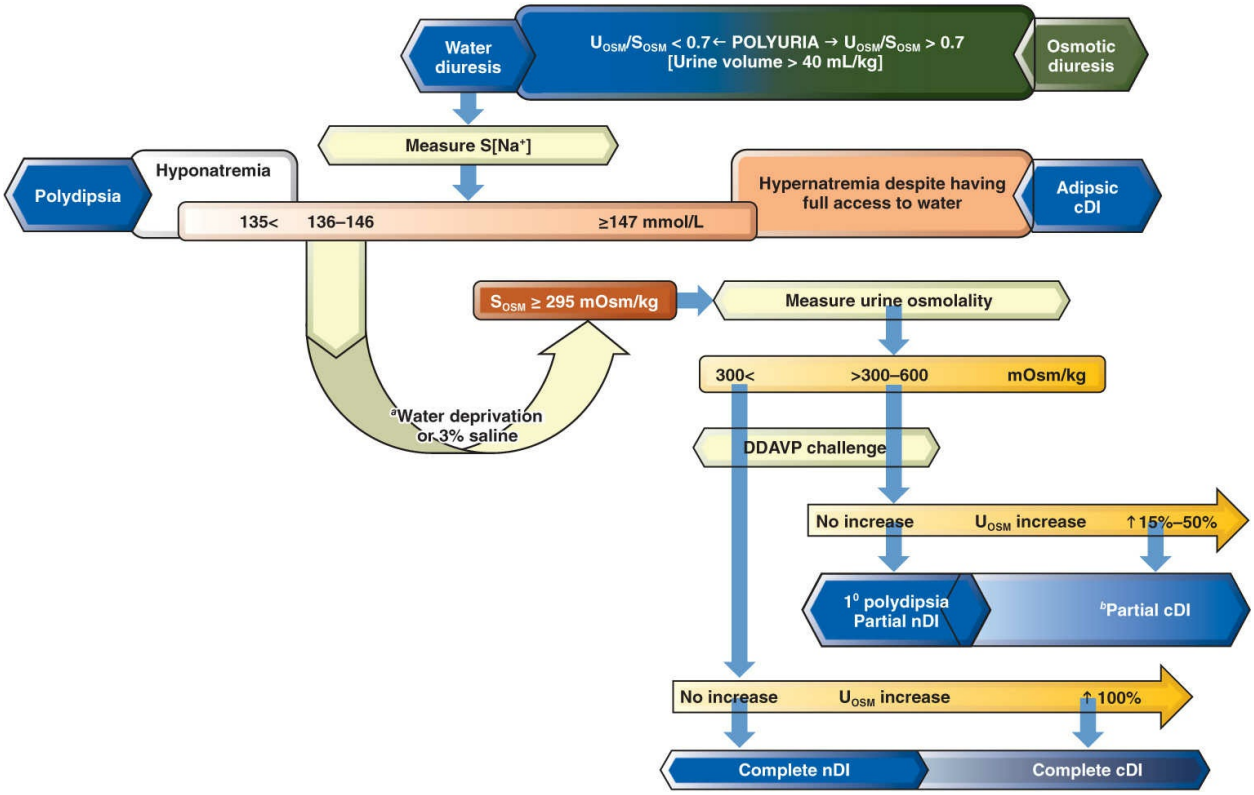

FIGURE 1.10 Evaluation of polyuria.

[a]Water deprivation or 3% saline infusion is not needed if patient presents with hypernatremia ≥145 mmol/L or serum osmolality ≥295 mOsm/kg.

[b]Partial cDI may have sufficient endogenous ADH secretion with water deprivation and hyperresponsiveness to the small ADH increase due to presumed upregulation of ADH receptors. The addition of DDAVP may not further concentrate the urine. This scenario could be mistaken as polydipsia. Clinical history of sudden onset, however, would favor central DI over polydipsia.

Abbreviations: cDI, central diabetes insipidus; DDAVP, desmopressin; nDI, nephrogenic diabetes insipidus; S_{OSM}, serum osmolality; U_{OSM}, urine osmolality.

- Combined solute and water diuresis is possible if:
  - ***Total*** urine osmolality (= 24-hour urine volume × U_{OSM}) >> 800 mOsm/d *and*
  - Large FWC, that is, urine volume × (1 − U_{OSM}/S_{OSM}) >> 0

Water deprivation testing

- Water deprivation testing is not necessary for the following:
  - Solute diuresis without concurrent aquaresis
  - Low U_{OSM} and low S[Na^+]: diagnosis of polydipsia is likely.
  - Adult patients with thirst sensation defect, S[Na^+] > 145 mmol/L despite

unlimited water access: diagnosis of adipsic DI is likely.

- There are two phases to a water deprivation test:
  - Phase 1: Aim is to induce a hyperosmolar state (S_{OSM} > 295 mOsm/kg or S[Na^+] > 145 mmol/L) to assess the concentrating ability of the kidneys. Hypertonic saline (0.05 mL/kg/min × ≤ 2 hours) may be considered if water deprivation is not an option.
    - Phase 1 of water deprivation testing is not necessary for the following:
      - U_{OSM} < s_{osm}, s[na^+] > 145 mmol/L in infants/children with a family history of nDI:
        - Proceed to phase 2 DDAVP challenge
        - If U_{OSM} does not increase by more than 100 mOsm/kg over baseline: diagnosis of nDI is likely. DNA testing for mutation analysis may be considered.
      - If a patient presents with S_{OSM} > 295 mOsm/kg or S[Na^+] > 145 mmol/L, omit water deprivation portion and proceed to phase 2 DDAVP challenge.
  - Phase 2: Once the patient has safely achieved the hyperosmolar goal S_{OSM} > 295 mOsm/kg, DDAVP is administered and the response to DDAVP is analyzed based on the changes in U_{OSM} and urine output.

Interpretation of water deprivation testing

- U_{OSM} > 300 to 600 mOsm/kg following phase 1 water deprivation:
  - Differential diagnoses: partial cDI, partial nDI, polydipsia
  - Response to DDAVP administration in phase 2 may set these conditions apart:
    - Partial cDI: U_{OSM} increases by 15% to 50% from phase 1.
      - Caveat: Patients with partial cDI may have sufficient endogenous ADH secretion with water deprivation and hyperresponsiveness to the small ADH increase due to upregulation of ADH receptors. The addition of DDAVP may not further concentrate the urine. This scenario could be mistaken as polydipsia or nDI. Clinical history of sudden onset, however, would favor cDI over polydipsia

or nDI. Additionally, patients with polydipsia typically present with hyponatremia.

- Primary polydipsia and nDI: no further increase in U_{OSM} after phase 1
  - Caveat: Chronic polydipsia suppresses the expression of both AQP2 and its receptors. An increase in ADH level may not appropriately induce free water reabsorption. Polydipsia may thus be mistaken as nDI.

- U_{OSM} < 300 mosm/kg following phase 1 water deprivation:
  - Presence of either complete nDI or complete cDI
  - Response to DDAVP administration in phase 2 sets these two conditions apart.
    - Complete nDI: no further increase in U_{OSM} from phase 1
      - Caveat: High ADH levels achieved during water deprivation/hypertonic saline infusion can partially overcome renal resistance to ADH, resulting in U_{OSM} > 300 Osm/kg
    - Complete cDI: U_{OSM} increases >100% from phase 1
- Other useful interpretations:
  - An increase in plasma or urine ADH in response to a rising S_{OSM} excludes cDI.
  - An increase in U_{OSM} as ADH secretion is increased excludes nDI.

Management of Polyuria

The use of copeptin in polyuric syndromes

- The diagnostic utility of copeptin in the evaluation of polyuria has been outlined as shown in **Figure 1.11**.

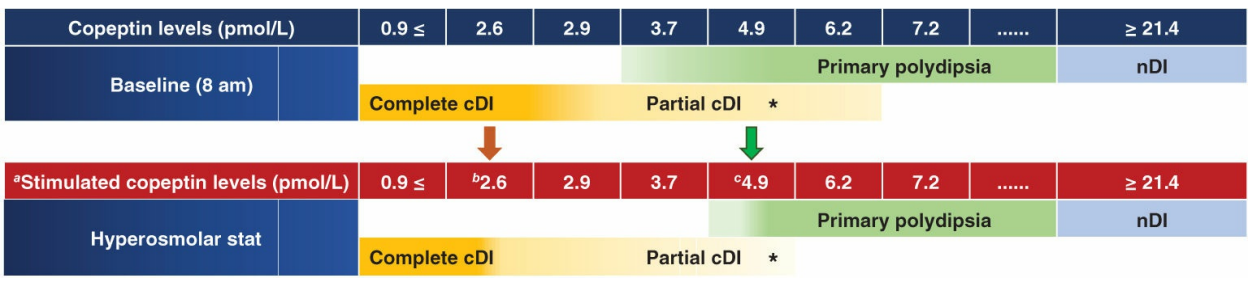

FIGURE 1.11 Plasma copeptin levels for the discrimination of polyuria–polydipsia syndromes.

[a]A "stimulated" copeptin level is measured following water deprivation testing or 3% saline infusion to achieve serum sodium ≥147 mmol/L.

[b]A stimulated copeptin cutoff value of ≥2.6 pmol/L (89% sensitivity and 82% specificity) has been suggested to differentiate other polyuria–polydipsia syndrome diagnoses from complete cDI.

[c]A stimulated copeptin cutoff value of ≥4.9 pmol/L (94% sensitivity and 96% specificity) has been suggested to differentiate between primary polydipsia and central DI.

*The ratio of change in copeptin levels over serum sodium concentration measured at 8 hours following water deprivation has been suggested to improve diagnostic accuracy in differentiating partial cDI from primary polydipsia. A value for $(\Delta \text{ copeptin}_{[0800–1600\ h]})/(S[Na^+]_{[1600\ h]}) \times 1{,}000 \geq 20$ pmol/L/mmol/L may provide a diagnostic accuracy of 94% with sensitivity of 85% and specificity of 100%.

Abbreviations: cDI, central diabetes insipidus; nDI, nephrogenic diabetes insipidus.

- The ratio of change in copeptin levels over $S[Na^+]$ measured at 8 hours following water deprivation has been suggested to improve diagnostic accuracy in differentiating partial cDI from primary polydipsia.
- A value for $(\Delta \text{ copeptin}_{[0800–1600\ h]})/(S[Na^+]_{[1600\ h]}^{+}) \times 1{,}000 \geq 20$ pmol/L/mmol/L may provide a diagnostic accuracy of 94% with sensitivity of 85% and specificity of 100%.

See **Table 1.9**.

Table 1.9 Management of polyuria

Conditions	Therapy
Polydipsia	Avoid anticholinergic agents, antihistamines, decongestants Behavioral therapy, patient education Medical therapy[a]: Atypical antipsychotics (varying benefit for psychogenic polydipsia): clozapine, olanzapine, risperidone
Adipsic diabetes insipidus	DDAVP
Central diabetes insipidus	DDAVP
Pregnancy-associated diabetes insipidus	DDAVP, delivery
Nephrogenic diabetes insipidus	General nonspecific therapy: Low-dose thiazide diuretic Low-sodium and low-protein diet (nutrition consult suggested to prevent malnourishment) Specific: Lithium induced: Amiloride if ongoing Li use

	Consider acetazolamide Malnutrition with poor medullary concentration gradient: consult nutrition Hypokalemia or hypercalcemia: correct electrolyte abnormalities and underlying causes Other nonspecific therapy: Nonsteroidal anti-inflammatory drugs (indomethacin 2 mg/kg/d)
Osmotic diuresis	Reduce solute load Control glucose in patients with diabetes mellitus

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DDAVP, desmopressin.

[a]Evidence level for efficacy is low. In the authors' opinion, these agents would only be considered if they are also needed for another indication.

CHAPTER 2

Acid–Base and Potassium Disorders

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ACID–BASE DISORDERS

Role of Kidneys in Acid–Base Regulation

Proximal tubules: Bicarbonate reabsorption (Fig. 2.1)

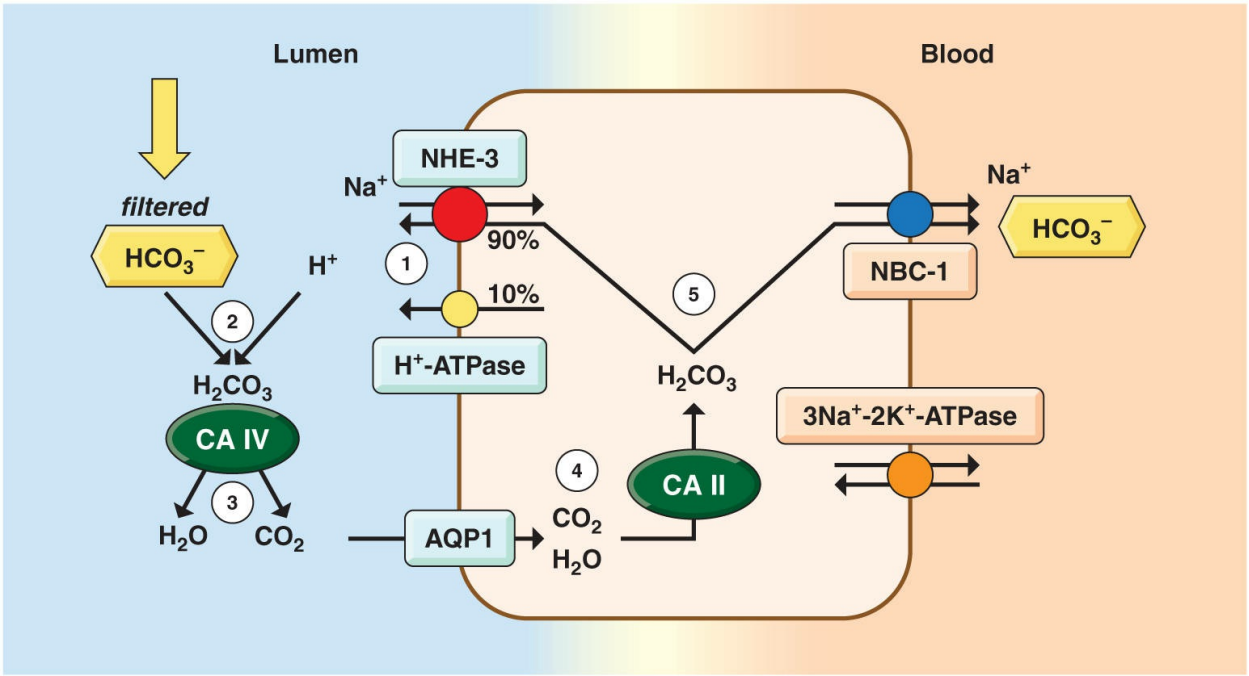

FIGURE 2.1 Bicarbonate reabsorption in the proximal tubule. 80% to 85% of HCO_3^- is reabsorbed in the proximal tubules. **1.** The Na^+-H^+ antiporter NHE3 and, to a lesser extent, H^+-ATPase secrete H^+ into the lumen. **2.** Secreted H^+ binds filtered HCO_3^- to form carbonic acid (H_2CO_3). **3.** CA IV

catalyzes the dissociation of H_2CO_3 into H_2O + CO_2. **4.** CO_2 diffuses into the cell, combines with H_2O (which enters the cell via AQP1) to reform H_2CO_3 (via the catalytic activity of CA II), then again redissociates to H^+ + HCO_3^-. **5.** H^+ is resecreted into the lumen, whereas HCO_3^- is reabsorbed via the Na^+-HCO_3^- cotransporter NBC1. Abbreviations: AQP1, aquaporin 1; CA II, carbonic anhydrase II; CA IV, carbonic anhydrase IV; NBC1, sodium bicarbonate cotransporter-1; NHE3, sodium hydrogen exchanger-3.

- 80% to 85% of filtered HCO_3^- is reabsorbed in the proximal tubules; 15% to 20% is reabsorbed in the thick ascending loop of Henle; ~5% is reabsorbed in the distal nephron. Although the amount of distal HCO_3^- reabsorption is small, this can increase in proximal renal tubular acidosis (pRTA).
- The Na^+-H^+ antiporter sodium hydrogen exchanger-3 (NHE3) and, to a lesser extent, H^+-ATPase secrete H^+ into the lumen where it binds filtered HCO_3^- to form carbonic acid (H_2CO_3). Carbonic anhydrase IV (CA IV) catalyzes the dissociation of H_2CO_3 into H_2O + CO_2. CO_2 diffuses into the cell and combines with H_2O to reform H_2CO_3, which redissociates into H^+ + HCO_3^-. H^+ is resecreted into the lumen, whereas HCO_3^- is reabsorbed via the sodium bicarbonate cotransporter-1 (NBC1).
- In acute metabolic acidosis, cytoplasmic NBC1 is recruited into basolateral membranes to enhance HCO_3^- reabsorption.
- In metabolic alkalosis, NBC1 is redistributed into the cytoplasm to reduce HCO_3^- reabsorption.
- In respiratory acidosis, NBC1 protein synthesis is upregulated.
- In volume depletion or renal hypoperfusion, angiotensin II (AII) stimulates NHE3 and NBC1.

Distal tubules: Hydrogen, bicarbonate, and potassium secretion/reabsorption (Fig. 2.2)

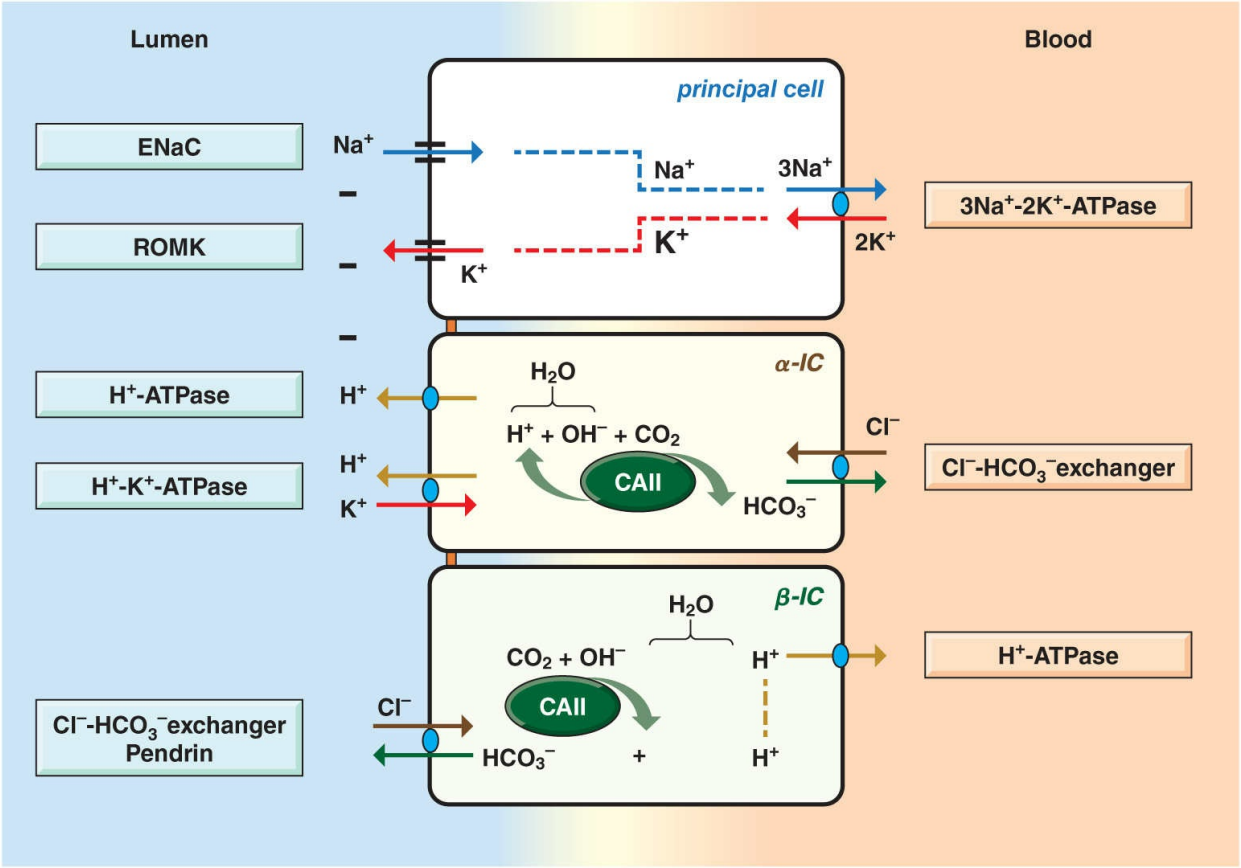

FIGURE 2.2 H^+, HCO_3^-, and K^+ handling in the collecting duct. Sodium delivery to the collecting duct enters the principal cells via the apical ENaC. The reabsorbed Na^+ is subsequently reabsorbed on the basolateral side in exchange for intracellular K^+ uptake via $3Na^+$-$2K^+$-ATPase. The increase in intracellular K^+ gives rise to a favorable chemical gradient for K^+ secretion. The apical uptake of Na^+ also creates an electronegative lumen that favors the secretion of positively charged K^+ via ROMK (in principal cells) and H^+ via H^+-ATPase and, to a lesser extent, H^+-K^+-ATPase by type A-intercalated cell (α-intercalated cells). Hypokalemia increases H^+-K^+-ATPase activity. Abbreviations: α-IC, α-intercalated cells; β-IC, β-intercalated cells; CA II, carbonic anhydrase II; ENaC, epithelial sodium channel; ROMK, renal outer medullary potassium channel.

- H^+ secretion occurs predominantly in the late distal tubule, connecting segment, and cortical and medullary collecting tubules at approximately 1 mEq/kg/d, reflecting daily (dietary) acid load.

Mechanisms of H^+ and K^+ secretions

- Sodium enters the principal cells via the apical amiloride-sensitive epithelial sodium channel (ENaC).
- The reabsorbed Na^+ is subsequently reabsorbed on the basolateral side in exchange for intracellular K^+ uptake via $3Na^+$-$2K^+$-ATPase. The increase in intracellular K^+ gives rise to a favorable chemical gradient for K^+

secretion.

- The apical uptake of Na^+ also creates a relative electronegative lumen that favors the secretion of positively charged K^+ via the renal outer medullary potassium channel (ROMK in principal cells) and H^+ via H^+-ATPase and, to a lesser extent, H^+-K^+-ATPase in type A-intercalated cells (α-intercalated cells or α-IC).
- Aldosterone stimulates both H^+ and K^+ secretion by increasing the expression of ENaC and Na^+-K^+-ATPase and increasing the activity of ROMK.
- The efficiency of H^+ secretion also depends in part on the presence of ammonia (NH_3), which serves to buffer the secreted H^+ and facilitate urinary excretion.

$$H^+ + NH_3 \rightarrow NH_4^+ \text{ (excreted into urine)}$$

NOTE

- Optimal H^+ and K^+ secretions require adequate Na^+ delivery to the distal nephron, intact ENaC activity, presence of aldosterone, and good urine flow.

- Potassium-depleted state enhances the activity of H^+-K^+-ATPase, which serves to increase K^+ reabsorption in exchange for H^+ secretion. (This partly explains how metabolic alkalosis may be present in association with severe hypokalemia.)

H^+ reabsorption

- Cortical collecting ducts (CCDs) have type B-intercalated cells (β-IC), which are thought to be mirror image of α-IC in terms of H^+/HCO_3^- secretion.
- β-IC secrete HCO_3^- in exchange for Cl^- into the lumen via the apical chloride–bicarbonate exchanger (known as pendrin) while reabsorbing H^+ on the basolateral cell surface. In contrast, α-IC secrete H^+ into the lumen while reabsorbing HCO_3^- on the basolateral side.
- Depending on the acid–base status, distal tubules can switch intercalated cell types to secrete either H^+ or HCO_3^-. Chronic metabolic acidosis increases the proportion of α-IC, whereas metabolic alkalosis increases the proportion of β-IC. Extracellular matrix proteins (e.g., hensin, galectin-3,

and others) along the intercalated cell basolateral surface have been suggested to play a role in this cell-type expression switch.

Ammoniagenesis: Proximal tubular production of NH_4^+, NH_3

- The substrate for ammoniagenesis is glutamine.
- Glutamine is taken up by proximal tubular cells via the sodium-dependent amino acid transporters (SNAT3), where NH_4^+ is formed in a multistep process (**Fig. 2.3**):

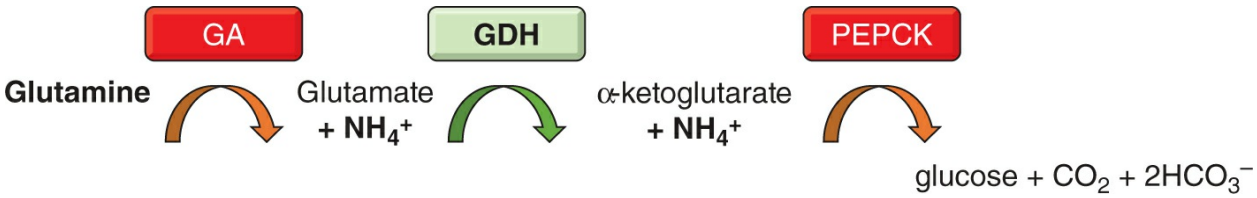

FIGURE 2.3 Ammoniagenesis. Rate-limiting enzymes for ammoniagenesis include GA and PEPCK. Both metabolic acidosis and hypokalemia stimulate GA, GDH, and PEPCK. Abbreviations: GDH, glutamate dehydrogenase; GA, phosphate-dependent glutaminase; PEPCK, phosphoenolpyruvate carboxykinase.

- Rate-limiting enzymes for ammoniagenesis include phosphate-dependent glutaminase (GA) and phosphoenolpyruvate carboxykinase (PEPCK).
- NH_4^+ is either transported as NH_4^+ into the lumen via NHE3 or freely diffuses into lumen as NH_3. AII upregulates NHE3, thereby increasing NH_4^+ secretion.
- Luminal NH_3 and NH_4^+ are reabsorbed at thick ascending limb of loop of Henle (TAL) into the interstitium where they are subsequently secreted back out into the lumen at the CCD with H^+ (via nonionic diffusion). NH_4^+ may be reabsorbed at TAL via the Na^+-K^+-$2Cl^-$ cotransporter (NKCC2). Secretion of NH_3 at the connecting segments and collecting tubules is facilitated by the nonerythroid glycoproteins RhBg and RhCg (**Fig. 2.4**).

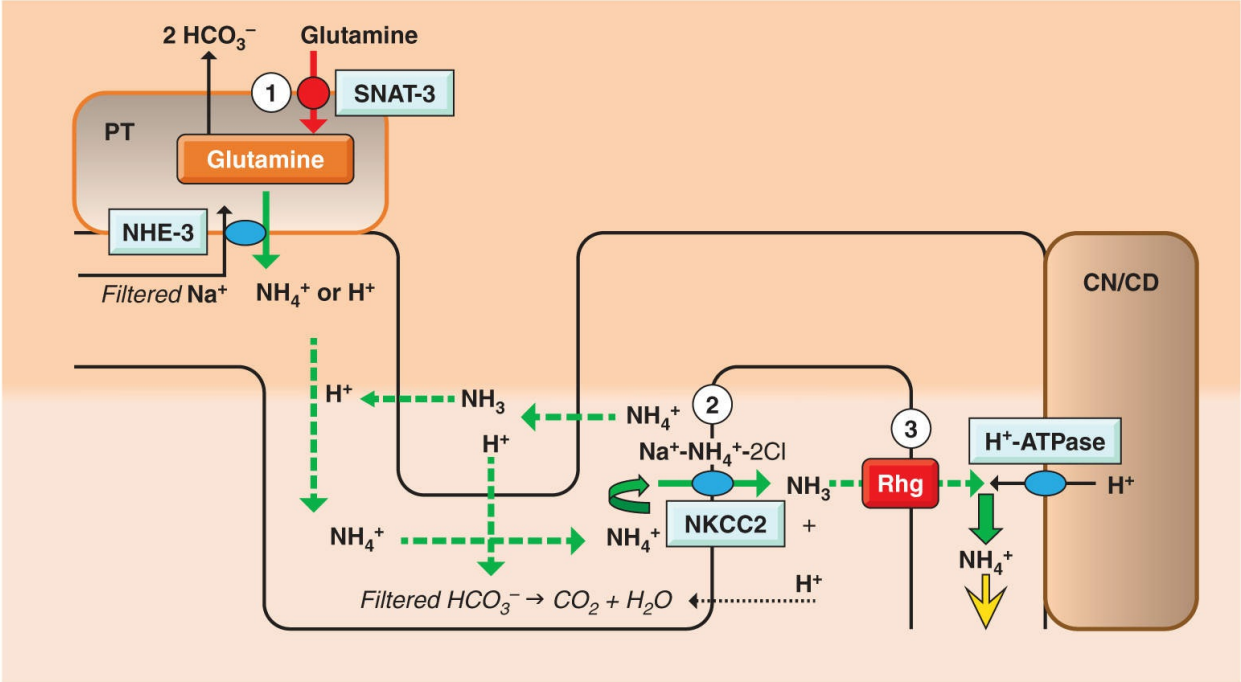

FIGURE 2.4 Ammoniagenesis within the nephron. **1.** NH_4^+ generated from glutamine in the proximal tubule is secreted into the lumen via NHE3. **2.** Luminal NH_4^+ may be reabsorbed at the loop of Henle via NKCC2. **3.** Secretion of NH_3 at the connecting segments and collecting duct is facilitated by nonerythroid glycoproteins RhBg and RhCg. Abbreviations: CD, collecting duct; CN, connecting segment; NHE3, sodium hydrogen exchanger-3; NKCC2, Na^+-K^+-$2Cl^-$ cotransporter; PT, proximal tubule; Rhg, nonerythroid glycoproteins B and C (RhBg, RhCg); SNAT-3, sodium-dependent amino acid transporter.

- Ammoniagenesis and ammonia transport along the nephron are stimulated by metabolic acidosis and hypokalemia.
  - Metabolic acidosis and hypokalemia:
    - Increase ammoniagenesis by increasing the expression of involved enzymes, including GA, glutamate dehydrogenase, and PEPCK
    - Facilitate the transport of ammonia along the nephron by increasing the expressions of SNAT3, NHE3, and Rh glycoprotein RhCg
  - Metabolic acidosis also:
    - Increases mobilization of glutamine from skeletal muscle and intestinal cells
    - Increases the expression of NKCC2

Diagnosis of Acid–Base Disorders

- In the evaluation of acid–base disorders, the use of either arterial or venous

blood gas (ABG and VBG, respectively) generally provides similar answers.

- Nonetheless, on average, the differences in ABG versus VBG for pH, pCO_2, and HCO_3^- (referred to as total CO_2 [tCO_2] in venous blood) are as follows:
  - pH (ABG) ≈ pH (VBG) + 0.03
  - pCO_2 (ABG) ≈ pCO_2 (VBG) − 4
  - HCO_3^- (ABG) ≈ tCO_2 (VBG) − 1
  - The measured venous tCO_2 from a routine chemistry panel is typically higher than the calculated [HCO_3^-] from an ABG. Although other factors may be contributory, the discrepancy between the two values has been largely explained by the fact that venous tCO_2 measures HCO_3^-, H_2CO_3, and dissolved CO_2 gas *and* pCO_2 is greater in venous blood.

NOTE In circulatory failure where alveolar gas exchange is intact but blood delivery to the lungs for gas exchange is severely reduced, an ABG may reveal normal oxygenation and normal to low pCO_2, whereas VBG reveals severe hypoxia and hypercapnia. Differences in pH, pCO_2, and HCO_3^- would thus widen, in which case ABG and VBG may not be used interchangeably to accurately predict acid–base disorders.

See **Appendix A** for a review of acid-base disorder determinations, practice problems, and complete list of differential diagnoses for all acid-base disorders.

High Serum Anion Gap Metabolic Acidosis

- Notable conditions with high serum anion gap (SAG) metabolic acidosis to know well for the Boards:

Glycols

Propylene glycol

- Propylene glycol is used as a solvent in a number of medications (e.g., topical sulfadiazine silver cream, intravenous nitroglycerin, multivitamins, phenytoin, lorazepam, diazepam, etomidate, enoximone).
- Propylene glycol is metabolized to L-lactate, hence high SAG metabolic acidosis.

Suspect propylene glycol induced lactic acidosis when there is a case of
- sepsis-like presentation with high SAG metabolic acidosis and high lactic acid levels, but absence of bacterial sepsis (e.g., alcoholic patient receiving high infusion of lorazepam; patient with severe burns receiving high amount of sulfadiazine cream).
- Other notable signs/symptoms associated with high propylene glycol accumulation: high serum osmolality, hemolysis, arrhythmias, hypotension, multiorgan failure, seizures, coma
- Management: supportive therapy, offending drug withdrawal

Ethylene glycol

- Ingestion of ethylene glycol (present in antifreeze) may result in kidney failure due to metabolism to oxalate and precipitation of calcium oxalate. See Figure 3.11 for calcium oxalate crystals.

Oxoproline also known as pyroglutamic acid (PA)

- Chronic acetaminophen use in malnourished chronically ill patients may be associated with high SAG metabolic acidosis due to excess production of oxoproline (OXO). This is due to the lack of negative feedback from glutathione as glutathione is also used in the metabolism of acetaminophen.
- Notable findings other than high SAG metabolic acidosis:
  - Acetaminophen level may be low or negative (as this is associated with long-term use of acetaminophen, not acute overdose). In contrast, in *acute acetaminophen poisoning*, acetaminophen level will be high, and lactate level may be high.
  - High serum osmolality gap (S_{OG}) due to accumulation of OXO/PA
  - Absence or low serum levels of lactate or ketones that could normally explain increased SAG
- Management: fluid support; consider acetylcysteine therapy to replete glutathione.

Lactic acidoses (Fig. 2.5)

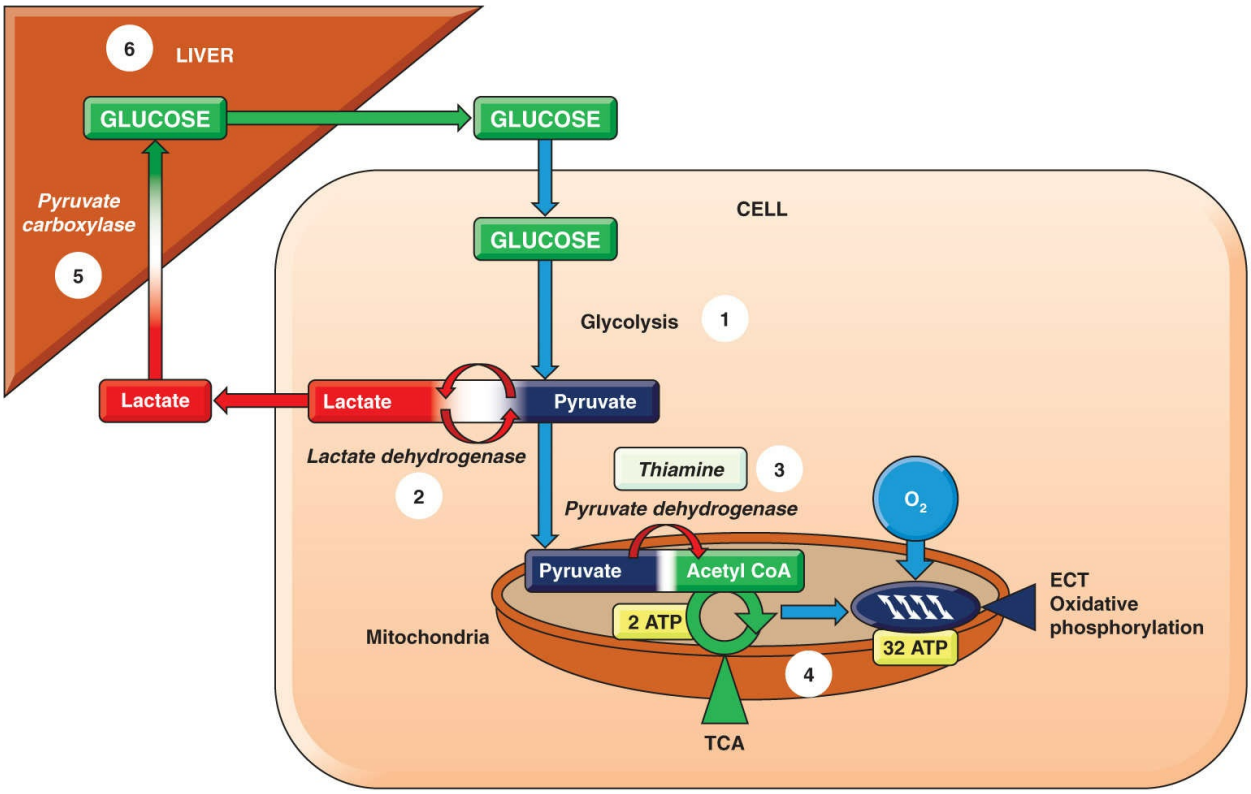

FIGURE 2.5 Lactic acidosis. Glucose is taken up by the cell where it undergoes glycolysis to form pyruvate. Pyruvate either forms lactate via lactate dehydrogenase or enters the mitochondria where it is converted to acetyl-CoA via pyruvate dehydrogenase. Thiamine is a cofactor for pyruvate dehydrogenase. In the mitochondria, acetyl-CoA enters the tricarboxylic acid cycle, where 2 ATPs are produced. NADH and $FADH_2$ formed from TCA are shuttled to the electron transport chain for oxidative phosphorylation, a process whereby 32 more ATPs are produced in the presence of oxygen. **Type A lactic acidosis** occurs under hypoxic conditions where oxidative phosphorylation is compromised by the lack of oxygen. This leads to anaerobic metabolism, accumulation of pyruvate, and subsequent conversion to lactate. **Type B lactic acidosis** occurs via defects/problems at any of the 6 components unrelated to the lack of oxygen.

1. Excessive glycolysis (seen in caffeine intoxication with overactive sympathetic nervous system stimulation, high-dose β_2-agonist used in the treatment of asthma, pheochromocytoma, metabolically active malignant cells)
2. Lactate dehydrogenase inhibition in the conversion of lactate to pyruvate (isoniazid)
3. Inadequate thiamine (metabolically active malignant cells or severe alcoholism in combination with malnutrition)
4. Drugs/toxins leading to mitochondrial injury and/or oxidative phosphorylation (methanol, propofol, linezolid, salicylate, cyanide, mangostin)
5. Inhibition of pyruvate carboxylase: Metformin is thought to cause lactic acidosis by inhibiting oxidative phosphorylation and pyruvate carboxylase, with the latter blocking the first step of gluconeogenesis.
6. Liver failure can limit gluconeogenesis and cause accumulation of lactic acid (nucleoside reverse transcriptase inhibitors didanosine, stavudine, acute fulminant liver failure).

Abbreviations: ATP, adenosine triphosphate; ECT, electron chain transport; TCA, tricarboxylic acid cycle.

Type A lactic acidosis

- Lactic acid stereoisomer: L-lactate
- Underlying cause: tissue hypoperfusion, hypoxia (including severe anemia), carbon monoxide poisoning
- Conditions associated with type A lactic acidosis: sepsis, severe prolonged hypotension, cardiogenic shock, vigorous exercise, seizures

Type B lactic acidosis

- Lactic acid stereoisomer: L-lactate or D-lactate
- Underlying cause: NOT associated with tissue hypoperfusion or hypoxia

Conditions associated with type B, L-lactic acid

- Enhanced glycogenolysis, lipolysis, glycolysis
  - Malignancies: leukemias, lymphoproliferative malignancies, tumors involving liver metastatic disease; may be ameliorated with thiamine
  - Toxic levels of caffeine, β_2-agonists or stimulation (e.g., treatment of asthma, pheochromocytoma); treat with β-blocker. **Note:** Lactic acidosis associated with the treatment of asthma with β_2-agonist is benign (unless, of course, respiratory status declines, in which case, lactic acidosis is due to type A).
  - Diabetic ketoacidosis (DKA)
- Inherited mitochondrial disease
- Acquired mitochondrial dysfunction, interference of oxidative phosphorylation:
  - Highly active retroviral therapy (nucleoside reverse transcriptase inhibitors): didanosine, stavudine; may be treated with uridine
  - Mangosteen (Southeast Asian fruit) contains α-mangostin, a potent inhibitor of mitochondria function
  - Drugs: metformin (inhibits pyruvate carboxylase that blocks the first step of gluconeogenesis and mitochondrial function), propofol (mitochondrial injury), linezolid (inhibits mitochondrial function)
  - Others: toxic alcohols, methanol (formic acid can inhibit mitochondrial function and increased anaerobic metabolism), ethylene glycol, salicylates (causes uncoupling of oxidative phosphorylation in

mitochondria), cyanide (mitochondrial toxin), isoniazid

- Impaired pyruvate dehydrogenase activity: severe thiamine deficiency (active malignant tumors or alcoholism with malnutrition)
- Impaired lactate clearance: acute fulminant liver failure

Conditions associated with type B, D-lactic acid

- Gut bacterial overgrowth:
  - D-Lactic acid is produced by gut bacterial overgrowth in short-bowel syndrome. This is NOT the same as what humans predominantly produce, which is L-lactate.
  - Clinical manifestations:
    - Laboratory findings: Typically, a high SAG metabolic acidosis is seen at presentation. However, patients may present with a normal SAG metabolic acidosis (hyperchloremic metabolic acidosis). Renal reabsorption of D-lactic acid is much lower than that for L-lactic acid. The high renal excretion of D-lactate can thus lead to a normal SAG in those with D-lactate and good kidney function with high urine flow.
    - D-lactic acid level > 3 mmol/L.
    - Patients with D-lactate typically present with encephalopathy, slurred speech, ataxia, gait disturbances, mimicking a “drunk.”
    - D-Lactic acidosis can be exacerbated following high carbohydrate ingestion and metabolic acidosis.
  - Treatment: oral metronidazole or vancomycin, supportive
- Diabetic ketoacidosis (DKA):
  - D-Lactate is derived from methylglyoxal, a metabolite of acetone and dihydroxyacetone phosphate, which are intermediates that can accumulate in DKA. D-Lactate may be elevated in severe DKA.
- Propylene glycol intoxication (case report)

Alcohols (methanol, glycols)

- Ingestion or infusion of any alcohol will increase the serum osmolality because the alcohol osmoles will be measured with routine serum

osmolality measurements. Whenever there is a suspicion for intoxication/poisoning, calculate S_{OG}.

- Serum osmolality gap (S_{OG}):
  - S_{OG} = [Measured S_{OSM} − Calculated S_{OSM}], where

    Calculated S_{OSM} = $(S[Na^+] + S[K^+]) \times 2 + BUN/2.8 + glucose/18$

    BUN = blood urea nitrogen
  - When there is no ingestion/infusion of exogenous osmoles (e.g., alcohols), S_{OG} < 12 mosm/kg.
  - An S_{OG} >> 12 mOsm/kg indicates the presence of osmoles that are not normally present in the serum, which may suggest ingestion/poisoning with various alcohols.
  - Increased S_{OG} should raise concerns for the presence of other osmoles, that is, intoxications (ethanol, methanol, ethylene glycol, isopropanol, or toluene), OXO, ketones, and/or lactate.
    - If only ethanol ingestion is suspected, the concentration of ethanol (mmol/L) should match ΔS_{OG}.
    - If the ethanol concentration does not fully account for the increase in normal S_{OG} [i.e., ΔS_{OG} > serum ethanol concentration (mmol/L)], then there must be other unknown osmoles in the blood, in which case evaluation for other concurrent ingestions such as methanol, isopropanol, and/or OXO/PA is warranted.
  - **Note:** The absence of an increased S_{OG} does not necessarily rule out alcohol poisoning if patient presents after the parent compound has been metabolized to its toxic metabolites.
  - See **Figure 2.6** and **Table 2.1** for metabolism and management of different alcohol intoxications.

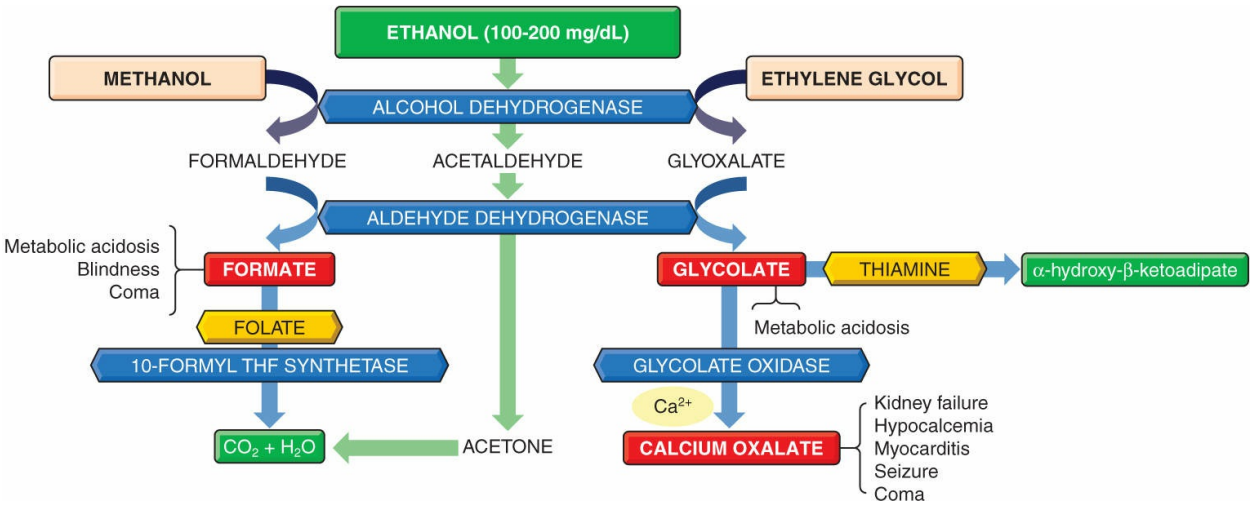

FIGURE 2.6 Metabolism of methanol and ethylene glycol. Both methanol and glycol alcohols undergo metabolism to their respective toxic metabolites via alcohol dehydrogenase. Ethanol is also a substrate for alcohol dehydrogenase and may be used as a competitive antagonist to reduce the metabolism of methanol and glycol alcohols to their respective toxic metabolites. Ethanol is metabolized by alcohol dehydrogenase and aldehyde dehydrogenase to form acetate, which is subsequently metabolized to CO_2 and H_2O. Optimal efficacy of ethanol as a competitive inhibitor of alcohol dehydrogenase occurs at levels ranging between 100 and 200 mg/dL. Abbreviation: THF, tetrahydrofolate.

Table 2.1 Alcohol intoxication

Alcohol	Methanol	Ethylene Glycol	Isopropyl Alcohol
Toxic metabolite	Formate	Oxalate	Acetone
Clinical complications	Blindness	Kidney failure	CNS depression, nausea, vomiting, usually not fatal
Treatment	• Fomepizole • Folinic acid 50 mg IV q6h to increase metabolism of formic acid to CO_2 + H_2O	• Fomepizole if ethylene glycol level >20 mg/dL and S_{OSM} > 20 mOsm/kg. Continue until <20 or <10 mg/dl in the presence of end- organ damage. • Alkalinize to keep pH >7.35 • IV thiamine 100 mg + pyridoxine 50 mg to increase metabolism of glyoxylate	• Supportive, airway protection **NOTE:** Isopropanol is metabolized by alcohol dehydrogenase to acetone, which is *not* an acid. Serum and urine "ketones" may be positive, but there is *no* metabolic acidosis or any increase in serum anion gap.
Dialysis indications	Level >50 mg/dL in association with severe metabolic acidosis or end-organ damage (use large dialyzer, blood flow > 300 mL/min). **NOTE:** 1. Fomepizole and ethanol are dialyzable. Dose adjustments are needed with		Refractory and severe hemodynamic instability in association with levels >500 mg/dL and osmolal gap >100 mOsm/kg

	dialysis. 2. Must monitor potassium, phosphorus, and magnesium and replace as needed.	

Notes: Both methanol and ethylene glycol intoxication can give rise to a high serum anion gap metabolic acidosis, but isopropyl alcohol does not cause metabolic acidosis. Isopropyl alcohol is metabolized to acetone, which can result in positive serum and urine ketones, but since acetone is not an acid or anion, there should be no metabolic acidosis or elevated serum anion gap respectively.
Abbreviations: CNS, central nervous system; NO, nitric oxide; q, every; IV, intravenous.

Ketoacidosis

- All forms of ketoacidosis (alcoholic, starvation, and DKA) occur when hepatic lipid metabolism is switched to a state of increased ketogenesis due to relative or absolute insulin deficiency.

Alcoholic ketoacidosis (AKA)

- Risks: individuals with a history of alcohol use, typically with recent history of binge drinking, poor oral intake, persistent vomiting, volume depletion
- Clinical manifestations: sweet ketone breath; high SAG metabolic acidosis may be severe, pH <7; mixed acid–base disorders may be present, including metabolic alkalosis from vomiting and volume depletion.
- Mechanisms of ketoacidosis in AKA:
  - Poor oral intake → ↓insulin and ↑glucagon, which lead to:
    - Increased lipolysis and free fatty acid (FFA) release from peripheral adipose tissues (lipase is normally inhibited by insulin)
    - Increased transport of FFA into mitochondria where FFA undergoes oxidation and ketone body formation
  - ↓Insulin reduces ketone body utilization by insulin-sensitive tissues.
  - Elevated ratio of the reduced nicotinamide adenine dinucleotide (NADH) to NAD^+ due to the metabolism of alcohol leads to:
    - Impaired conversion of lactate to pyruvate (increased lactate levels)
    - Impaired gluconeogenesis
    - A shift in hydroxybutyrate (β-OH) to acetoacetate (AcAc) equilibrium toward β-OH. In contrast to DKA, the predominant ketone body in AKA is β-OH. Routine clinical assays for ketonemia may only test for AcAc and acetone, but not for β-OH. Assays

specific for the detection of β-OH will be necessary in suspected cases of AKA.

  - Volume depletion → ↓renal perfusion, reduced urinary excretion of ketoacids
- Treatment:
  - Glucose + normal saline (dextrose [D5] increases insulin, stimulates oxidation of NADH to NAD^+)
  - Thiamine to reduce risk of precipitating Wernicke encephalopathy or Korsakoff syndrome associated with glucose administration
  - Electrolytes monitoring and replacement (particularly those associated with refeeding syndrome, e.g., phosphorus, magnesium, potassium)

Starvation ketoacidosis (SKA)

- Occurs when hepatic glycogen stores are exhausted
- Ketoacidosis is typically mild to moderate, with ketoanion levels of only 3 to 5 mmol/L. The ketone bodies produced in SKA, in turn, stimulate pancreatic islets to release sufficient insulin to control lipolysis, which renders SKA a self-limiting process. The AG reflects the ketoanion level, which also should not be very high.

Diabetic ketoacidosis (DKA)

- The lack of insulin leads to increased mobilization of FFA from adipose tissue to the liver and hepatic lipid metabolism switch to ketogenesis.
- *Key points* to remember in the management of DKA:
  - Excess hydration with normal saline and resultant high urine flow can lead to rapid urinary loss of ketone bodies, thereby converting a high SAG metabolic acidosis to a normal SAG metabolic acidosis (i.e., hyperchloremic metabolic acidosis). Ketone bodies are the source of rapid bicarbonate generation with insulin administration. The loss of ketone bodies may thus prolong the acidemic state. (The treatment of DKA in anuric dialysis patients typically only requires insulin administration and gentle fluid resuscitation to match poor oral intake and/or associated fluid loss, such as vomiting. The purpose of normal saline infusion in DKA is to primarily replace volume loss from osmotic

diuresis and/or fluid loss from vomiting, not to "correct" the DKA. It is insulin administration that corrects DKA.)

- Severe hypokalemia and hypophosphatemia may follow insulin administration and fluid resuscitation. In cases with life-threatening electrolyte deficiencies, repletion of these electrolytes must be done prior to insulin administration.

NOTE Serum ketones may also be seen with isopropyl alcohol intoxication (i.e., isopropanol, rubbing alcohol). Isopropyl alcohol is metabolized by alcohol dehydrogenase to acetone, which evaporates with breathing. The acetone is the ketone seen with isopropyl alcohol intoxication and gives the fruity breath odor. Acetone is not an acid or an anion. Thus, isopropyl alcohol intoxication does not cause metabolic acidosis or elevated SAG respectively.

Salicylate intoxication

- See Chapter 11 Acute Kidney Injury/ICU Nephrology

Kidney failure

- High SAG metabolic acidosis typically occurs with estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m^2.
- The increased SAG is due to the accumulation of urates, sulfates, and phosphates. For less advanced kidney failure with eGFR > 30 mL/min/1.73 m^2, metabolic acidosis generally has normal SAG due to adequate renal excretion of organic anions.

Normal SAG Metabolic Acidosis

- Normal SAG metabolic acidosis is traditionally categorized as renal versus extrarenal causes, where the former refers to renal tubular acidosis (RTA).

Renal tubular acidosis (RTA)

- RTA may be suspected when there is a normal SAG metabolic acidosis, low urine ammonium level or positive urine anion gap (U_{AG}), and urine osmolality gap (U_{OG}) <100 mosm/kg (**Fig. 2.7**).

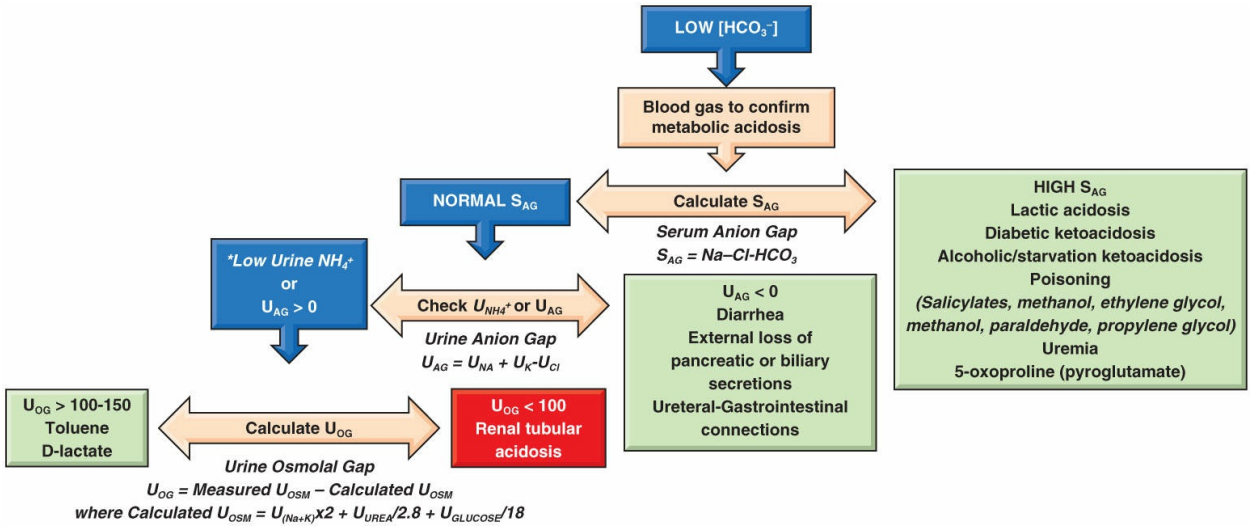

FIGURE 2.7 Evaluation of metabolic acidosis. *, Reference range for 24-hour urine ammonium is 15 to 56 mmol.

- A 24-hour urine ammonium level may be used in patients with normal AG metabolic acidosis to diagnose RTA.
  - Reference range for 24-hour urine ammonium is 15 to 56 mmol per Mayo Medical Laboratories.
  - Low urine ammonium (NH_4^+) and high urine pH suggest distal RTA (dRTA). In poor ammoniagenesis associated with hyperkalemia, urine pH may be low (see **Distal RTA**).
  - High urine ammonium (NH_4^+) and low urine pH suggest ongoing gastrointestinal (GI) losses. Patients with these findings are susceptible to uric acid and calcium oxalate stones.
- If 24-hour urine NH_4^+ is not available, U_{AG} may be used to estimate the NH_4^+ level. Simplified interpretation of U_{AG}:

  Assumptions:

  - The number of cations equals the number of anions in the urine.
  - Major cations in the urine include measured Na^+, K^+, and unmeasured NH_4^+ and other cations.
  - Major anions in the urine include measured Cl^- and unmeasured HCO_3^- and other anions.

  Thus,

$$Na^+ + K^+ + NH_4^+ + \text{unmeasured cations} = Cl^- + HCO_3^- + \text{unmeasured anions}$$

Rearranging the equation,

and assuming negligible levels of unmeasured cations and anions:

$$Na^+ + K^+ - Cl^- = HCO_3^- - NH_4^+$$

Interpretations:

- In a patient with extrarenal metabolic acidosis (e.g., diarrhea), the kidneys will attempt to correct the underlying metabolic acidosis by increasing bicarbonate reabsorption (lower urine HCO_3^-) while increasing ammonium excretion (higher urine $NH4^+$). This would result in a negative U_{AG}.

$$\textbf{Urine } Na^+ + K^+ - Cl^- = \downarrow\mathbf{HCO_3^-} - \uparrow\mathbf{NH_4^+} < 0$$

- In contrast, in a patient with pRTA, bicarbonate wasting far exceeds maximal NH_4^+ excretion, hence positive U_{AG}.

$$\textbf{Urine } Na^+ + K^+ - Cl^- = \uparrow\mathbf{HCO_3^-} - NH_4^+ > 0$$

- In a patient with dRTA, there is reduced NH_4^+ excretion; U_{AG} may also be greater than 0.

$$\textbf{Urine } Na^+ + K^+ - Cl^- = HCO_3^- - \downarrow\mathbf{NH_4^+} > 0$$

- In toluene intoxication, there will be increased Na^+ and K^+ excretion along with the unmeasured hippurate/benzoate excretion. The quantity $[Na^+ + K^+ - Cl^-]$ will, therefore, be greater than 0 but may have nothing to do with RTA. Using the unsimplified equation above:

$$\uparrow\mathbf{Na^+} + \uparrow\mathbf{K^+} - Cl^- > 0$$

NOTE In order for U_{AG} to be valid, it is important rule out concurrent urinary excretion of high amounts of anions such as ketoanions and hippurate/benzoate, or the presence of urinary infections with high level of $NH4^+$ from urea-splitting organisms.

pRTA (i.e., RTA type 2): Impairment of HCO_3^- reabsorption

Clinical Presentation of pRTA

- Serum [HCO_3^-] is typically greater than 15 mmol/L.
- Urine pH varies with serum [HCO_3^-], that is, urine pH >5.5 if patient is receiving alkalinizing therapy and serum [HCO_3^-] > 24 mmol/L, but urine pH will be appropriately low, pH <5.5, in the presence of severe metabolic acidosis.
- Hypokalemia

Etiologies of pRTA

- To understand the etiologies of pRTA, review normal bicarbonate reabsorption at the proximal tubules (**Fig. 2.1**). Any defect that interferes with normal bicarbonate reabsorption can lead to pRTA.
- Isolated defects:
  - Autosomal dominant pRTA (*SCL9A3* gene) encoding NHE3 transporter
  - Autosomal recessive pRTA (*SLCA4A4* gene) encoding NBC1: associated with mental retardation, ocular abnormalities (glaucoma, cataracts, band keratopathy)
  - Sporadic pRTA: nonfamilial, transient type described in infancy, no defect isolated; immaturity of NHE3 function
- Isolated defects are rare. Typically, pRTA is associated with other proximal tubular transport defects (Fanconi syndrome).
  - Fanconi syndrome: multiple proximal tubular transport defects leading to aminoaciduria, glucosuria, uricosuria, and phosphaturia
  - Genetic conditions associated with Fanconi syndrome: cystinosis, galactosemia, tyrosinemia, hereditary fructose intolerance, Lowe syndrome (oculocerebrorenal syndrome), Alport syndrome, Wilson disease, and mitochondrial cytopathies
  - Acquired conditions: multiple myeloma, heavy metals, amyloidosis, paroxysmal nocturnal hemoglobinuria, drugs (cisplatin, ifosfamide, aminoglycosides, imatinib, tenofovir, valproic acid), renal transplantation. **Also see Chapter 6 Tubular, Interstitial, and Cystic Disorders.**
- Drugs that block CA II activity: acetazolamide, topiramate. and zonisamide (antiepileptic drugs). (Unlike pRTA from other causes where there is no increased stone risk, CA II inhibitor–induced pRTA may be

associated with increased calcium phosphate and calcium oxalate stone risk. Reduced citrate excretion with these drugs is thought to be the stone-promoting factor.)

Diagnosis of pRTA

- Fractional excretion of HCO_3^- ($FeHCO_3$) >15% and urine pH typically >7.5 following HCO_3^- load (Loading protocol: Infuse 0.5 to 1.0 mmol/kg body weight/hour to increase serum [HCO_3^-] concentration >20 mmol/L. Bicarbonate loading must be done AFTER the correction of hypokalemia.)
- $FeHCO_3 = [(U_{HCO3} \times S_{Cr})/(P_{HCO3} \times U_{Cr})] \times 100\%$

Management of pRTA

- Bicarbonate replacement 5 to 15 mmol/kg/d (**Note:** *Alkalinization can worsen hypokalemia*)
- Potassium replacement
- Thiazide diuretics → induce volume contraction → enhance proximal reabsorption of bicarbonate. (**Note:** *Thiazides can also worsen hypokalemia.*)
  - Vitamin D and phosphate supplements for patients with rickets and hypophosphatemia

dRTA (i.e., RTA type 1): Impairment of H^+ secretion

Clinical presentation of dRTA

- Metabolic acidosis may be severe, serum [HCO_3^-] may be much lower than 15 mmol/L.
- Growth impairment
- Polyuria
- Hypercalciuria, nephrocalcinosis, nephrolithiasis: chronic metabolic acidosis increases bone resorption, thus hypercalciuria, and reduces urinary citrate excretion, thus hypocitraturia. The hypercalciuria, hypocitraturia, and high urine pH in most forms of dRTA facilitate calcium phosphate crystallization / stone formation. Also see Kidney Stones in **Chapter 3**.
- Typically, patients with dRTA present with high urinary pH (e.g., >5.5). However, urinary pH could be less than 5.5 if ammoniagenesis is suboptimal. The latter may be seen in dRTA type 4 with concurrent

hyperkalemia because hyperkalemia inhibits ammoniagenesis. NH_3 is needed to buffer/facilitate H^+ secretion: $NH_3 + H^+ \rightarrow NH_4^+$. The lack of NH_3 leaves more free H^+ in tubular lumen, which lowers urine pH.

- Of note, patients with dRTA type 4 do not have increased risk of nephrocalcinosis, which is likely due to their low urine pH.

Etiologies of dRTA (also see Hypokalemia and Hyperkalemia sections)

- To understand the etiologies of dRTA, review normal H^+ secretion at the CCD (**Fig. 2.2**). Any defect that interferes with normal H^+ secretion can lead to dRTA.
- Normo-, hypokalemic dRTA:
  - Isolated defect/mutation of apical H^+-ATPase: autosomal recessive (mutation of H^+-ATPase β1-subunit may be associated with progressive sensorineural deafness)
  - Isolated defect/mutation of basolateral Cl^-/HCO_3^- exchanger exchange (anion exchanger AE-1) in α-IC: autosomal dominant
  - Autoimmune diseases: Sjögren, rheumatoid arthritis, systemic lupus erythematosus, primary biliary cirrhosis, hypergammaglobulinemia.
  - Medications: lithium, ifosfamide (more commonly causes pRTA than dRTA), amphotericin, rarely bisphosphonates (zoledronate)
  - H^+ back-leak: Amphotericin is a multiplanar lipophilic molecule that can insert itself into tubular membrane and act as an ionophore, allowing urinary H^+ to leak back into tubular cells and circulation. Liposomal formulation of amphotericin essentially covers amphotericin with a lipophobic surface, thereby reducing the drug's ability to insert itself into cell membrane **(Fig. 2.8).**

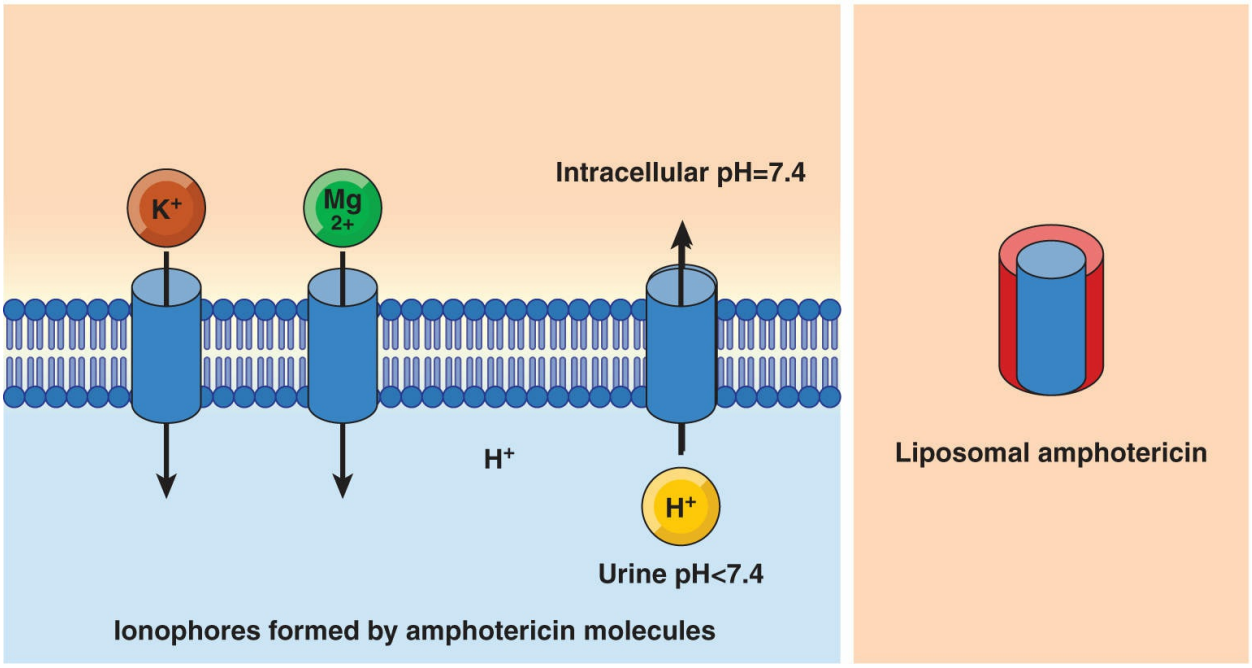

FIGURE 2.8 Amphotericin: metabolic acidosis and electrolyte wasting. **Left**: The lipophilic multiplanar amphotericin molecule inserts itself into tubular cell membrane to form ionophores (nonspecific electrolyte channels). The direction of electrolyte movement depends on the concentration difference between the intracellular and urinary space. Intracellular concentrations of K^+ and Mg^{2+} are much higher than those in the urine, thus favoring K^+ and Mg^{2+} leakage/wasting into the urine. Urine concentration of H^+, however, is much greater than that intracellularly, which favors H^+ "back-leak," thus development of metabolic acidosis. **Right**: The aim of "liposomal" amphotericin formulation is to coat the molecule with a lipophobic layer (represented here as the red outer layer) to minimize its insertion into tubular cell membranes.

- Hyperkalemic dRTA (RTA type 4):
  - Aldosterone deficiency or aldosterone resistance, diabetic kidney disease, tubulointerstitial nephropathy, sickle cell nephropathy, obstructive uropathy
  - Medications: K-sparing diuretics (amiloride, triamterene), trimethoprim, pentamidine, calcineurin inhibitors (tacrolimus, cyclosporine), nonsteroidal anti-inflammatory drugs, inhibitors of the renin–angiotensin–aldosterone system (RAAS) (renin inhibitors, angiotensin-converting enzyme inhibitors [ACEIs], angiotensin-receptor blockers [ARBs], spironolactone, eplerenone), heparin
  - Factors affecting transmembrane voltage (e.g., obstructive uropathy, K-sparing diuretics)
  - Pseudohypoaldosteronism type 1 (PHA1) (ENaC mutation) and type 2

(i.e., Gordon syndrome, condition due to loss-of-function mutations of "with-no-lysine (K) kinase 1" (WNK1) or WNK4 resulting in NaCl cotransporter (NCC) hyperactivity and increased paracellular chloride reabsorption). See **Hyperkalemia** section.

Diagnosis of dRTA

- Testing options:
  - NH_4Cl (100 mg/kg lean body weight) oral load over 1 hour, or
  - Combined administration of loop diuretic (to increase Na^+ delivery to ENaC) and mineralocorticoid fludrocortisone (to increase H^+ [and K^+] secretion following Na^+ entry via ENaC):
- Interpretation: Individuals with normal acid secretion can lower urine pH due to enhanced H^+ secretion, but those with dRTA cannot.

Management of dRTA

- Treatment of underlying disease
- Bicarbonate supplements 1 to 2 mmol/kg lean body weight/day. Caution: Correction of severe hypokalemia must be done *prior* to alkalinizing therapy in all patients with concurrent hypokalemia and metabolic acidosis to avoid worsening of existing hypokalemia.
- If there is hyperkalemia associated with a hypoaldosterone state: consider fludrocortisone and/or furosemide; dietary K^+ restriction may also be necessary.

Mixed RTA (i.e., RTA type 3)

- Coexistence of both pRTA and dRTA
- Conditions associated with RTA type 3:
  - Mixed RTA may be seen in premature infants and children. This is generally transient and thought to be due to delayed development of tubular acid–base regulation.
  - Mutation of CA II (Guibaud–Vainsel syndrome)
    - Rare, autosomal recessive
    - Coexistence of pRTA and dRTA
    - Failure to maximally acidify urine, decreased NH_4^+ excretion, high

urinary citrate level

- Osteopetrosis (increased bone calcification, thick dense bones on plain radiographs) due to failure of osteoclasts to secrete acid to dissolve bone minerals
- Cerebral calcification, mental retardation, sensorineural deafness

Other conditions associated with normal SAG metabolic acidosis

Intake/ingestion

- Infusion of NH_4Cl
- Hyperalimentation containing acidic amino acids and hydrochloric acid
- Toluene intoxication
  - Patients with good kidney function present with normal SAG metabolic acidosis because toluene metabolites, hippurate and benzoate anions, are freely filtered and excreted. The filtered anions drive the excretion of Na^+ and K^+ cations. This results in a positive U_{AG} because

$$U_{AG} = \uparrow U_{Na} + \uparrow U_K - U_{Cl} > 0$$

  - The presence of hippurate/benzoate in the urine also increases urine osmolality. Thus, measured urine osmolality will be much higher than what is normally expected. That is, there will be an increase in U_{OG}, where U_{OG} is defined as:

$$U_{OG} = [\text{Measured } U_{OSM} - \text{Calculated (normally expected) } U_{OSM}]$$

where

$$\text{Calculated } U_{OSM} = [U_{[Na+K]\ mmol/L} \times 2 + U_{UREA\ mg/dL}/2.8 + U_{GLUCOSE\ mg/dL}/18]$$

  - Normal U_{OSM} gap (U_{OG}) is 10 to 100 mOsm/kg.
  - With toluene intoxication, U_{OG} may be >100 to 150 mOsm/kg.

Gastrointestinal (GI) causes

- Diarrhea
  - Mechanisms of normal SAG metabolic acidosis:
    - High intestinal HCO_3^- loss in exchange with Cl^- and increased renal

Na^+-Cl^- reabsorption

- The associated volume depletion and reduced distal Na^+ delivery to ENaC at the CCD reduce renal H^+ secretion.

- Laboratory findings consistent with diarrhea:
  - Normal AG metabolic acidosis
  - $U_{AG} < 0$ (in contrast, $u_{ag} > 0$ in RTA. See **Interpretations of U_{AG}** above)
  - High U_{OG} due to increased NH_4^+ secretion
  - Urine pH may be high (e.g., >5.5) due to associated hypokalemia and metabolic acidosis–stimulated ammoniagenesis.

    In cases with normal or reduced ammoniagenesis:

    $NH_3 + \mathbf{H}^+ \rightarrow NH_4^+$

    (In the presence of normal or low NH_3 levels, more of the secreted H^+ exist as free cations which keeps the urine pH low.)

    Diarrhea with increased ammoniagenesis:

    $\uparrow\mathbf{NH}_3 + H^+ \rightarrow \uparrow\mathbf{NH}_4^+$

    The increased ammoniagenesis in diarrheal state provides high buffering capacity for urinary H^+. The lower concentration of free H^+ results in a high urine pH.

- Ureterosigmoid anastomosis, ileal conduit
  - Mechanisms for normal AG metabolic acidosis:
    - Intestinal reabsorption of urinary $NH_4^+ + Cl^-$. The reabsorbed NH_4^+ consumes an equimolar HCO_3^- to form urea in the liver.
    - Intestinal reabsorption of urinary Cl^- in exchange for HCO_3^- loss
  - Worsening of metabolic acidosis in patients with either ureterosigmoid anastomosis or ileal conduit should prompt evaluation for distal intestinal or ileal loop obstruction, respectively. The worsened metabolic acidosis could be due to:
    - Resultant urinary obstruction, thereby suboptimal renal H^+ secretion
    - Prolonged exposure of intestinal mucosa to urine, leading to increased NH_4^+ reabsorption and HCO_3^- wasting via Cl^-/HCO_3^-

exchange
    - Special notes regarding metabolic complications with urinary diversions
- D-Lactic acidosis in patients with short-bowel syndrome with good kidney function and high urine flow
    - Although D-lactic acidosis may present with elevated SAG at early onset, the SAG may readily normalize due to the ability of normal kidneys to rapidly excrete D-lactic acid.
    - Conversely, a high SAG metabolic acidosis may be seen if D-lactic acid is not readily cleared due to poor kidney function and/or low urine flow.

Kidney causes

- RTA as previously discussed
- Treatment of DKA with excessive volume repletion

Correction of metabolic acidosis

- Alkalinization:
    - Calculating HCO_3^- deficit:
        - In general,

          HCO_3^- deficit (mmol) = 0.5 × lean body weight (kg) × [24 − serum HCO_3^-]
        - For severe metabolic acidosis,

          HCO_3^- deficit (mmol) = [0.4 + 2.6/actual serum HCO_3^-] × lean body weight (kg) × [24 − serum HCO_3^-]
- Alkalinization may be detrimental in the following conditions:
    - CO_2 retainers (e.g., individuals with chronic obstructive pulmonary disease)
    - Severe hypokalemia
    - Severe hypocalcemia
    - Volume overload
    - Hypernatremia (each ampule of sodium bicarbonate contains 45 to 50 mmol of sodium)

Chloride-Sensitive Metabolic Alkalosis

- In renal hypoperfusion, there is avid proximal tubular reabsorption of NaCl, thus minimal residual Cl^- for distal delivery. The limited distal Cl^- delivery reduces HCO_3^- secretion via the Cl^--HCO_3^- exchanger (i.e., pendrin) in distal tubules. It is this retained HCO_3^- that partly contributes to metabolic alkalosis observed in patients with hypovolemia (**Fig. 2.9**).

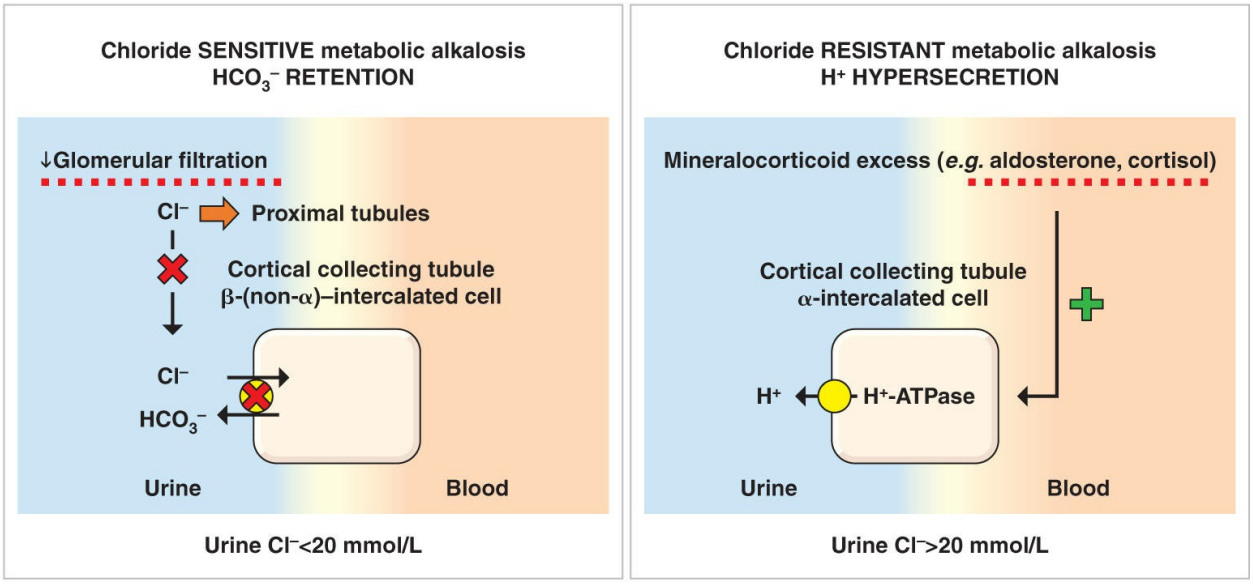

FIGURE 2.9 Chloride-sensitive versus chloride-resistant metabolic alkalosis. **Left**: In hypovolemia, most filtered Cl^- are reabsorbed proximally. This leads to reduced distal Cl^- delivery for Cl^--HCO_3^- exchange. The low distal Cl^- delivery is reflected in the low urinary Cl^- concentration. The HCO_3^- retention partly contributes to metabolic alkalosis in volume-depleted states. The infusion of chloride in this case can increase Cl^--HCO_3^- exchange and partly corrects the underlying metabolic alkalosis, hence chloride-sensitive metabolic alkalosis. **Right**: Metabolic alkalosis is driven by mineralocorticoid-stimulated H^+ secretion, a process independent of distal Cl^- delivery. Chloride infusion in this case does not correct the underlying metabolic alkalosis, hence chloride-resistant metabolic alkalosis. Accordingly, urine Cl^- generally reflects chloride intake, which is typically >20 mmol/L.

- Since there is low distal Cl^- delivery, urine chloride will be low, typically <20 mmol/l.
- Chloride infusion would increase distal Cl^- delivery for Cl^--HCO_3^- thereby correcting the metabolic alkalosis, hence "chloride-sensitive" metabolic alkalosis.
- Renal hypoperfusion also contributes to metabolic alkalosis by reducing HCO_3^- filtration and increasing Na^+-H^+ antiporter activity in proximal tubules.

Common causes of chloride-sensitive metabolic alkalosis

- Vomiting, nasogastric suction, gastrocystoplasty for bladder augmentation, diuretics, villous adenoma, congenital chloridorrhea, posthypercapnia (recovery from chronic hypercapnia), low dietary chloride intake

Special notes for chloride-sensitive metabolic alkalosis

- Vomiting:
  - The loss of H^+ in the vomitus is equivalent to HCO_3^- "loading."
  - There are three phases of vomiting:
    - Acute phase: The high HCO_3^- load leads to increased glomerular filtration of HCO_3^- and accompanying losses of the cations Na^+ and K^+.
      - Urine Na^+ would thus be high even if patient is hypovolemic.
      - Urine K^+ would be high.
      - Urine chloride, however, would be low as expected for the hypovolemic state.
      - Urine pH is high because of filtered HCO_3^- load.
    - Later phase: Once the vomiting stops, all the HCO_3^- load has been filtered, and patient becomes hypovolemic:
      - Both Na^+ and Cl^- would be low.
      - Aldosterone is stimulated in the hypovolemic state, which drives K^+ and H^+ secretion.
      - Urine K^+ concentration would be high.
      - Urine pH can be low.
    - Postvomiting: In the unsupported patient without fluid/electrolyte repletion, urine Na^+, Cl^-, and K^+ would all be low.
- Severe metabolic alkalosis with serum [HCO_3^-] >45 mmol/L is almost always due to gastric cause. Concurrent urine [Cl^-] <10 mmol/l and hypokalemia should raise concerns for surreptitious vomiting.
  - Management: The use of proton-pump inhibitors or histamine type 2 blockers may reduce gastric H^+ loss and partly ameliorate vomiting or nasogastric drainage–induced metabolic alkalosis.
- Surreptitious diuretic use: Patients may present with metabolic alkalosis

and temporally varying, but parallel, urinary Na^+ and Cl^- concentrations (either both very low <20 mmol/l or both very high >>20 mmol/L) due to intermittent use of diuretics.

- Congenital chloridorrhea:
  - Mutation of small intestinal Cl^--HCO_3^- exchanger leads to severe Cl^--rich diarrhea and chloride-sensitive metabolic alkalosis.
  - The use of proton-pump inhibitor has been suggested to reduce GI chloride loss.
- Posthypercapnia: Chronic hypercapnia (chronic CO_2 retention) results in compensatory renal HCO_3^- retention at the expense of a Cl^- loss to maintain optimal acid–base status. The acute correction of hypercapnia (e.g., with acute mechanical ventilation) leaves behind the residual compensatory high serum HCO_3^- and low Cl^- state, which presents as chloride-sensitive metabolic alkalosis.

Chloride-Resistant Metabolic Alkalosis

- This is predominantly due to hypersecretion of acid (H^+) or causes other than reduced activity of the Cl^--HCO_3^- exchanger (**Fig. 2.9**).
- This form of metabolic alkalosis is independent of distal urinary chloride delivery seen in chloride-sensitive metabolic alkalosis. Urine chloride is thus expected to reflect dietary chloride intake, which is typically >20 mmol/L.
- Chloride infusion in this condition would not correct the metabolic alkalosis, hence “chloride-resistant” metabolic alkalosis.

Common causes of chloride-resistant metabolic alkalosis

- Mineralocorticoid excess: Direct effect: increased H^+ secretion from α-IC in collecting duct; Indirect effect: increased ENaC activity resulting in negative luminal charge generation and facilitated H^+ secretion
- Glucocorticoid excess: increased activity of NHE3 and both expression and activity of NBC1 in proximal tubules
- Severe hypokalemia
  - Increases ammoniagenesis, hence facilitated H^+ secretion
  - Increases H^+ secretion via increasing NHE3 and NBC1 activities in

proximal tubule
    - Reduces NKCC2 activity, leading to increased sodium delivery to ENaC, generation of negatively charged lumen, and subsequent facilitated H^+ secretion
    - Increases H^+-K^+-ATPase activity in the collecting duct
    - Reduces pendrin expression and activity in β-IC in the collecting duct
- Exogenous alkali (crack cocaine with alkali load, citrate from transfusion products or regional anticoagulation used in continuous renal replacement therapy, transplacental transfer from mother with metabolic alkalosis, excessive calcium carbonate ingestion)
    - **Note:**
        - In contrast to milk-alkali syndrome where serum phosphorus may be normal to high (from milk), calcium carbonate–induced metabolic alkalosis may be associated with low serum phosphorus due to its phosphorus-binding effect. The latter is also known as "calcium-alkali syndrome."
        - The combined use of polystyrene sulfonate (Kayexalate) and either aluminum or magnesium hydroxide or calcium carbonate may result in bicarbonate generation and absorption. For interested readers, see **Appendix A** for proposed reactions.
        - Similar reactions with newer resins are not yet known. However, patiromer may be expected to be at higher risk than sodium zirconium cyclosilicate because the former has nonspecific cation binding whereas the latter has selectivity for potassium.
- Pendred syndrome
    - Rare
    - Syndrome with mutation of pendrin (Cl^--HCO_3^- exchanger in β-IC in the collecting duct) where patients may present with goiter, sensorineural deafness, and metabolic alkalosis. (Pendrin is also present in thyroid gland and ear.)
    - Pendrin is also involved in the electroneutral reabsorption of NaCl in β-IC by acting in concert with the sodium-driven Cl^--$2HCO_3^-$ exchanger (known as NDCBE). The NCC in the distal convoluted tubules (DCTs)

complimentarily acts with β-IC in the collecting duct to reabsorb NaCl. Reduced NCC function (e.g., mutations or use of NCC inhibitors) will result in compensatory increased Na^+ reabsorption by β-IC and vice versa. Inhibition of both NCC and pendrin can result in severe hypovolemia, metabolic alkalosis, and hypokalemia (**Fig. 2.10**).

- Clinical implications:
  - The use of thiazide diuretics in patients with Pendred syndrome can precipitate severe hypovolemia, metabolic alkalosis, and hypokalemia.
  - Pendrin expression has been shown to be downregulated by acetazolamide. Combined use of thiazides and acetazolamide may synergistically induce significant diuresis.

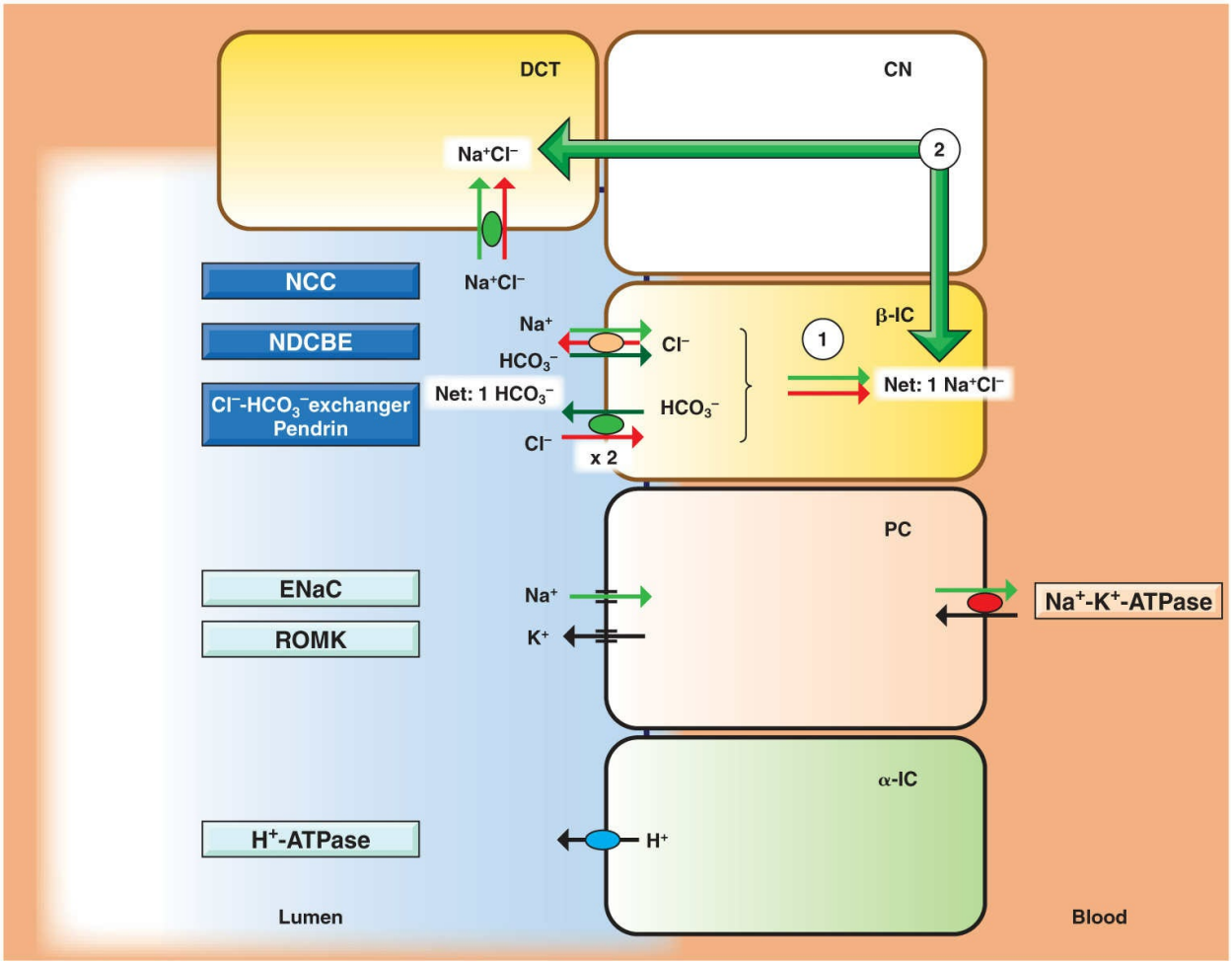

FIGURE 2.10 Complementary electroneutral sodium chloride reabsorption by NCC and NDCBE. 1. In β-IC, pendrin is involved in both HCO_3^- secretion and the electroneutral reabsorption of NaCl by acting in concert with the sodium-driven Cl^--$2HCO_3^-$ exchanger (known as NDCBE). Two cycles of Cl^--HCO_3^- exchange by pendrin and one cycle of $Na+/Cl^-/HCO_3^-$ exchange by NDCBE lead to a net of one HCO_3^- secretion and one NaCl electroneutral reabsorption. 2. The NCC in the distal convoluted tubule complimentarily acts with the pendrin/ NDCBE duo in β-IC cells in the collecting duct to reabsorb NaCl. That is, reduced function of NCC (e.g., mutations or use of NCC inhibitors) will result in compensatory increased Na^+ reabsorption by β-IC and vice versa. Inhibition of both NCC and pendrin leads to exaggerated reduced distal Na^+ reabsorption, increased Na^+ delivery to ENaC, and subsequent increased K^+ and H^+ secretion, all leading to severe hypovolemia, metabolic alkalosis, and hypokalemia. Abbreviations: α-IC, α-intercalated cells; β-IC, β-intercalated cells; CN, connecting segment between distal convoluted tubule and collecting duct; DCT, distal convoluted tubule; ENaC, epithelial sodium channel; NCC, sodium chloride cotransporter; PC, principal cell; ROMK, renal outer medullary potassium channel.

Correction of severe metabolic alkalosis

- Severe metabolic alkalosis (serum HCO_3^- [tCO_2] >45 mmol/L) is not well tolerated due to associated severe hypokalemia, hypocalcemia (reduced

ionized calcium), and hypoxemia.

- Acidification: The amount of NH_4Cl or HCl needed to correct severe metabolic alkalosis, pH >7.55, is:
  - = HCO_3 excess (mmol) = 0.5 × lean body weight (kg) × [serum HCO_3^- − 24], for female
  - = HCO_3 excess (mmol) = 0.6 × lean body weight (kg) × [serum HCO_3^- − 24], for male

Respiratory Alkalosis

- Common causes: pneumonia, pulmonary embolism, head trauma, hyperthyroidism, pregnancy, cirrhosis, living at high altitude, early bacterial sepsis (gram-positive or gram-negative organism), meningitis, drugs (theophylline, salicylate); myocardial infarction, atrial fibrillation, flutter, tachycardia
- Acute severe respiratory alkalosis may be associated with severe hypophosphatemia. See Chapter 3.

Respiratory Acidosis

- Common causes: chronic obstructive pulmonary disease, obstructive sleep apnea, obesity-hypoventilation syndrome, neuromuscular weakness or chest wall/diaphragm abnormality, central nervous system depression (drugs or lesions); hypothyroidism, laryngeal/tracheal stenosis

Practice Acid–Base Problems (See Appendix A)

POTASSIUM

Potassium Physiology and Homeostasis

Background

- Total body K^+ stores in adults: ~3,000 to 4,000 mEq (50 to 55 mEq/kg body weight)
- Unlike Na^+, 98% of K^+ is intracellular. Intracellular K^+ concentration ~140 mmol/L, whereas plasma K^+ ($P[K^+]$) ~4 to 4.5 mmol/L.
- The optimal $P[K^+]$ level is between 4.1 and 4.7 mmol/L.

Ranges below 3.5 or greater than 5.5 mmol/L have been suggested to be
  - associated with worse all-cause mortality in both hospitalized and ambulatory patients with hypertension (HTN).
  - However, in patients with chronic kidney disease (CKD), hyperkalemia is much more tolerable compared to those without CKD. A serum K^+ range of 5.5 to 6.0 mmol/L in CKD patients is associated with lower mortality compared with the lower range of 3.5 to 3.9 mmol/L.
- The differential location of Na^+ and K^+ is maintained by (3)Na^+-(2)K^+-ATPase in cell membrane, which pumps 3Na^+ out in exchange for 2K^+ into cell (3:2 ratio).
- Functions of K^+:
  - Cell metabolism, regulation of protein and glycogen synthesis
  - Major determinant of resting membrane potential across cell membranes: This is necessary for the generation of action potential required for normal neural and muscular function.

Potassium homeostasis

"Major determinants of P[K^+] and total body content traditionally include input, output, and cellular shifts. Studies involving other regulatory systems such as gastric-sensing feed forward and circadian rhythm regulation are ongoing.

Input

- blood transfusions (particularly old blood products due to extracellular K^+ leakage), dietary (salt substitutes [KCl], high K^+-containing foods), supplements

Output, bodily loss

- skin (sweats, extensive burns), respiratory (airway secretions), GI tract (large volume vomiting, nasogastric suctions, fistulas/drainages, diarrhea, renal excretion)

Cellular K+ shift, major determinants (Fig. 2.11)

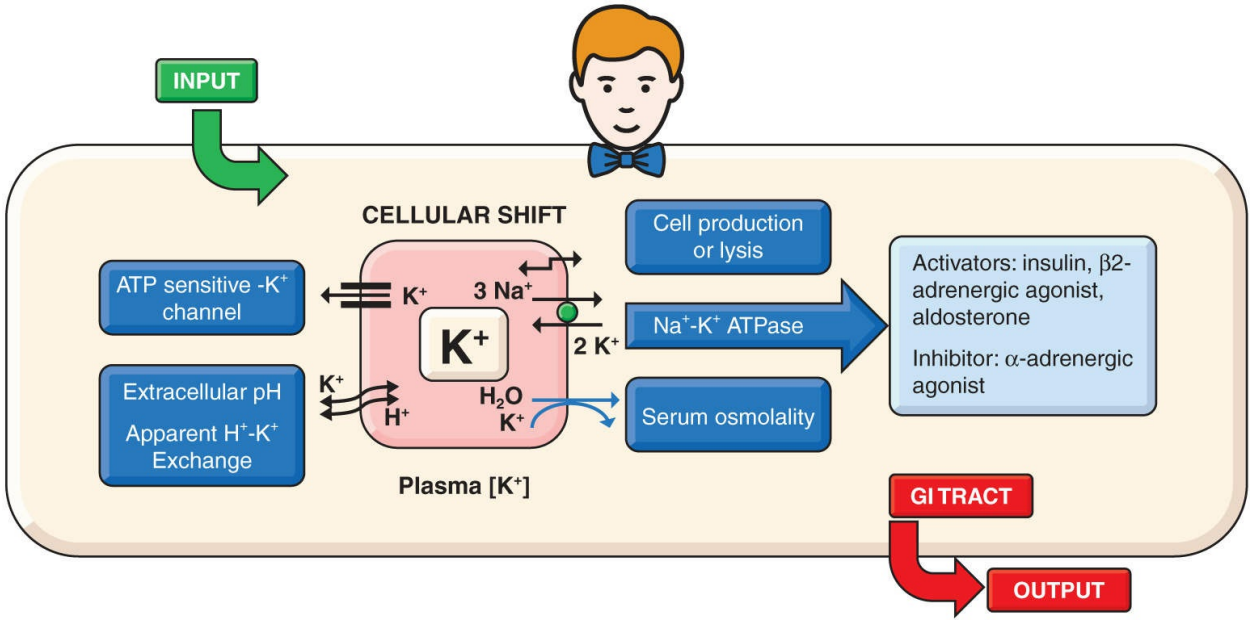

FIGURE 2.11 Mechanisms of cellular K^+ shift. Abbreviation: GI, gastrointestinal.

- pH, acid–base status:
  - Low extracellular pH leads to extracellular K^+ shift, whereas high extracellular pH leads to intracellular K^+ shift as an end result of coupling of various transporters. The H^+/K^+ cellular exchange is not via a direct H^+-K^+ exchanger (For interested readers, see **Fig. 2.12**).

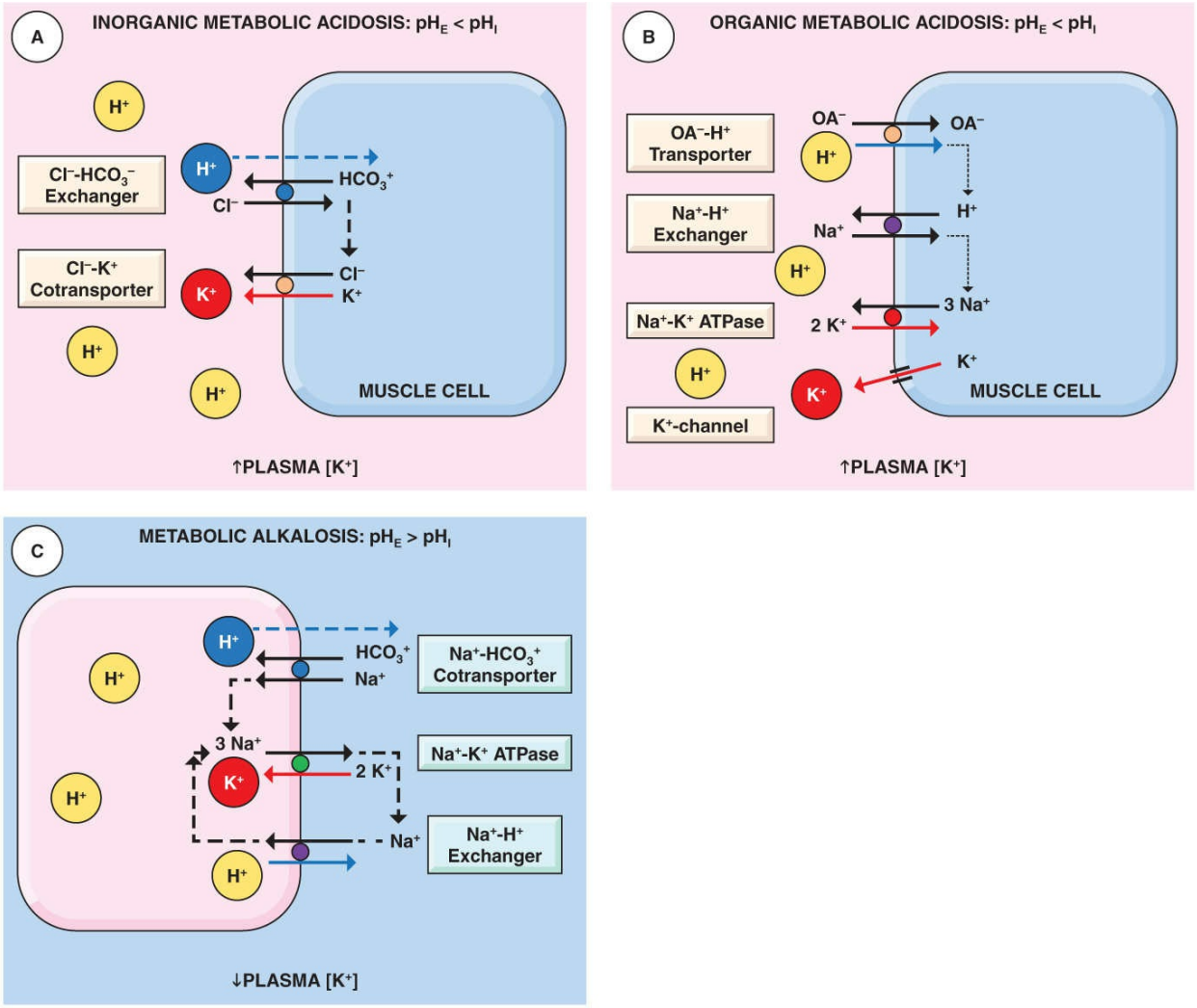

FIGURE 2.12 Metabolic acidosis or alkalosis and apparent K^+-H^+ exchange in skeletal muscle cells. Changes in extracellular pH (H^+ concentration) can lead to increased activities of various transporters, all acting in concert to shift K^+ in the opposite direction of favorable H^+ movement, thereby giving rise to an "apparent direct K^+-H^+ exchange." **A.** H^+/K^+ exchange for inorganic acids. **B.** H^+/K^+ exchange for organic acid. The transport of organic acids into the cell increases the Na^+-H^+ exchanger activity and subsequent Na^+-K^+-ATPase. The cellular uptake of K^+ reduces net extracellular K^+ shift compared to that observed with inorganic acid. This explains milder hyperkalemia associated with metabolic acidosis associated with organic acids. C. H^+/K^+ exchange in metabolic alkalosis.*Dashed blue arrow line*: The neutralization of H^+ by HCO_3^- gives rise to the apparent movement of H^+ across cell membrane. Abbreviations: OA^-, organic acid; pH_E; extracellular pH; pH_I, intracellular pH.

- This effect is most pronounced with inorganic metabolic acidosis and less pronounced with organic acidosis (e.g., lactic acid, ketoacid), metabolic alkalosis, and respiratory acidosis/alkalosis. (Organic acids have carbon elements.)
- Respiratory acidosis minimally affects renal K^+ secretion due to

relatively well-restored blood pH with renal compensation.

- In general, alkalemia stimulates distal renal K^+ secretion, with greater effect seen in metabolic compared with respiratory alkalosis. Elevated intracellular pH increases activities of ENaC, ROMK, and Maxi-K (see **Renal Potassium Handling** section).

- Respiratory alkalosis also increases K^+ secretion in parallel to the compensatory HCO_3^- secretion.

- P[K^+] concentration: Passive movement in or out of cells depends on acute P[K^+] concentration changes.
- Extracellular osmolality: Hyperosmolality shifts water out of cells, leading to:
  - Higher intracellular K^+ concentration compared with that extracellularly, hence more favorable gradient for K^+ exit into plasma
  - Extracellular K^+ shift due to solvent-drag effect
- Na^+-K^+-ATPase:
  - Stimulated by insulin, aldosterone, β_2-agonists (e.g., drug-induced cellular K^+ uptake thus hypokalemia: albuterol, terbutaline, dobutamine, isoproterenol)
  - Inhibited by α-agonists, presumably via inhibition of renin release, thus downstream hypoaldosteronism. (**Note:** α-Agonists are vasoconstrictive agents, such as phenylephrine, and the commonly used agent norepinephrine in the critical care setting. These agents may cause hyperkalemia via their α-agonistic activity in at-risk individuals.) Dopamine has weak-to-moderate α-1 activity and could contribute to minimal increase in serum potassium if used at high doses.
    - Epinephrine has strong α-1 but also moderate β_2-adrenergic activities. Simultaneous infusion of epinephrine with K^+ has been shown to improve K^+ tolerance, presumably via β_2-induced increased cellular uptake.
- Adenosine triphosphate (ATP)–sensitive K^+ channels (KATP):
  - The main regulator of KATP is the ATP/ADP ratio. An elevated ratio leads to channel closure, whereas a reduced ratio in the presence of

Mg^{2+} determines channel opening. KATP closure inhibits K^+ efflux extracellularly.
    - Exercise: ATP depletion during exercise opens up KATP and allows for extracellular K^+ shift. The local increase in interstitial K^+ concentration enhances vasodilatation and, thus, blood flow and energy delivery to exercising muscles. This effect is impaired with K^+ depletion.

- Cell lysis: Cellular K^+ release into plasma: tumor lysis, rhabdomyolysis, hemolysis, bowel infarction, any tisssue necrosis
- Cell production/anabolism: K^+ uptake for cell production (i.e., red blood cells, platelets) with folic acid or vitamin B_{12} therapy for megaloblastic anemia; refeeding syndrome

Reactive versus predictive systems

- A reactive system is based on:
    - A negative feedback system where plasma potassium concentration and serum aldosterone levels regulate renal potassium excretion
    - A feedforward system where dietary potassium determines urinary potassium excretion, independent of plasma potassium or aldosterone levels. This system is regulated by yet to be determined potassium-sensing gut factor(s).
- A predictive system regulates renal potassium excretion based on a circadian rhythm, independent of plasma levels or dietary intake.
    - Urinary potassium excretion is lowest during nighttime and early morning and highest from noon to afternoon (which coincides with normal eating hours).

Renal potassium handling

Renal potassium handling (**Fig. 2.13**): K^+ balance depends on K^+ reabsorption and secretion:

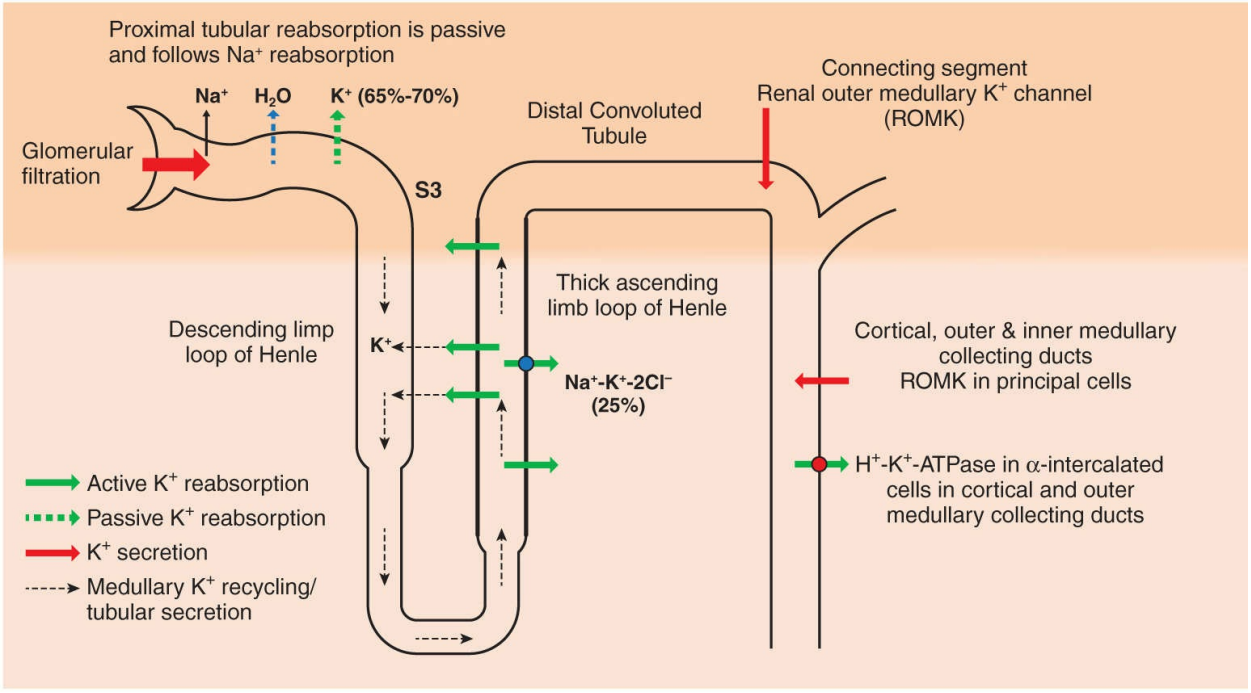

FIGURE 2.13 Renal potassium handling.

K^+ reabsorption

- Proximal tubules: passive paracellular reabsorption
- TAL: active reabsorption via Na^+-K^+-$2Cl^-$ as well as passive paracellular reabsorption
- Cortical and outer medullary collecting duct α-IC H^+-K^+-ATPase
  - Activity of H^+-K^+-ATPase is increased with K^+ depletion and reduced with high K^+.
  - Aldosterone stimulates H^+-K^+-ATPase activity.
  - Progesterone is thought to stimulate H^+-K^+-ATPase activity to retain K^+ during pregnancy.

K^+ secretion

- Medullary K^+ recycling:
  - Reabsorbed medullary K^+ is secreted back into the lumen at the S3 segment of late proximal tubules and descending limb of loop of Henle for subsequent reabsorption at TAL.
  - Maintenance of high medullary K^+ concentration is thought to minimize passive K^+ back-leak.

- Regulated K^+ secretion via ROMK, Maxi-K^+ channel, and K^+-Cl^- cotransporter:
  - Apical ROMK (**Fig. 2.2**):
    - K^+ secretion via ROMK occurs as follows:
      1. Na^+ is delivered to aldosterone-sensitive distal nephron segment, including the late DCT, connecting tubule (CNT), and CCD.
      2. The delivered Na^+ is reabsorbed via apical ENaC into principal cells. This generates a negatively charged lumen.
      3. The intracellular Na^+ is subsequently reabsorbed in exchange for cellular K^+ entry via the basolateral Na^+-K^+-ATPase.
      4. The accumulated intracellular K^+ within principal cells exits into tubular lumen, a movement favored by the favorable K^+ concentration difference between the cellular and luminal space and the negative luminal charge generated by Na^+ cellular entry via ENaC.
      5. A good tubular flow is necessary to maintain the favorable electrochemical gradient for continuing K^+ secretion. Additionally, a high tubular flow may also stimulate ENaC, thereby enhancing K^+ secretion via mechanisms outlined above.
    - Factors affecting K^+ secretion via ROMK as outlined above:
      - Rate of distal Na^+ delivery to aldosterone-sensitive distal nephron segment
      - Intact apical ENaC and ROMK
      - Intact basolateral Na^+-K^+-ATPase
      - Good tubular flow rate
      - Aldosterone upregulates the expression of ENaC and Na^+-K^+-ATPase and increases ROMK activity, thus enhancing K^+ secretion.
      - Normal functioning aldosterone receptor
      - Others: ADH (thought to increase the number of luminal ROMK channels), adequate functioning nephron mass (eGFR typically >15 to 20 mL/min/1.73 m^2)
  - Apical Maxi-K^+ channel, also known as Big K (BK) channel:

- BK channel is present along the entire nephron, but only known to exert its flow-mediated K^+ secretion in DCT and CCD.
- BK channel is quiescent at basal state but gets activated with increased luminal flow. This explains exaggerated K^+ wasting in patients with high tubular flow with diuretics or Bartter syndrome (BS).

- An apical KCl cotransporter is also thought to play a role in late DCT and CCD K^+ secretion.

NOTE The initial acute response to a K^+ load is intracellular uptake, a process facilitated by catecholamines and insulin. Renal elimination of K^+ occurs over the next 6 to 8 hours.

Aldosterone paradox

- Refers to the ability of aldosterone to stimulate renal Na^+ retention without K^+ secretion in volume-depleted state while stimulating K^+ secretion without salt retention in hyperkalemia.
- In the hypovolemic state, AII acts in concert with aldosterone to enhance activities of both NCC and ENaC to increase Na^+ reabsorption. Concurrently, AII inhibits ROMK activity. The net effect is Na^+ reabsorption without concurrent K^+ wasting.
- In the K^+-loading state, low level of AII or high K^+ level inhibits NCC activity, which leads to increased Na^+ delivery to ENaC. This leads to increased Na^+ entry via ENaC thus facilitated K^+ secretion via ROMK. Additionally, the increased aldosterone level in response to K^+ loading increases the activity of both ENaC and ROMK to increase K^+ secretion. The net effect is K^+ secretion without excessive Na^+ reabsorption.
- The effects of aldosterone and AII on Na^+ and K^+ transport via NCC, ENaC, and ROMK are mediated by the interactions of WNK4 and WNK1 (long WNK1 and kidney-specific WNK1). For interested readers, see **Figure 2.14** for mechanisms.

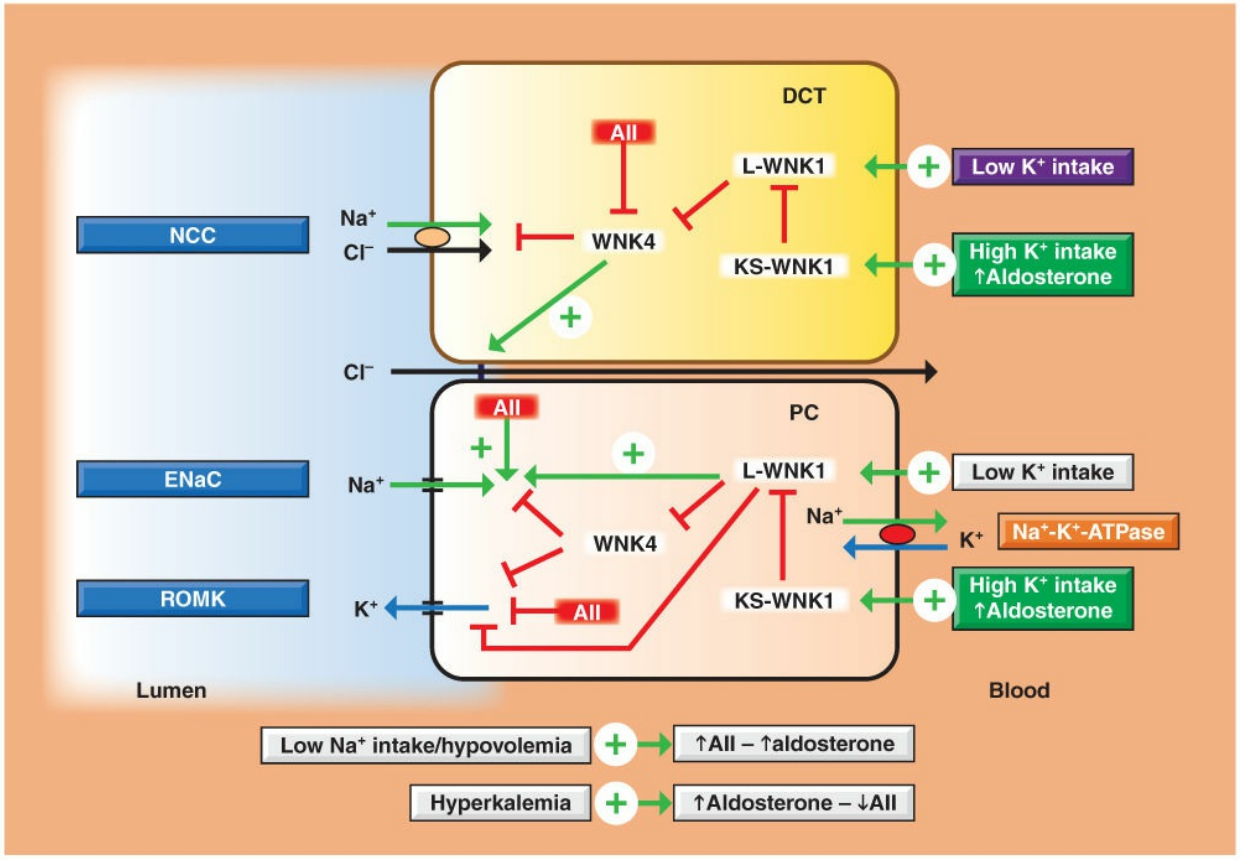

FIGURE 2.14 Sodium and potassium regulation by renin–angiotensin–aldosterone system and "with no K (lysine) kinases" in the aldosterone-sensitive nephron.

- **Under basal conditions**, WNK4 inhibits NCC, ENaC, and ROMK via increased internalization or reduced activity/surface expression of the affected transporters/channels.
- **In the hypovolemic state**, AII stimulates Na^+ reabsorption via NCC and ENaC. The increased Na^+ reabsorption at NCC reduces Na^+ delivery to ENaC, which reduces the ability of the principal cell to generate the negatively charged lumen necessary for facilitated K^+ secretion via ROMK. K^+ secretion is thus limited. Additionally, AII reduces apical ROMK expression via both WNK4-dependent and WNK4-independent mechanisms. The net effect is increased Na^+ reabsorption without concurrent K^+ wasting.
- **In K^+ loading**, KS-WNK1 is increased, which effectively releases L-WNK1 inhibitory effect on WNK4, thus allowing WNK4 to inhibit NaCl reabsorption via NCC. The increased Na^+ delivery to ENaC leads to increased Na^+ reabsorption via ENaC, thus increased generation of a negative lumen and subsequent facilitated K^+ secretion via ROMK. Additionally, KS-WNK1 stimulates ENaC and concurrently releases the inhibitory effect of L-WNK1 on ROMK to effectively enhance K^+ secretion via ROMK. The increased aldosterone associated with hyperkalemia also regulates Na^+ and K^+ via the induction of serum- and glucocorticoid-inducible kinase SGK1. SGK1 reduces the internalization of ENaC and ROMK from apical surfaces, leading to increased Na^+ reabsorption and K^+ secretion. The net effect in the hyperkalemic state is increased K^+ secretion without concurrent excessive Na^+ reabsorption. Note: The difference in Na^+ and K^+ regulation between hypovolemia and K^+ loading is the presence of AII in the former and lack thereof in the latter.
- **In low-K^+ diet**, L-WNK1 is increased, which leads to reduced apical ROMK expression, thus reduced K^+ secretion. However, the higher L-WNK1 also leads to increased Na^+ reabsorption via

both NCC and ENaC. The increased Na^+ reabsorption in association with a low-K^+ diet is thought to be responsible for salt-sensitive hypertension in association with low-K^+ diet in modern time. Epidemiologic studies suggest an association between hypokalemia and a rise in BP of 5 to 10 mm Hg. Potassium supplement has been shown to improve BP.

Abbreviations: AII, angiotensin II; DCT, distal convoluted tubule; KS-WNK1, kidney-specific WNK1; L-WNK1, long WNK1; NCC, sodium chloride cotransporter; PC, principal cell in cortical collecting duct; WNK, with-no-lysine (K) kinase; ENaC, epithelial sodium channel; ROMK, renal outer medullary potassium channel; BP, blood pressure.

Diagnosis of potassium disorders (dyskalemias)

Common indices used to determine renal versus extrarenal causes of potassium disorders are listed in **Table 2.2**. None of the indices is without limitations. Nonetheless, in the authors' opinion, the more indices used in any patient case, the better the diagnostic accuracy.

Table 2.2 Common indices used in the evaluation of potassium disorders

HYPERkalemia	Renal Cause	Extrarenal Cause	HYPOkalemia	Renal Cause	Extrarenal Cause
Spot [K^+] (mmol/L)	<15	>40	Spot [K^+] (mmol/L)	>15	<40
Transtubular K^+ gradient	<3	>7	Transtubular K^+ gradient	>3	<7
Spot [K^+]/[Cr] (mEq/g Cr)	<15	>25	Spot [K^+]/[Cr] (mEq/g Cr)	>15	<25
24-Hour urine K^+ (mEq/d)	<25	>40	24-Hour urine K^+ (mEq/d)	>25	<40

Notes: Ranges given above are not absolute. Spot urine [K^+] is the least accurate index, whereas 24-hour urine K^+ is the gold standard but most cumbersome to obtain. A concurrent urine [Na^+] <20 mmol/l may indicate that low distal tubular na^+ delivery is the limiting factor to potassium secretion. none of the indices above is without limitations. nonetheless, in the authors' opinion, the more indices used in any patient case, the better the diagnostic accuracy. see text for causes of hyperkalemia and hypokalemia.

Hyperkalemia

Clinical manifestations

- Muscle weakness, cardiac arrhythmias
- Electrocardiogram (ECG) changes:
  - Peaked T waves: tall peak (sharp tented) T waves; T wave taller than R wave in ≥2 precordial leads
  - Flattened P waves; prolonged PR interval

- Changes associated with high risk of cardiac arrest: widened QRS complex; merging of S and T waves; bradycardia, idioventricular rhythm; sine wave formation; ventricular fibrillation

Causes and mechanisms of hyperkalemia (Fig. 2.15)

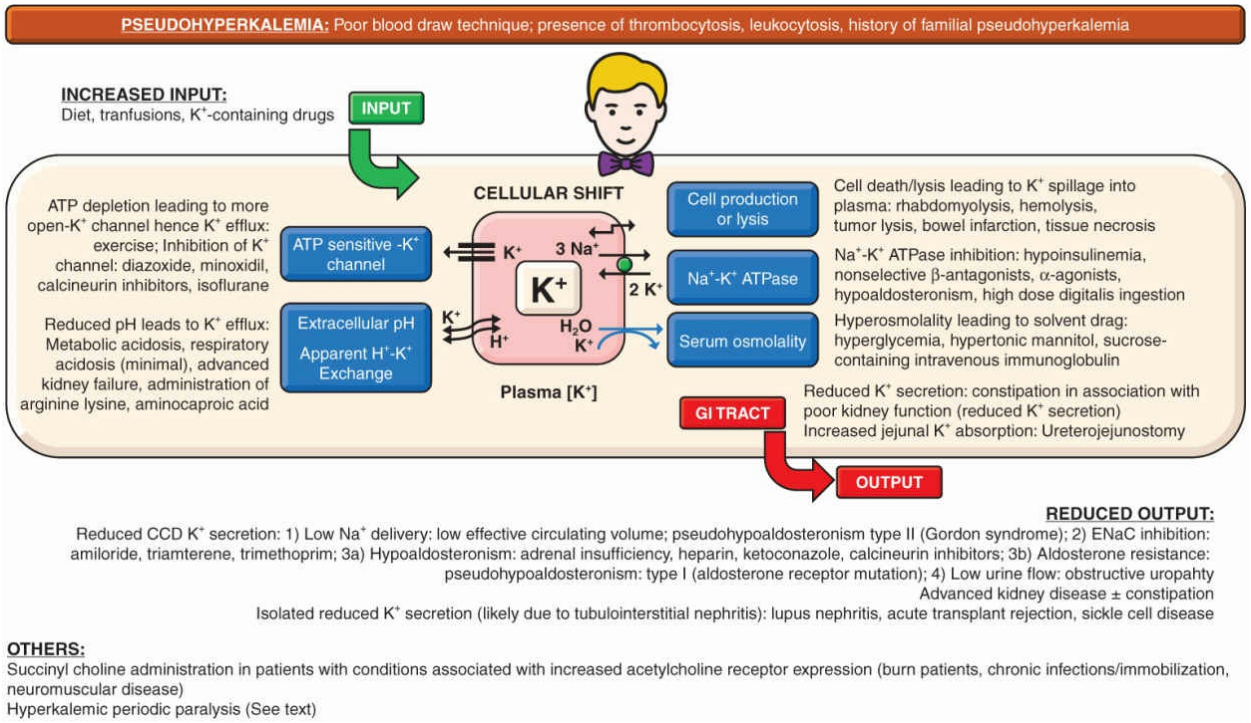

FIGURE 2.15 Etiologies of hyperkalemia. Abbreviations: CCD, cortical collecting duct; GI, gastrointestinal; ENaC, epithelial sodium channel.

Pseudohyperkalemia

- Hyperkalemia is only present in vitro NOT in vivo.
- Correction (treatment) of hyperkalemia is not necessary.
- Common conditions associated with pseudohyperkalemia:
  - Excessive fist clinching with blood draw: exercising (of hand) reduces local ATP and opens up KATP, allowing extracellular K^+ shift.
  - Mechanical trauma, hemolysis with blood draw: release of intracellular K^+
  - Thrombocytosis, for example, for every 100,000 platelets/μL, serum K^+ can increase by ~0.15 mmol/L because K^+ moves out of platelets after clotting has occurred in the test tube. Diagnosis: obtain P[K^+] (i.e., [K^+] measured from blood sample collected in heparin-containing tube to

avoid clotting process). If serum [K^+] (i.e., [K^+] measured in usual manner in non-anticoagulated blood) is greater than P[K^+], that is, S[K^+] − P[K^+] >0.3 mmol/L, pseudohyperkalemia is likely present.

- Pseudohyperkalemia may also be seen with erythrocytosis and leukocytosis (typically >70,000/cm^3), with the exception below.
- "Reverse" pseudohyperkalemia:
  - Condition where P[K^+] > S[K^+] (not the usual S[K^+] > P[K^+])
  - Due to cell fragility and lysis with centrifugation, traumatic blood handling (shuttling pneumatic tube system) and/or heparin induced K^+ leakage from white blood cells
  - Reported with chronic lymphocytic leukemia
  - To minimize cell lysis, hand-carry specimen to lab immediately following blood draw and avoid heparin-containing tubes
- Benign familial (autosomal dominant) pseudohyperkalemia and/or associated stomatocytosis: passive K^+ leaks from red blood cells into serum when the blood sample is left at room temperature. This K^+ leakage does not occur in vivo. Diagnosis: serial S[K^+] measurements while blood is allowed to cool down to room temperature leads to increasing S[K^+] levels.

Increased K^+ Input

- Dietary: high K^+-containing foods, salt substitutes (typical salt substitute contains 10 to 13 mEq KCl/g or 283 mEq KCl/tablespoon), mixed fruit juices
- K^+-containing medications: KCl, high-dose penicillin K, K-citrate, poly-citrate
- Supplements: fruit/herbal extracts
- Red blood cell transfusion due to K^+ leakage, particularly with massive transfusions or transfusions of prolonged stored blood

NOTE Hyperkalemia from intake alone is not common, except in cases of accidental large quantity ingestion, or moderate ingestion in those with poor kidney function and/or reduced mineralocorticoid activity.

Reduced Bodily K^+ Loss/Output

- GI: severe, chronic constipation with concurrent poor kidney function
- Kidneys: see **Reduced Renal K^+ Loss** section below

Extracellular K^+ Shift

- Extracellular pH:
  - Metabolic acidosis:
    - Inorganic acids (e.g., HCl or sulfuric acid), but not organic acids, cause K^+ shift. See **Figure 2.12**.
    - Organic acidosis seen with kidney failure or administration of arginine hydrochloride or aminocaproic acid may cause K^+ shift.
    - Lactic acidosis or ketoacidosis has smaller effect on hyperkalemia, partially due to concurrent entry of both anion and hydrogen ion into cells via a sodium-organic anion cotransporter, thus eliminating the need for K^+ shifting out of cells to maintain electroneutrality.
  - Respiratory acidosis:
    - No significant effect on extracellular K^+ shift unless severe and prolonged.
  - Extracellular osmolality:
    - Increased osmolality (e.g., hyperglycemia, sucrose-containing intravenous immune globulin, radiocontrast media, hypertonic mannitol) leads to extracellular K^+ shift due to:
      - Extracellular H_2O shift with hyperosmolality increases intracellular K^+ concentration, hence greater concentration gradient favoring extracellular shift.
      - Extracellular H_2O shift drags K^+ along: "solvent-drag" effect.

NOTE Hyperkalemia is often observed in fasting blood draws (e.g., early morning preoperative blood draw) in type 2 diabetic patients. This is thought to be due to the lack of endogenous insulin secretion with fasting. To correct this hyperkalemia, administer 5% dextrose (D5) water or saline solutions and/or insulin depending on the degree of hyperglycemia.

- Therapy with somatostatin or somatostatin agonist (octreotide) can lead to a fall in insulin and hyperkalemia in susceptible individuals.
- Cell death/increased tissue catabolism: tumor lysis (cytotoxic or radiation therapy), hemolysis, rhabdomyolysis, bowel infarction, soft-tissue trauma,

severe accidental hypothermia

- Altered Na^+-K^+-ATPase activity:
  - Reduced insulin
  - Reduced β_2-adrenergic activity reduces cellular K^+ uptake:
    - Digitalis overdose (digoxin, ingestion of common oleander or yellow oleander): inhibition of Na^+-K^+-ATPase
    - β2-Antagonists: (1) inhibit catecholamine-stimulated renin release, hence aldosterone; (2) most important: inhibit Na^+-K^+-ATPase activity. Nonselective agents, therefore, cause more hyperkalemia compared with β1 selective antagonists.

      Nonselective β-antagonists: alprenolol, bucindolol, carteolol, carvedilol (+ α-antagonism), labetalol (+ α-antagonism), nadolol, penbutolol, pindolol, propranolol, timolol

      Selective β1-antagonists: acebutolol, **atenolol**, betaxolol, bisoprolol, celiprolol, esmolol, **metoprolol**, nebivolol (bolded agents are commonly used in patients with kidney disease)
- Exercise-induced hyperkalemia:
  - Delay in cellular K^+ reuptake via Na^+-K^+-ATPase following K^+ exit from cells during depolarization
  - Exercise-induced reduction in ATP reduces ATP-dependent inhibition of K^+ channels, hence more open K^+ channels and increase K^+ leak extracellularly.
  - Extracellular K^+ shift is thought to be adaptive because higher K^+ concentration has a vasodilatory effect, hence improved blood flow and energy supply to exercising muscles.
  - Exercise-induced hyperkalemia is reversed within a few minutes of rest.
- KATP: Opening of K^+ channels leading to K^+ efflux may occur in the following:
  - Lack of ATP as seen with exercise
  - Medications: calcineurin inhibitors (cyclosporine, tacrolimus), diazoxide, minoxidil, isoflurane
- Hyperkalemic periodic paralysis:

- Autosomal dominant, varying penetrance
- Rare channelopathy involving α_1-subunit of skeletal muscle Na^+ (SCN4A) channels
- Age of onset: infancy to second decade of life
- May be associated with prolonged QT interval (Anderson syndrome), malignant hyperthermia, or paramyotonia congenital von Eulenburg (paradoxical myotonia may be prominent feature, which is worsened with activity or aggressive lowering of $S[K^+]$)
- Episodic weakness or paralysis may be precipitated by rest after activity, changes in daily level of activity especially in cool temperature, K^+ administration.
- Attacks last 10 to 60 minutes, rarely 1 to 2 days; abrupt paralysis onset may result in falls.
- Stiffness may be aborted with walking, high-carbohydrates (candy) intake.
- $S[K^+]$ is most often normal but may be (minimally) high or even low during recovery.
- Diagnosis:
  - Compound muscle amplitude test
  - Genetic testing for a *small number* of mutations is available
- Treatment: Diet: high carbohydrates, candy; avoid high K^+-containing foods; consider diuretics (thiazides, loop diuretics), β-agonists such as albuterol.

- Administration of succinylcholine to susceptible patients with conditions where there is upregulation of acetylcholine receptors (e.g., neuromuscular disease, severe trauma, burns, chronic immobilization or infections). Succinylcholine activation of acetylcholine receptors causes cell depolarization and large K^+ efflux.
- Heparin may cause hyperkalemia by several mechanisms:
  - Inhibition of aldosterone production via reduction in the number and affinity of AII receptors in zona glomerulosa
  - Inhibition of the final enzymatic steps of aldosterone formation (18-hydroxylation)

- Adrenal hemorrhage
- K^+ leakage out of white blood cells in heparin-containing test tubes

- Sofosbuvir-associated hyperkalemia:
  - Hyperkalemia associated with the use of sofosbuvir-based regimen in patients with CKD stage 5 and hepatitis C virus infection has been reported.
  - Etiology is not clear but vaguely suggested to involve associated bradycardia and altered intracellular Ca^{2+} levels, acute interstitial nephritis, and/or dysfunction of potassium channel.

Reduced Renal K^+ Loss

- Recall, renal K^+ secretion depends on (1) distal Na^+ delivery, (2) generation of transepithelial potential difference (negative lumen) via Na^+ entry into ENaC in principal cells at aldosterone-sensitive distal nephron segment, (3) distal urine flow, (4) presence of aldosterone, (5) sensitivity to aldosterone, (6) kidney mass/function.
- Reduced renal K^+ secretion may occur when:
  - Distal Na^+ delivery to cortical and corticomedullary collecting tubules is reduced:
    - Reduced effective circulating volume (heart failure, cirrhosis, volume depletion, etc.), severe dietary sodium restriction
    - Diagnosis: clinical history, $U[Na^+] < 20$ mmol/l, enhanced urinary k^+ excretion (i.e., increase $u[k^+]$) with saline infusion
    - Enhanced proximal Na^+ uptake at DCTs, hence reduced Na^+ delivery to more distal collecting tubules (pseudohyperaldosteronism type 2/Gordon syndrome, calcineurin inhibitors).
  - Generation of transepithelial potential difference (negative lumen) via Na^+ entry into ENaC in principal cells at aldosterone-sensitive distal nephron segment is compromised; Inhibitors of ENaC include triamterene, amiloride, trimethoprim, and pentamidine.
  - Distal urine flow is compromised: obstructive uropathy, reduced glomerular filtration
  - Lack of aldosterone:

Hypoaldosteronism: diabetes mellitus with type 4 RTA, primary adrenal insufficiency

- Medications: RAAS inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors (prostaglandins normally enhance renin secretion), heparin (low-molecular weight as well), ketoconazole, drospirenone-containing oral contraceptives (e.g., Yaz, Yasmin): drospirenone has mineralocorticoid-antagonist activity.
- A study published in 2017 involving >150,000 participants from the Geisinger health care system over 3-year follow-up revealed that the adjusted risks for hyperkalemia (serum K^+ >5.0 mmol/L) associated with the use of antihypertensive agents were 1.54 for ACEI, 1.13 for β-blockers, 1.07 for ARB.

- Resistance to aldosterone:
  - Medications: aldosterone antagonists (spironolactone, eplerenone)
  - Pseudohypoaldosteronism type-1 (PHA1) (Also discussed in Chapter 1)
    - Hyperkalemia associated with metabolic acidosis and salt wasting
    - Autosomal dominant form (AD PHA1):
      - Aldosterone-receptor mutation
      - Treatment: high-dose fludrocortisone, salt support
    - Autosomal recessive form (AR PHA1):
      - Inactivating mutations in α-, β-, or γ-subunits of ENaC; associated with pulmonary infections
      - More severe than AD PHA1
      - Salt wasting in multiple organs requiring ENaC for salt transport (lungs, kidneys, colon, sweat, salivary glands)
      - High sodium chloride content in sweat and salivary testing
    - Treatment: high salt support; NSAIDs have been reported to be beneficial in AR PHA1.
  - Pseudoaldosteronism type 2 (Gordon syndrome, i.e., familial hyperkalemic hypertension [FHH]) (**Fig. 2.14**):
    - FHH is characterized by:
      - Enhanced paracellular Cl^- reabsorption

        - Enhanced Na^+ reabsorption via NCC in DCT, leading to reduced Na^+ availability for delivery to CCD. Reduced Na^+ availability at CCD reduces its ability to secrete K^+ and H^+ → hyperkalemia and metabolic acidosis.
        - The increased Na^+ and Cl^- reabsorption leads to volume expanded state, which suppresses RAAS. Reduced aldosterone also contributes to hyperkalemia and metabolic acidosis.
    - Clinical manifestations: HTN in early adulthood, non-AG metabolic acidosis and hyperkalemia, hypercalciuria, osteoporosis, nephrolithiasis
    - Reported NCC regulatory molecules with mutations leading to FHH: WNK1, WNK4 (inactivating mutations of WNK4 or activating mutations of WNK1) and, possibly, others that regulate WNK1 and WNK4.
        - Wnk4 mutation in FHH leads to increased Na^+ reabsorption via NCC and ENaC as well as enhanced paracellular chloride reabsorption.
        - Mutations in WNK4 also downregulate the transient receptor potential V5 channel (TRPV5, calcium channel) and decrease Ca^{2+} reabsorption in DCT, thus hypercalciuria and osteoporosis.
    - Treatment: thiazide diuretics
  - Kidney transplant
    - Concurrent hyperkalemia and salt-sensitive HTN observed in the transplant setting has been attributed to CNI-induced activation of the thiazide sensitive NCC.
    - Treatment: thiazide diuretic
- Kidney mass/function is reduced:
  - Reduced overall capacity for renal K^+ secretion
  - Reduced Na^+-K^+-ATPase activity with uremia may also reduce cellular uptake.
- Others:
  - Ureterojejunostomy: increased absorption of urinary K^+ by jejunum
  - Selective impairment of K^+ secretion/excretion from various

mechanisms: tubulointerstitial disease, lupus nephritis, acute transplant rejection, sickle cell disease

NOTE Common clinical scenarios with multiple reasons for hyperkalemia:

Diabetic patient: (1) neurogenic bladder leading to urinary stasis; (2) low aldosterone state due to reduced sympathetic stimulation for renin release, adrenal atrophy, use of renin–angiotensin–aldosterone inhibitors; (3) insulin deficiency leading to reduced cellular K^+ uptake via Na^+-K^+-ATPase, hyperosmolality from hyperglycemia leading to cellular K^+ efflux, metabolic acidosis with DKA leading to K^+ efflux, hypovolemia leading to reduced Na^+ delivery to collecting tubules

Patient with cirrhosis or heart failure: (1) use of spironolactone, (2) low effective circulating volume leading to poor Na^+ delivery to collecting tubules, (3) recurrent kidney injuries, (4) use of non-selective beta blockers or other inhibitors of the renin angiotensin system.

Management of Hyperkalemia (Table 2.3)

- For patients with relatively good kidney function and non-life threatening ECG changes:
  - If hypovolemic, initiate volume resuscitation with normal saline.
  - If hypervolemic, use loop diuretic.
- For severe hyperkalemia with high-risk ECG changes and kidney failure, emergent hemodialysis is indicated.
- For chronic management of hyperkalemia:
  - Review for and remove offending agent.
  - Consider nutrition consult for low-K^+ diet (≤60 to 75 mEq/d ~2,400 to 3,000 mg/d).
  - Ensure a good bowel regimen.
  - Consider potassium-binding resins: sodium polystyrene polysulfone (Kayexalate, poor efficacy), patiromer (Veltassa), sodium zirconium cyclosilicate (Lokelma). See **Table 2.3** for important differences among these agents.

Table 2.3 Therapeutic options for hyperkalemia

Therapeutic Options		Dosing	Onset	Comments
Stabilize cardiac membrane potential	Calcium gluconate	10 mL of 10% of Ca-gluconate infused over 10 min **NOTE**: 1 ampule of $CaCl_2$ = 3 ampules	1–3 min	$CaCl_2$ can be irritating to vein Do not give calcium in HCO_3 line Caution with calcium infusion in patients with digoxin

		of Ca-gluconate in terms of elemental Ca^{2+}		toxicity-induced hyperkalemia (risk and benefit unclear)
Increase intracellular shift	Insulin *plus* glucose	10 units of regular insulin *plus* glucose supplement if serum glucose level is <250 mg/dL	15–30 min	Reduce insulin dose to 5 units in advanced CKD due to increased risk of hypoglycemia
	Albuterol—β_2-adrenergic agent	10–20 mg nebulizer	15–30 min	Risk of tachycardia, precipitation of myocardial infarction Lactic acidosis type B may occur (see **Lactic Acidosis** section)
	$NaHCO_3$	1 mEq/kg (if pH <7.2 or advanced CKD)	15–30 min	Do not give in calcium line Avoid if high $CaxPO_4$ product or pCO_2, low K^+ or Ca^{2+}, or volume overload $NaHCO_3$ is not effective if patient is not acidemic
Increase GI excretion	Sodium polystyrene sulfonate (SPS)—Cation exchange resin	30–60 g oral or per rectum up to qid and/or laxative (20% sorbitol) if oral	Variable; 1–2 h	Site of action is colon/rectum **Colonic ischemia and necrosis** reported both with and without concurrent use of sorbitol (highest risk seen with 70% sorbitol compared with 30% formulation) **Contraindicated in bowel obstruction, ileus, postanesthesia**
	Patiromer (Veltassa)—Synthetic polymer with calcium as exchange counterion	8.4–25.2 g qd; administer other oral medications ≥3 h from patiromer and ≥6 h for those with delayed gastric emptying	7 h	K^+-binding capacity ~two times that of SPS Site of action is colon **May bind Mg^{2+} and NH_4^+, hypomagnesemia may be seen; may be associated with beneficial reduction in aldosterone level, albuminuria, and blood pressure**
	Sodium zirconium cyclosilicate (Lokelma)—Na^+-K^+ cation exchanger	5–10 g qd	1 h	K^+-binding capacity is nine times that of SPS and 125 times more selective for K^+ than Ca^{2+} or Mg^{2+} Binds K^+ throughout GI tract **Na^+ retention is a significant side effect** **Reduction in K^+ may be seen**

				as early as 1 h following treatment
Increase renal excretion	Volume resuscitation; loop/thiazide diuretics; fludrocortisone	Therapeutic option is based on volume status, mineralocorticoid activity status	Variable	Per clinician's judgment
Blood removal	Hemodialysis (HD)	Dosing per clinician	Immediate	HD is preferred over peritoneal dialysis or continuous renal replacement therapy due to its more rapid K^+ clearance.

Note: Important characteristics of different gastrointestinal potassium binders are bolded.
Abbreviations: CDK, chronic kidney disease; qid, four times daily; qd, every day; GI, gastrointestinal; pCO_2, CO_2 pressure.

Hypokalemia

Clinical manifestations

- Muscle weakness, rhabdomyolysis, fatigue, ileus, constipation, leg cramps, respiratory difficulty, HTN
- ECG changes: U waves, T-wave flattening, ST-segment depression, arrhythmias, asystole
- Effects on kidneys: nephrogenic diabetes insipidus, hypokalemic nephropathy, tubulointerstitial and cystic changes
  - Hypokalemic nephropathy (**Fig. 2.16**):
    - Histopathology: intracytoplasmic vacuoles in tubular cells, chronic inflammation, interstitial fibrosis
    - Pathogenesis: presumed imbalance in vasoactive mediators leading to net vasoconstriction and medullary ischemia
    - Common clinical findings: low urine specific gravity, polyuria, tubular proteinuria, and inactive urinary sediment

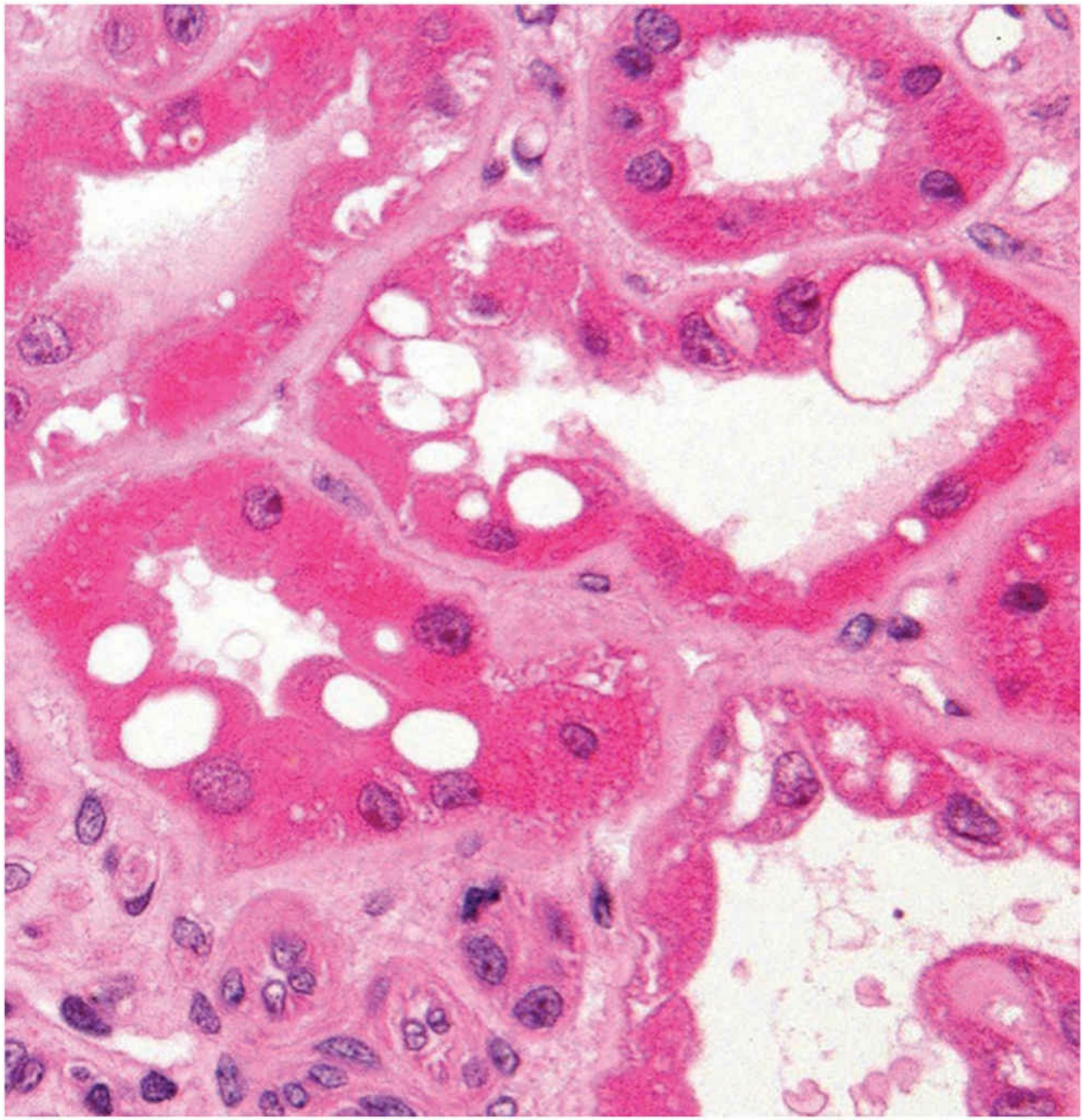

FIGURE 2.16 Hypokalemic nephropathy. Tubular epithelial cells containing large irregular cytoplasmic vacuoles and showing acute injury with focal loss-of-brush border staining and cytoplasmic volume. (Hematoxylin and eosin stain [H&E] ×60.)

- 40% of patients with hypokalemia also have hypomagnesemia. Explanations for concurrent electrolyte disturbances include:
  - Underlying abnormality/pathology can cause both (e.g., cisplatin, amphotericin, diuretics use, poor dietary intake, diarrhea)
  - Mg^{2+} is a gatekeeper for ROMK. Low Mg^{2+} level leaves ROMK open,

thus K^+ wasting.

- Mg^{2+} is a cofactor in Na^+-K^+-ATPase, H^+-K^+-ATPase.
- Enhanced aldosterone state causing both hypokalemia and hypomagnesemia

Causes and mechanisms of hypokalemia (Fig. 2.17)

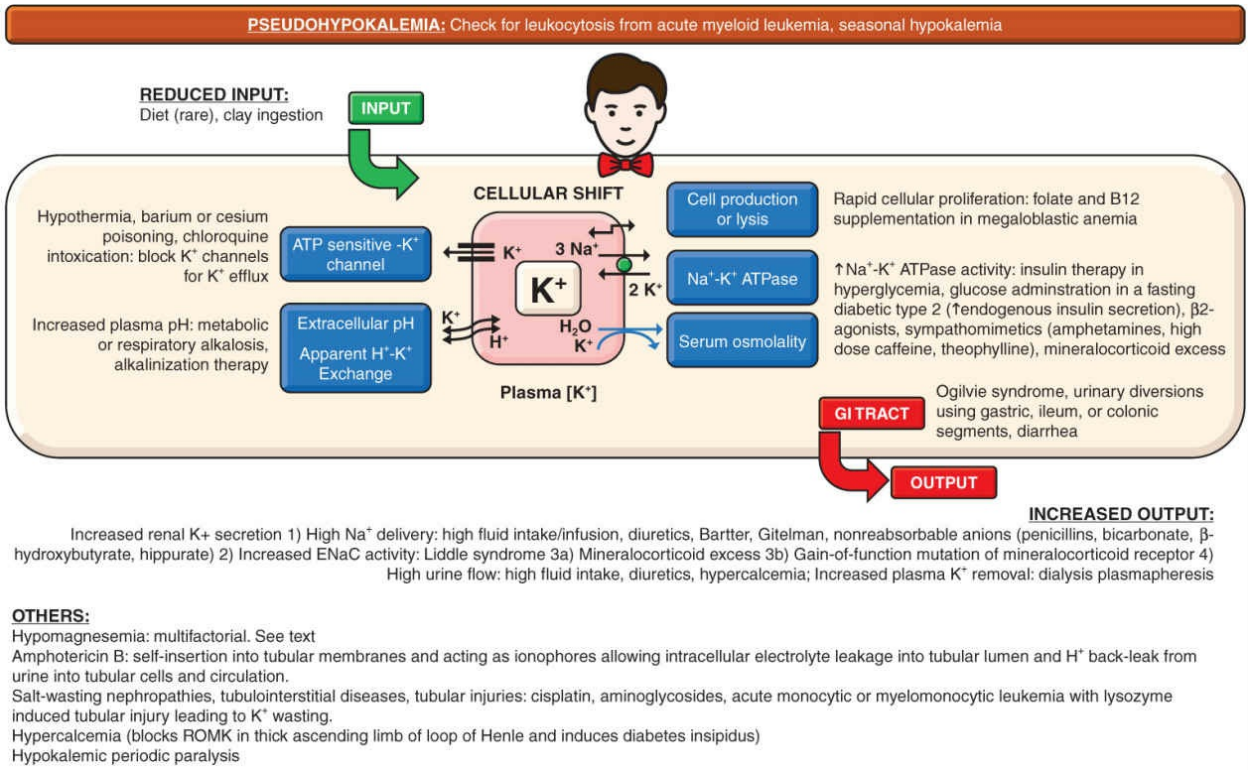

FIGURE 2.17 Etiologies of hypokalemia. Abbreviations: ATP, adenosine triphosphate; ENaC, epithelial sodium channel; ROMK, renal outer medullary potassium channel.

Pseudohypokalemia

- Hypokalemia only occurs in vitro not in vivo.
- Correction (treatment) of hypokalemia is not necessary.
- Pseudohypokalemia may be seen in patients with acute (or chronic) myeloid leukemia due to continuing cellular K^+ uptake into rapidly proliferating cells even after the blood is drawn. There may be associated pseudohypoglycemia and hypophosphatemia.
- Seasonal pseudohypokalemia: This is due to increased intracellular K^+ uptake via increased Na^+-K^+-ATPase activity with transport of blood tubes in warm ambient temperatures

Decreased K^+ Input

- Inadequate dietary intake, severe malnutrition (rare due to kidneys' ability to minimize K^+ loss to 5 to 20 mmol/L)
- Clay ingestion "geophagia." Clay can bind K^+ in the intestines.

Increased Bodily K^+ Loss/Output

- GI loss: severe diarrhea, vomiting/nasogastric suction, bowel cleansing (phenolphthalein laxatives, sodium polystyrene sulfonate)
  - Ogilvie syndrome (acute colonic pseudo-obstruction associated with a secretory diarrhea with very high K^+ content due to activation of colonic K^+ secretion. This condition is associated with various acute illnesses/stressors. Associated electrolyte abnormalities include hypokalemia, hypomagnesemia, and hypocalcemia)
  - Hypokalemia associated with vomiting predominantly occurs via renal K^+ loss due to volume depletion induced hyperrenin, hyperaldosteronism, and bicarbonaturia. Direct K^+ loss from gastric fluid is minimal because its K^+ content is only 5 to 10 mmol/L.
  - Diarrhea [K^+] typically ranges from 10 to 40 mmol/L but can be >100 mmol/L in colonic fluid in Ogilvie syndrome.
- Excessive sweats, extensive burns
- Dialysis, plasmapheresis
- Urinary loss: see **Increased Renal K^+ Loss** below

Intracellular K^+ Shift due to Increased Extracellular pH

- In metabolic and respiratory alkalosis, net intracellular K^+ uptake may be observed. The effect on K^+ shifting is less pronounced in respiratory compared to metabolic processes.
- Increased Na^+-K^+-ATPase activity:
  - Insulin administration or endogenous insulin release with glucose administration (e.g., 5% dextrose fluids).

    Note: In diabetic patients with poorly controlled glucose and preexisting life-threatening hypokalemia, provide K^+ replacement prior to insulin administration to avoid further fall in preexisting low S[K^+].

Increased β_2-adrenergic activity increases cellular K^+ uptake: stress, coronary ischemia, delirium tremens, thyroid hormone, β_2-agonists (albuterol, terbutaline, dopamine, dobutamine, pseudoephedrine), sympathomimetic stimulants (e.g., amphetamines, high-dose caffeine), theophylline toxicity

- Inhibition of KATP blocks K^+ efflux during repolarization: hypothermia, barium/cesium poisoning, chloroquine intoxication
- Hypokalemic periodic paralysis:
  - Rare channelopathy (autosomal dominant, varying penetrance)
  - 90% with mutation of the α_1-subunit of dihydropyridine (DHP)-sensitive Ca^{2+} channel, 10% with mutation of the SCN4A channel
  - Clinical manifestations:
    - Muscle weakness or paralysis in association with a fall in $S[K^+]$: upper > lower extremity, proximal > distal weakness
    - May be associated with hypophosphatemia and hypomagnesemia
    - Attacks often begin in adolescence
    - Triggered by strenuous exercise, followed by rest; high-carbohydrate high-sodium meals or administration of glucose, insulin, or glucocorticoids; sudden changes in temperature, excitement, loud noise, or flashlights
  - Associated conditions:
    - Andersen syndrome associated with prolonged QT and sudden death
    - Thyrotoxicosis due to Graves disease: more common in Asian or Latin/Native American males (propranolol may reverse attacks pending definitive therapy). Of note, patients with thyrotoxicosis hypokalemia periodic paralysis may also have elevated bone alkaline phosphatase for unclear reason.
  - Diagnosis: electromyograms during attacks or with exercise
  - Treatment:
    - Potassium supplement (slow and low dose due to rebound)
      - If patient can swallow and breathe adequately, administer 15 to 30 mEq of KCl, K-citrate, or K-bicarbonate at 30 to 60 minute intervals.

        - If patient cannot swallow, infuse 15 mEq KCl over 15 minutes, then 10 mEq/h in 500 mL dilutant; 5% mannitol dilutant is preferred over normal saline (sodium may worsen condition). *Do not* use glucose (due to endogenous insulin secretion and exacerbation of hypokalemia).
    - Cardiac monitoring is required with intravenous KCl administration.
    - Prevention: β_2-blockers, K^+ supplement, low-carbohydrate diet, K^+-sparing diuretics, CA inhibitor (acetazolamide)
- Barbiturate coma therapy (BCT)
    - BCT is used for refractory intracranial HTN to reduce cerebral blood flow, metabolic rate thus oxygen consumption, and intracranial pressure (ICP).
    - BCT using thiopentone may be associated with life-threatening dyskalemias.
    - Initial hypokalemia:
        - Hypokalemia has been reported in 65% to 89%.
        - Severe hypokalemia (<2.0 mmol/l) has been reported in 25% of patients.
        - Refractory life-threatening hypokalemia may occur.
        - Median onset of hypokalemia is 11 hours (6 to 23 hours) after BCT induction with S[K^+] nadir at 25 hours.
    - Rebound hyperkalemia (may be severe) following BCT cessation:
        - Mean peak S[K^+] occurs at 31 hours (28 to 56 hours).
        - Abrupt BCT cessation leading to S[K^+] increase within 2 hours has been reported.
    - Mechanisms of the initial hypokalemia are not clear but thought to involve:
        - Inhibition of neuronal voltage–dependent outward potassium current
        - Inhibition of phosphofructokinase, causing a reduction in pyruvate and lactate production. The resultant increase in intracellular pH promotes intracellular K^+ shift.
        - Increase in β_2-stimulation of Na^+-K^+-ATPase activity:
            - The increased ICP may inherently induce a surge of endogenous

catecholamine release and β_2-stimulation of Na^+-K^+-ATPase pump.
    - BCT may stimulate Na^+-K^+-ATPase activity.
- Management:
  - Hypokalemia during BCT:
    - Avoid overly aggressive K^+ replacement.
    - Maintain S[K^+] goal at 3 mmol/L with cardiac monitoring.
    - Keep total K^+ supplement to less than 100 mEq has been suggested.
  - Slow taper of BCT over 12 to 24 hours has been suggested to reduce rapid and severe rebound hyperkalemia.
  - Monitor S[K^+] and treat as needed over 72 hours following BCT discontinuation.

Increased Renal K^+ Loss

- Recall, renal K^+ secretion depends on (1) distal Na^+ delivery, (2) generation of transepithelial potential difference (negative lumen) via Na^+ entry into ENaC in principal cells at aldosterone-sensitive distal nephron segment, (3) distal urine flow, (4) presence of aldosterone (mineralocorticoid), (5) sensitivity to aldosterone (mineralocorticoid), (6) kidney mass/function.
- Enhanced renal K^+ secretion may occur with:
  - Increased distal Na^+ delivery to cortical and corticomedullary collecting tubules:
    - Diuretics, high fluid intake/intravenous fluid infusion
    - BS and Gitelman syndrome (GS)
    - Recall, increased tubular flow also activates Maxi-K (BK) channel, which increases K^+ loss.
  - Generation of transepithelial potential difference (negative lumen) via Na^+ entry into ENaC in principal cells at aldosterone-sensitive distal nephron segment is increased with:
    - Liddle syndrome
      - Autosomal dominant, gain-of-function mutation in the β- and γ-

subunits of ENaC (PY motif) that reduces the "housekeeping" recognition of ENaC by Nedd4-2 for internalization and degradation, resulting in an increased number of functioning apical ENaC.

- Affected patients present with HTN due to excess Na^+ retention; relative hyporenin and hypoaldosteronism due to volume expansion; but hypokalemia and metabolic alkalosis due to facilitated renal K^+ and H^+ secretion following increased Na^+ entry into the undegraded apical ENaC.
- Treatment: ENaC inhibition with amiloride. Because this mutation manifests as an end-organ defect, kidney transplantation is curative.

■ Nonreabsorbable anions delivery to collecting tubules can enhance K^+ secretion due to the favorable electrical gradient. Additionally, any increased Na^+ delivery associated with the anions will also enhance the generation of the favorable electrochemical gradient for K^+ secretion. Examples of nonreabsorbable anions: bicarbonate (vomiting and pRTA), β-hydroxybutyrate in DKA, high-dose penicillin derivative administration, hippurate from toluene with glue sniffing.

- High distal urine flow: high-volume intake/infusion, diuretics
- Increased mineralocorticoid activity (**Fig. 2.18**)

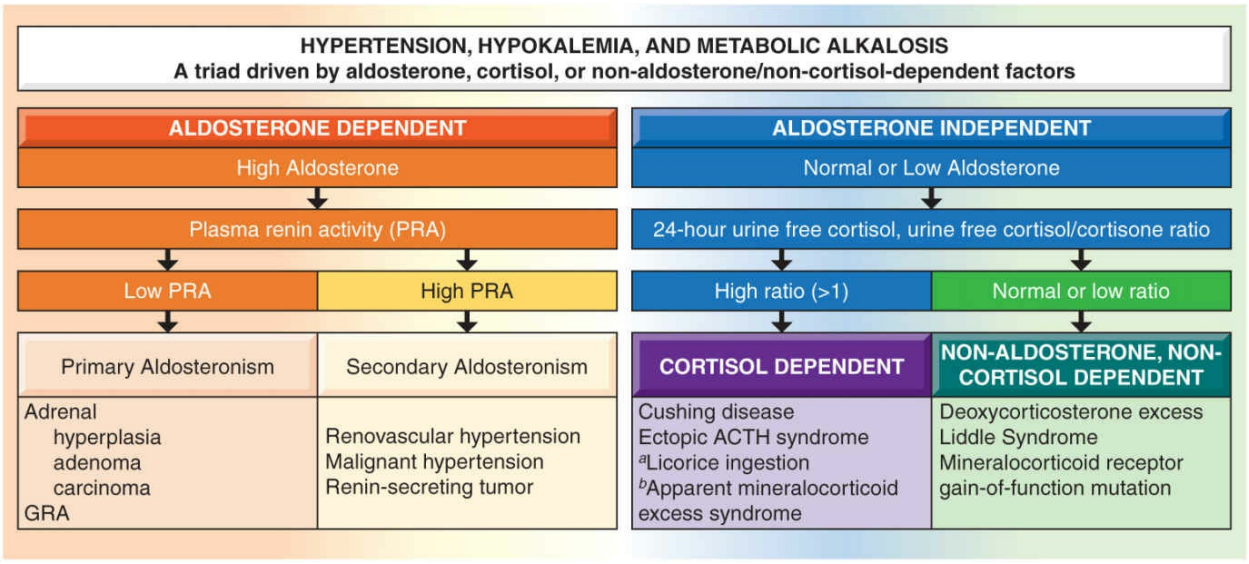

FIGURE 2.18 Evaluation of mineralocorticoid excess in patients with the triad of hypertension, hypokalemia, and metabolic alkalosis. Abbreviations: PRA, plasma renin activity level; FC/C, free cortisol to cortisone ratio; GRA, glucocorticoid-remediable aldosteronism; ACTH, adrenocorticotropin hormone.

[a]Glycyrrhizic acid and its hydrolytic product glycyrrhetinic acid from licorice are potent competitive inhibitors of 11-β-hydroxysteroid dehydrogenase, the enzyme required to metabolize cortisol to its inactive form, cortisone.

[b]Apparent mineralocorticoid excess: Mutation of 11-β -hydroxysteroid dehydrogenase enzyme; urine free cortisol/cortisone ratio typically exceeds 5.

- Clinical manifestations: classically present with the triad of HTN, hypokalemia, and metabolic alkalosis
- The aforementioned clinical triad may be categorized as aldosterone dependent, cortisol dependent, or aldosterone and cortisol independent
- Aldosterone dependent:
  - Secondary aldosteronism:
    - High renin level leads to aldosterone synthesis.
    - Source of renin: hypoxia-induced (renovascular HTN) or unregulated synthesis (renin-secreting tumors)
  - Primary aldosteronism:
    - Aldosterone synthesis is independent of renin levels.
    - Sources of aldosterone: adrenal hyperplasia, adenoma, or carcinoma; glucocorticoid-remediable aldosteronism
    - Glucocorticoid-remediable aldosteronism (also known as dexamethasone suppressible hyperaldosteronism):
      - Autosomal dominant with formation of a chimeric gene due to unequal crossover of sequences at meiosis, where the hybrid gene contains the promoter of 11-β-hydroxylase enzyme (enzyme for cortisol synthesis) and aldosterone synthase gene (enzyme for aldosterone synthesis).
      - Stimulation of the promoter with adrenocorticotropin hormone (ACTH) upregulates both cortisol and aldosterone synthesis. Recall that aldosterone is normally upregulated by AII.
      - Clinical manifestations: early moderate-to-severe HTN,

hemorrhagic stroke and ruptured aneurysms (brain magnetic resonance angiography [MRA] every 5 years after puberty has been recommended), normo- to hypokalemia (the former due to the diurnal variation of ACTH).

- Diagnosis: genetic testing for crossover between aldosterone synthetase and 11-β-hydroxylase; biochemical evaluation: suppressed plasma renin activity and high serum aldosterone, increased levels of 18-hydroxy-cortisol, ACTH, and 18-oxo-cortisol

- Treatment: glucocorticoid- (to suppress ACTH) or mineralocorticoid-receptor (MR) antagonism (spironolactone, eplerenone) and/or ENaC antagonism (amiloride) to counteract the effects of the excess aldosterone

- Cortisol dependent:
  - Sources of cortisol:
    - Excess production (Cushing syndrome and ectopic ACTH release)
    - Reduced conversion of cortisol to inactive cortisone by 11-β-hydroxysteroid dehydrogenase type 2 (11-βHSD2)
      - Licorice: Glycyrrhizic acid and its hydrolytic product, glycyrrhetinic acid, from licorice are potent competitive inhibitors of 11-βHSD2.
      - Mutation of 11-βHSD2: syndrome of apparent mineralocorticoid excess (AME)
  - Diagnosis of excess cortisol:
    - Both urinary-free cortisol and cortisone will be high in conditions with excess production of cortisol.
    - An increased ratio of cortisol to cortisone (>1) with normal urinary cortisone excretion would be consistent with reduced 11-βHSD2 activity (e.g., licorice ingestion). Cortisol-to-cortisone ratio in normal individuals is <0.5.
    - A cortisol-to-cortisone ratio >5 is likely consistent with AME.
- Aldosterone and cortisol independent:

- Liddle syndrome (see above)
- Deoxycorticosteroid (DOC) excess:
  - DOC has mineralocorticoid activity.
  - Conditions associated with DOC excess:
    - Congenital adrenal hyperplasia involving inactivating mutations of 11-α-hydroxylase or 17-β-hydroxylase
    - Deoxycorticosterone-producing tumors
    - Drug induced: abiraterone acetate
      - Abiraterone is an inhibitor of androgen synthesis used in the treatment of metastatic or castration-resistant prostate carcinoma or androgen receptor–positive breast carcinoma.
      - Abiraterone inhibits 17α-hydroxylase, which reduces downstream cortisol synthesis. Hypocortisolism activates ACTH, which drives upstream synthesis of DOC. DOC has mineralocorticoid activity that can lead to fluid retention, hypokalemia, and HTN.
      - Treatment: eplerenone up to 200 mg/d or low-dose dexamethasone (0.5 mg/d)

- Activating mutation of mineralocorticoid receptor (Geller syndrome):
  - Autosomal dominant disorder where the conformation of Mineralocorticoid receptor (MR) is altered and constitutively activated
  - HTN may worsen during pregnancy. Progesterone and its derivatives may activate transcription of the mutated MR.
  - Spironolactone (normally an MR antagonist) may now act to stabilize the mutated receptor in its active conformation. Thus, spironolactone may worsen HTN.
- Others:
  - Amphotericin B: This is a multiplanar molecule that is lipophilic on the outside and hydrophilic on the inside surface. The molecule inserts itself into tubular cell membrane and acts as an ionophore, allowing electrolytes to flow in the direction of favorable chemical gradient. The formulation of liposomal amphotericin covers up the

lipophilic surface of amphotericin and reduces its insertion into tubular membranes, thus minimizing intracellular electrolyte losses into the urinary space and back-leak of H^+ into circulation (**Fig. 2.8**).

- Magnesium deficiency can lead to K^+ wasting at the TAL. Mg^{2+} is a "gatekeeper" against K^+ exit via ROMK into the lumen.
- Salt wasting nephropathies, tubular injuries (tubulointerstitial diseases, cisplatin, aminoglycosides), acute monocytic or myelomonocytic leukemia with lysozyme induced tubular injury, leading to K^+ wasting

- Hypercalcemia reduces the activity of both ROMK and NKCC2 in TAL thereby inducing a hypokalemic metabolic alkalosis similar to loop diuretics (see Bartter syndrome type 5).

Management of Hypokalemia

- If S[K^+] <3 mmol/l, stat ecg, cardiac monitor
- If safe, avoid the following until *life-threatening* hypokalemia has been corrected:
  - The use of glucose-containing solutions
  - Correction of hyperglycemia with insulin administration
  - Alkalinization
- Use central lines if >10 mEq/h replacement is needed.
- Consider femoral line over internal jugular or subclavian line if >20 mEq/h replacement is needed to avoid cardiac irritation.
- Check magnesium levels and replace as necessary.

Bartter versus Gitelman syndromes

Traditionally, BS and GS are likened to taking loop and thiazide diuretics, respectively. As such, these syndromes are associated with salt loss, polyuria, normotension or hypotension, and "compensatory" activation of RAAS. Similar to taking diuretics, both BS and GS are associated with hypokalemia and metabolic alkalosis.

In BS, increased synthesis of the vasodilatory prostaglandin PGE2 also

contributes to the normotensive state despite having stimulated RAAS. Impaired chloride reabsorption via NKCC2 results in reduced chloride concentration in macula densa cells (specialized TAL cells), which falsely translates to low chloride delivery to the juxtaglomerular apparatus. This false signal leads to increased synthesis of prostaglandin PGE2 (hyperprostaglandin E syndrome) which activates RAAS. The use of NSAIDs (indomethacin) can lead to improvement of symptoms and electrolyte abnormalities in patients with BS and hyperprostaglandin E syndrome.

Common findings of BS and GS

- Triad: **normotension**, hypokalemia, and metabolic alkalosis
- Elevated plasma renin activity and aldosterone level

NOTE The clinical findings of hypokalemia and metabolic alkalosis may be found in diuretic abuse, surreptitious vomiting/bulimia, chloridorrhea, and Barrter/Gitelman syndromes. Urine chloride in diuretic abuse is variable with intermittent use (high during use, low post use), low with vomiting, low in chloridorrhea, and persistently elevated in Bartter/Gitelman syndromes. Urine sodium in diuretic abuse is also variable with use (high during use, low post use), high in acute vomiting and low post-vomiting, low in chloridorrhea, and persistently elevated in Bartter/Gitelman syndromes.

Differences between BS and GS

- Age of onset is typically antenatal and neonatal with BS and early infancy/adulthood in GS.
- Hypercalciuria is common in BS, whereas hypocalciuria is common in GS.
- Severe hypomagnesemia is more common in GS.
- Exceptions to all above have been reported.
- Distinction:
  - Genetic analysis
  - Response to thiazide: There is an increase in excretion of NaCl in patients with BS, but not with GS.

Bartter syndromes (Fig. 2.19)

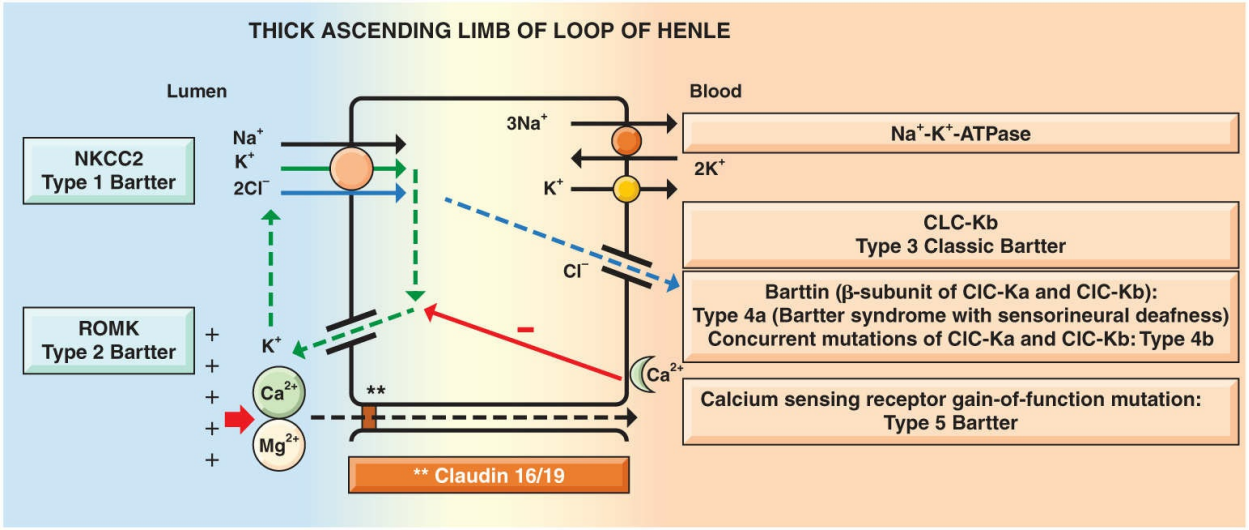

FIGURE 2.19 Transport mutations in Bartter syndrome. Abbreviations: NKCC2, Na^+-K^+-$2Cl^-$ cotransporter; ROMK, renal outer medullary potassium channel.

Inheritance pattern

- Autosomal recessive inheritance: BS types 1 to 4
- Autosomal dominant: BS type 5
- X-linked: transient BS

Bartter syndrome types

- Type 1
  - Antenatal/neonatal BS
  - Mutation of NKCC2
- Type 2:
  - Antenatal/neonatal BS
  - Mutation of ROMK
- Type 3 (i.e., classic BS):
  - Typically presents in infancy/early childhood
  - Mutation of ClC-Kb (see **Physiologic Functions of ClC** below)
  - Patients with BS 3 typically present with more severe chloride depletion because ClC-Kb is present in both TAL and distal nephron (DCT).
  - Calcium excretion is variable. This is likely due to the presence of ClC-Kb in both TAL and DCT. ClC-Kb dysfunction could contribute to hypercalciuria in TAL but hypocalciuria in DCT. The net effect in tubular calcium reabsorption may thus be variable.

- Type 4a: BS and sensorineural deafness (BSND)
  - Mutation of Barttin subunit of ClC-Kb. Barttin subunit is required in both ClC-Ka and ClC-Kb for normal function.
- Type 4b: BSND, concurrent mutation of ClC-Ka and ClC-Kb
  - Patients with BS 4a and 4b typically present with severe phenotypes, including growth retardation, poor response to NSAIDs, and even early end-stage renal disease (ESRD).

  Notes on physiologic functions of ClC-Ka and ClC-Kb:

  - ClC-Ka and ClC-Kb are present in distinct parts of the ascending loop of Henle.
    - ClC-Ka is present in the thin ascending limb of Henle and provides passive transepithelial chloride reabsorption.
    - ClC-Kb is present in the TAL, DCT, and CCD intercalated cells. ClC-Kb is necessary for optimal NKCC2 activity in outer medullary and cortical TAL. Loss of ClC-Kb function leads to suboptimal NKCC2 activity.
  - Both ClC-Ka and ClC-Kb are expressed in the marginal cells of the stria vascularis in the inner ear and contribute to K^+ secretion into the endolymph necessary for sensory transduction in inner ear hair cells. Simultaneous loss of function of both ClC-Ka and ClC-Kb, but not ClC-Kb alone, leads to sensorineural deafness.
- Type 5:
  - Gain-of-function mutation of calcium-sensing receptor (CaSR)
  - Activation of CaSR leads to reduced intracellular cyclic adenosine monophosphate (cAMP) production and subsequent increased production of 20-hydroxyeicosatetraenoic acid. The latter inhibits ROMK and NKCC.
  - In addition to hypokalemia and metabolic alkalosis, this condition is associated with salt wasting, hypercalciuria, hypocalcemia, and hypomagnesemia.
- Transient antenatal BS: loss-of-function mutations of melanoma-associated antigen D2 (MAGE-D2). MAGE-D2 normally interacts with NKCC2 to

increase their cell-surface expression and activity. Mutation in MAGE-D2 reduces NKCC2 expression in TAL and NCC in DCT. This form of BS is X-linked and transient in nature.

- Drug-induced Bartter-like syndrome (aminoglycosides, calcimimetics, amphotericin B, heavy metal intoxication): Gentamicin can bind and activate basolateral CaSR in TAL to induce a Bartter-like syndrome. The Bartter-like effect may last up to 2 to 6 weeks following drug cessation.

Clinical manifestations common to Bartter syndromes (BSs)

- Commonly occur in the antenatal or neonatal period, except BS type 5 that may present in late childhood or early adulthood
- Intrauterine growth restriction, polyhydramnios, failure to thrive
- Nephrocalcinosis (less common in BS types 3 and 4)
- Laboratory findings in addition to hypokalemia and metabolic alkalosis: hypercalciuria, high urine PGE2 level, and/or hypomagnesemia
- Reduced concentrating and diluting capacity
- Secondary focal segmental glomerulosclerosis, presumably adaptive to stimulated RAAS, has been reported in patients with BS.
- **Note:** K^+ recycling back into the lumen via ROMK creates a positively charged lumen. The positively charged lumen facilitates divalent cation (Ca^{2+}, Mg^{2+}) reabsorption paracellularly, a process facilitated by the tight junction proteins claudin 16 (i.e., paracellin 1) and 19. Any transporter defect leading to suboptimal K^+ recycling or mutation of claudin 16/19 can induce Ca^{2+} and Mg^{2+} wasting. Urinary calcium wasting explains nephrocalcinosis commonly observed among BSs.

Transport mutations in GS (Fig. 2.20)

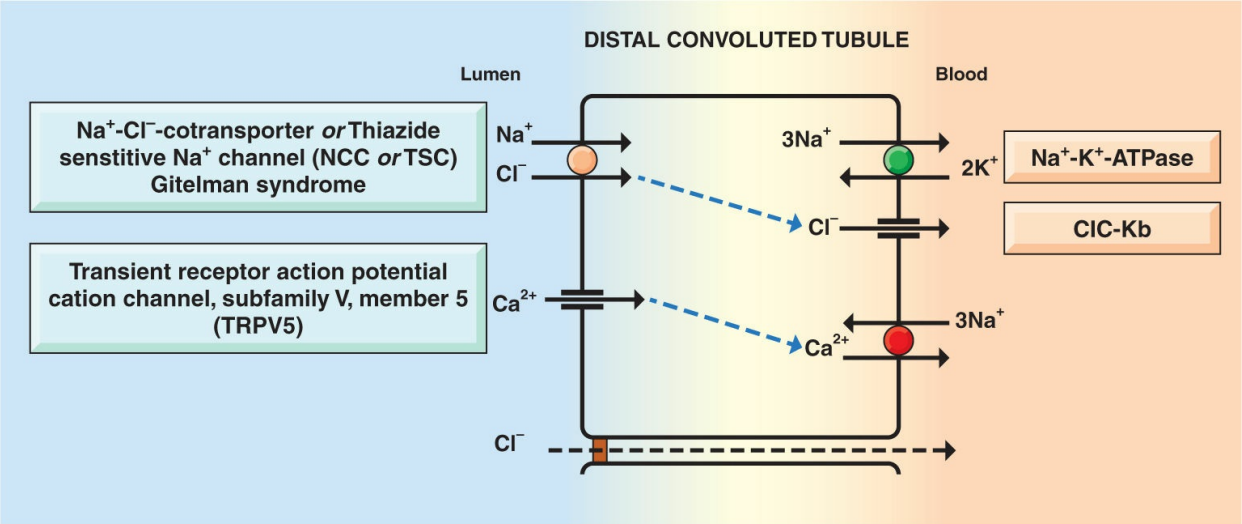

FIGURE 2.20 Transport mutation in Gitelman syndrome.

Mutations associated with GS

- Loss-of-function mutation of NCC is responsible for GS.
- Note that ClC-Kb is also present in DCT. This may partly explain mixed BS and GS phenotypes and lack of hypercalciuria with mutations involving ClC-Kb function.

Drug-induced Gitelman-like syndrome

- Although rare, cisplatin has been reported to cause a Gitelman-like syndrome. Pathogenesis is unknown but proposed to be due to cisplatin-induced *NCC* gene injury and DCT apoptosis.

Clinical manifestations of GS

- May present in early childhood or adulthood
- Symptoms are associated with volume depletion and electrolyte disturbances: dizziness, salt craving, polyuria possibly due to chronic hypokalemia–induced nephrogenic diabetes insipidus, hypotension, neuromuscular irritability, weakness, cramps.
- HTN may present later in life in some patients with GS, presumably due to the chronic activation of RAAS without the countereffect of PGE2 as seen in patients with BS.
- Laboratory findings in addition to hypokalemia and metabolic alkalosis: Hypomagnesemia is present in 100% of patients (although may be absent at early disease presentation), hypocalciuria, normal urinary PGE2 level.

- Hypocalciuria and chondrocalcinosis: Reduced Na^+ reabsorption stimulates basolateral Na^+-Ca^{2+} exchanger activity and thereby increases Ca^{2+} reabsorption and risk for systemic chondrocalcinosis. See **Figure 2.20**.
- Unlike BS, hypomagnesemia is present in almost all patients with GS and is often severe. Reasons are not clear but may be suggested below:
  - There are apoptotic and/or histologic changes in DCT in patients with GS that could affect DCT Mg^{2+} reabsorption, but not in patients with BS. These changes are thought to occur later than other electrolyte disturbances and, thus, the absence of hypomagnesemia in early disease.
  - Compensatory DCT Mg^{2+} reabsorption with loop Mg^{2+} wasting

Diagnosis of BS and GS

- Suggested laboratory studies to obtain:
  - Blood gas and routine chemistry, serum magnesium:
    - Confirm the presence of hypokalemia and metabolic alkalosis.
    - Severe hypomagnesemia is more common and severe in GS than BS.
  - Urine studies:
    - Urine osmolality: Isosthenuric or hyposthenuric urine (i.e., urine osmolality < serum osmolality) is typically present in patients with bs but may be normally concentrated per volume status in those with gs.
    - Urine chloride is persistently elevated.
    - Urine calcium-to-urine creatinine ratio: Low ratios suggest GS, whereas high ratios suggest BS. A ratio of <44 mg/g is typical for gs and >200 mg/g for BS.

Management of BS and GS

- Potassium and magnesium supplement as needed
- Consider renin–angiotensin–aldosterone inhibitors (K-sparing diuretic)
- Cyclooxygenase COX-2 inhibitors may be considered in poorly controlled BS with hyperprostaglandin syndrome.

Special Notes regarding Metabolic Complications with Urinary Diversions (Table 2.4)

Table 2.4 Metabolic disturbances with urinary diversions

	Acid–Base Disturbances	Electrolyte Disturbances	Comments
Gastric segment (used as a patch for bladder augmentation)	**Metabolic alkalosis**	Hyponatremia, hypokalemia	• Metabolic alkalosis is thought to be due to increased gastrin secretion from the gastric patch that stimulates gastric HCl secretion and urinary acid excretion.
Jejunum (ureterojejunostomy)	Metabolic acidosis	Hyponatremia, **hyperkalemia**	• Hyperkalemia is thought to be due to increased K^+ absorption by jejunum. • The jejunum also avidly absorbs free water and potentially contributes to hyponatremia.
Ileal and colonic segments (ileal conduit, ureterosigmoid anastomosis)	Metabolic acidosis	Hypokalemia	• When ileal and colonic segments are exposed to urine, HCO_3^- is secreted in exchange for Cl^- absorption by the gut mucosa. • Urinary urea is metabolized to NH_4^+ and HCO_3^- by intestinal bacteria. While HCO_3^- is excreted into the stool, NH_4^+ is absorbed by colonic mucosa and transported to the liver via portal circulation where they undergo metabolism into urea + H^+.

Notes: In general, the longer the intestinal segment used and the longer the contact time between urine and intestinal segment, the worse the metabolic complications. Metabolic acidosis is typically worse for ureterosigmoid anastomosis than ileal conduit due to greater contact time between the urine and the longer segment involved with the former procedure. Important differences are bolded.

- Gastric segment:
  - May be used as a patch for bladder augmentation
  - Hypokalemia and metabolic alkalosis may occur.
  - Metabolic alkalosis is thought to be due to increased gastrin secretion from the gastric patch that stimulates gastric HCl secretion and urinary acid excretion.
- Jejunum segment:
  - May be used for ureterojejunostomy
  - Hyperkalemia and metabolic acidosis may occur.
  - Hyperkalemia is thought to be due to increased K^+ absorption by jejunum.

- Jejunum segment also avidly absorbs electrolyte free water, thereby potentially contributes to hyponatremia in patients with high free water intake.

- Ileum and colon segments:
  - May be used as ileal conduit, ureterosigmoid anastomosis
  - Hypokalemia and metabolic acidosis may occur.
  - Metabolic acidosis:
    - When ileal and colonic segments are exposed to urine, HCO_3^- is secreted in exchange for Cl^- absorption by the gut mucosa.
    - Urinary urea is metabolized to NH_4^+ and HCO_3^- by intestinal bacteria. While HCO_3^- is excreted into the stool, NH_4^+ is absorbed by colonic mucosa and transported to the liver via portal circulation where they undergo metabolism into urea plus H^+.
- In general, the longer the intestinal segment used and the longer the contact time between urine and intestinal segment, the worse the metabolic complications. Metabolic acidosis is typically worse for ureterosigmoid anastomosis than ileal conduit due to greater contact time between the urine and the longer segment involved with the former procedure.
- As urine contact time is typically short with ileal conduit due to rapid drainage into an external collection bag, metabolic acidosis should not occur. If severe metabolic acidosis develops in patients with ileal conduit, a loopogram should be considered to rule out obstruction.

CHAPTER 3

Calcium, Phosphorus, Magnesium, Stones

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DISORDERS OF CALCIUM METABOLISM

Calcium Background

- Calcium is mostly bound and associated with bones (~99% of total body calcium, ~1 kg).
- Extracellular calcium concentration ranges from: 9.0 to 10.6 mg/dL
  - 40% to 50% is protein bound (mostly albumin). Corrected total serum calcium concentration (S_{Ca}) for patients with hypoalbuminemia may be estimated as:

    $$= \text{Measured } S_{Ca} + 0.8 \times (4.0 - \text{serum albumin concentration})$$

  - 55% is diffusible (ultrafilterable)
    - 40% to 50% exists as free ionized calcium.
    - 10% is complexed (e.g., to bicarbonate, citrate, phosphate anions).
- Intracellular calcium concentration is minute at approximately 100 nmol/L but may increase up to 10- to 100-fold during various cellular functions.
- Physiologic roles of calcium: skeletal composition, neuromuscular excitation, cardiac and muscle contractility/function

Calcium Metabolism

Gastrointestinal (GI) tract (Fig. 3.1)

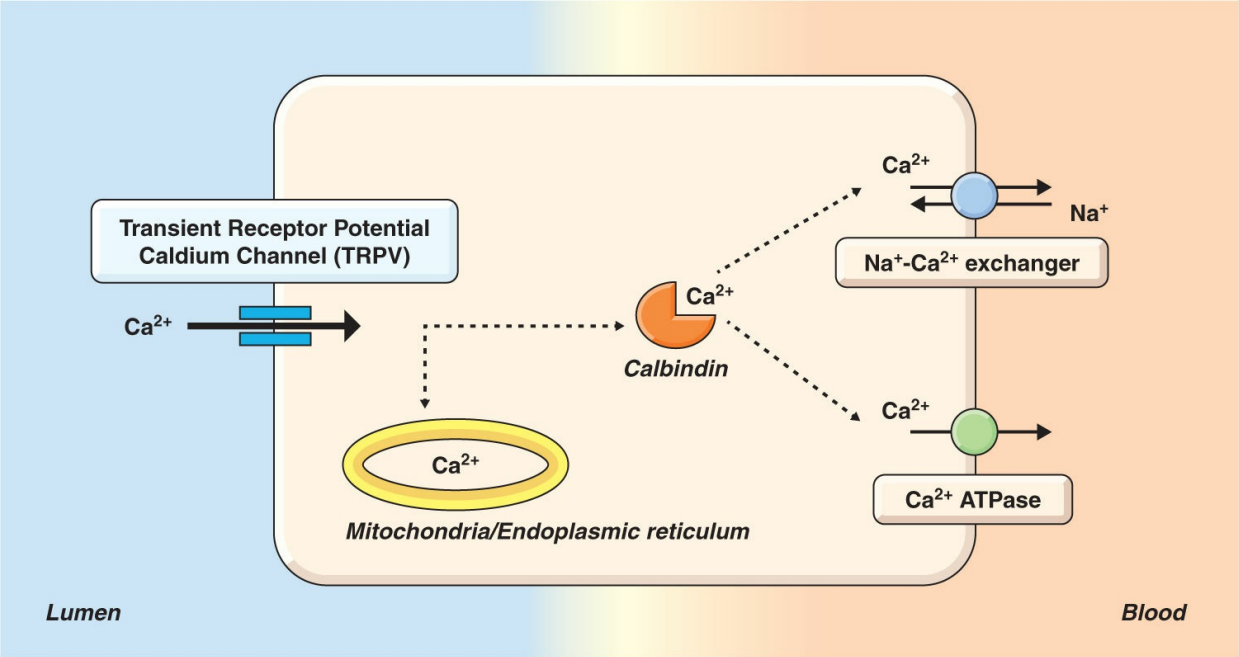

FIGURE 3.1 Epithelial calcium transport is similar in both enterocytes and renal distal tubules. In enterocytes, the responsible calcium channel is TRPV6. In renal distal tubules, the channel is TRPV5.

- Dietary calcium intake is approximately 1 g/d. 20% is absorbed by the GI tract.
  - *Paracellular* absorption does not depend on vitamin D but is based on the favorable intraluminal gradient at the jejunum and ileum when calcium intake is high.
  - *Transcellular* absorption occurs primarily in the duodenum when calcium intake is low:
    - Apical uptake by enterocytes is via the transient receptor potential TRPV6 calcium channel.
    - Cytoplasmic Ca^{2+} is taken up into mitochondria or endoplasmic reticulum or transported into the basolateral side via Ca^{2+}-ATPase, or in the presence of high intracytoplasmic Ca^{2+} concentration, via the Na^{+}-Ca^{2+} exchanger.
    - Calbindin D_{9k} mediates Ca^{2+} transport across enterocytes into circulation.
- Hormonal upregulation of GI absorption:

- Calcitriol [1,25$(OH)_2$D]: 1,25$(OH)_2$D binds to its receptor (VDR) to increase TRPV6 expression, calbindin D_{9k}, and Ca^{2+}-ATPase, all acting in concert to increase Ca^{2+} absorption.
- Others: parathyroid hormone (PTH), estrogens, prolactin, growth hormone

- Intestinal Ca^{2+} absorption may be:
  - Increased in acromegaly (growth hormone, calcitriol), pregnancy and puberty (calcitriol), and excess vitamin D ingestion
  - Decreased with older age; diet with low Ca^{2+}/PO_4^{2-} ratio or high vegetable fiber, fat, or fructose; estrogen deficiency; corticosteroid use; or various medical conditions, including diabetes, kidney failure, malabsorptive disorders

Renal handling (Fig. 3.2)

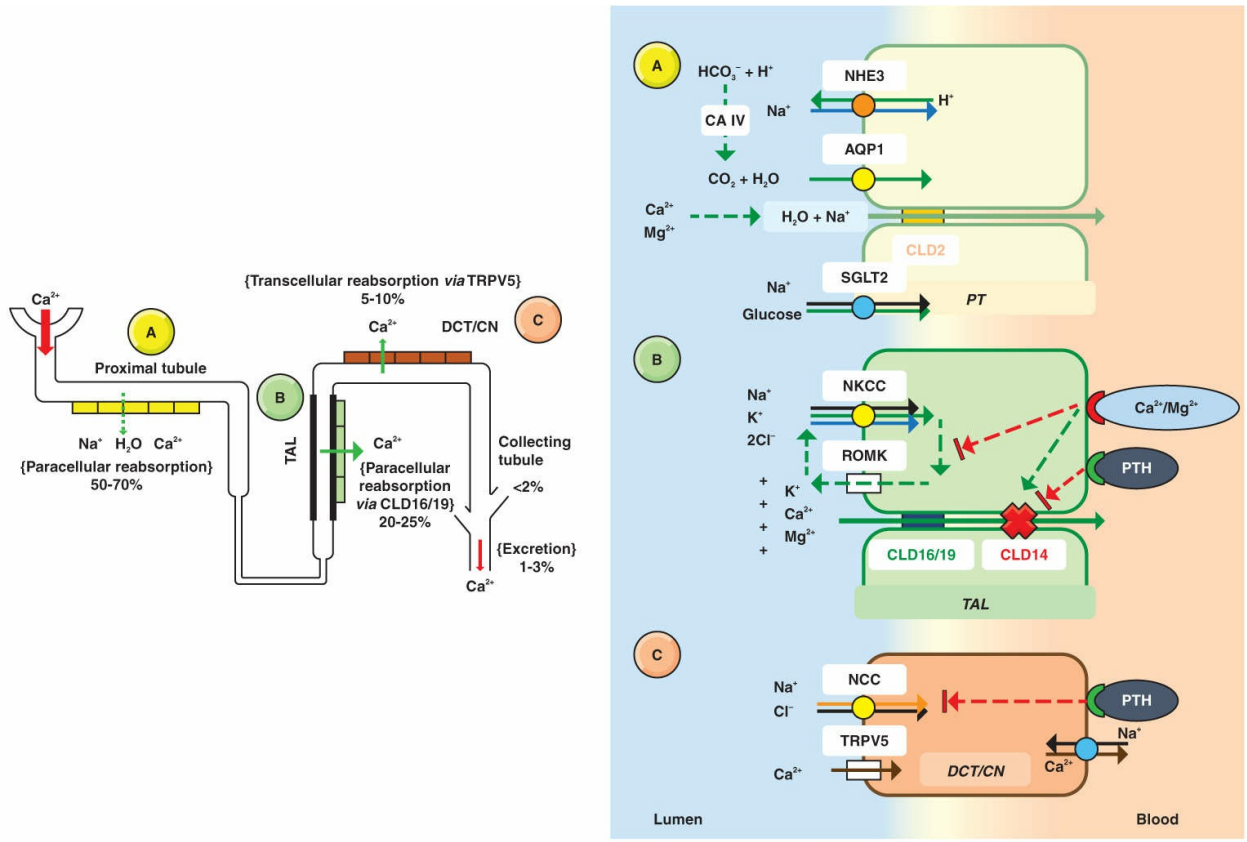

FIGURE 3.2 Renal handling of calcium. Ultrafilterable Ca^{2+} load is determined by glomerular filtration rate, glomerular surface, PTH-regulated ultrafiltration coefficient, and acid–base status. **A.** Ca^{2+} reabsorption follows sodium and water reabsorption paracellularly in the proximal tubules. Anything that inhibits sodium reabsorption at this segment may lead to calciuria (e.g., carbonic anhydrase inhibitor, SGLT2 inhibitor). **B.** Ca^{2+} reabsorption at the TAL occurs paracellularly, a process facilitated by the CLD16/19 complex and inhibited by CLD14. The binding of Ca^{2+} to CaSR inhibits ROMK while stimulating CLD14. The former results in reduced intraluminal K^+ recycling, reduced positively charged lumen, thus increased calciuria/magnesiuria, while the latter results in inhibition of Ca^{2+}/Mg^{2+} paracellular reabsorption. In contrast, PTH inhibits CLD14 and results in increased paracellular reabsorption of Ca^{2+}/Mg^{2+}. **C.** Ca^{2+} reabsorption at the DCT/CN occurs transcellularly via the calcium channel TRPV5. PTH can inhibit NCC, thus Na^+ entry at this segment. The reduced intracellular Na^+ favors basolateral Na^+ entry via the Na^+-Ca^{2+} exchanger, thereby enhancing Ca^{2+} reabsorption. Additionally, PTH increases TRPV5 expression for Ca^{2+} reabsorpion. Abbreviations: AQP1, aquaporin 1; CA, carbonic anhydrase; CLD, claudin; DCT/CN, distal convoluted tubule/connecting segment; NCC, sodium chloride cotransporter; NHE3, sodium hydrogen exchanger; NKCC, sodium potassium 2 chloride cotransporter; PTH, parathyroid hormone; ROMK, renal outer medullary potassium channel; SGLT2, sodium glucose cotransporter 2; TAL, thick ascending limb of Henle loop; TRPV5, transient receptor potential cation channel subfamily V5.

Glomerular filtration

- 8 to 10 g of calcium is filtered daily.
- Ultrafilterable Ca^{2+} load is determined by glomerular filtration rate (GFR), glomerular surface, ultrafiltration coefficient K_f, and plasma calcium

concentration.
  - PTH reduces glomerular K_f, hence ultrafiltered Ca^{2+} load.
  - Respiratory and metabolic acidoses increase plasma ionized Ca^{2+} (iCa^{2+}), hence increased ultrafilterable Ca^{2+} load and wasting.
  - Acidemia enhances bone release of Ca^{2+}, hence increased ultrafilterable Ca^{2+} load and potential renal wasting.
- Despite the high amount of glomerular filtration of calcium, daily urinary excretion is ≤200 mg/d, due to effective tubular reabsorption along the entire nephron.

Proximal tubules

- Ca^{2+} is reabsorbed paracellularly via convection along with Na^+ and water. Low intraluminal Na^+ at this segment enhances Na^+ and water as well as Ca^{2+} reabsorption. This is the reason for dietary sodium restriction in patients with kidney stones.
- Drugs that reduce proximal tubular Na^+ reabsorption hence Ca^{2+} reabsorption include:
  - Any osmotic diuretic agent that limits Na^+ and water reabsorption reduces proximal Ca^{2+} reabsorption. Example: mannitol.
  - Tenapanor, a sodium hydrogen exchanger 3 (NHE3) inhibitor, may be associated with calciuria.
  - Carbonic anhydrase inhibitors that reduce sodium transport via indirect inhibition of NHE3 may also lead to calciuria.
  - Sodium glucose cotransporter type 2 (SGLT2) inhibitors

Thick ascending limb of Henle loop (TAL)

- Ca^{2+} reabsorption occurs paracellularly. This process is regulated by multiple factors.
  - Facilitators:
    - The positive luminal charge created by K^+ recycling via renal outer medullary potassium channel (ROMK) following Na^+-K^+-$2Cl^-$ reabsorption that drives Ca^{2+} and Mg^{2+} paracellular reabsorption.
    - Claudin 16/19 paracellular shunt for Ca^{2+} and Mg^{2+} reabsorption
  - Inhibitors:

        - Paracellular claudin 14
    - Regulators:
        - Activation of calcium-sensing receptor (CaSR) by high extracellular Ca^{2+} inhibits ROMK, hence reduced intraluminal K^{+} recycling and the associated positively charged lumen that drives paracellular Ca^{2+} reabsorption.
        - PTH enhances TAL paracellular Ca^{2+} reabsorption by inhibiting claudin 14 expression upon binding to the PTH receptor (PTH1R).
    - Drugs that affect Ca^{2+} reabsorption at TAL:
        - Calcimimetics activate CaSR.
        - Loop diuretics reduce paracellular Ca^{2+} reabsorption by inhibiting sodium potassium 2 chloride cotransporter (NKCC2), subsequent ROMK activity, thus the positive luminal charge necessary to facilitate Ca^{2+} reabsorption.

Distal convoluted tubules and connecting segment (DCT/CN)

- Luminal uptake of Ca^{2+} occurs transcellularly via the apical TRPV5 calcium channel, followed by reabsorption into the basolateral side via Ca^{2+}-ATPase and Na^{+}-Ca^{2+} exchanger.
- Regulators of Ca^{2+} reabsorption at DCT/CN
    - PTH increases Ca^{2+} reabsorption at DCT/CN by:
        - Increasing TRPV5 activity and abundance
        - Inhibiting the sodium chloride transporter (NCC): see Mechanism below
    - Calcitriol increases TRPV5 expression
- Drugs that affect Ca^{2+} reabsorption at the DCT/CN:
    - Thiazides and amiloride increase Ca^{2+} reabsorption. Implicated mechanisms:
        - The relative volume depletion associated with thiazide diuretic use may increase proximal tubular Ca^{2+} reabsorption.
        - The inhibition of Na^{2+} reabsorption at the DCT/CN by thiazides/amiloride, respectively, hyperpolarizes the membrane voltage, thereby facilitating Ca^{2+} influx. This effect has been shown

to be inhibited by dihydropyridine-type calcium channel blockers (CCBs).

Calcium Regulation (Fig. 3.3)

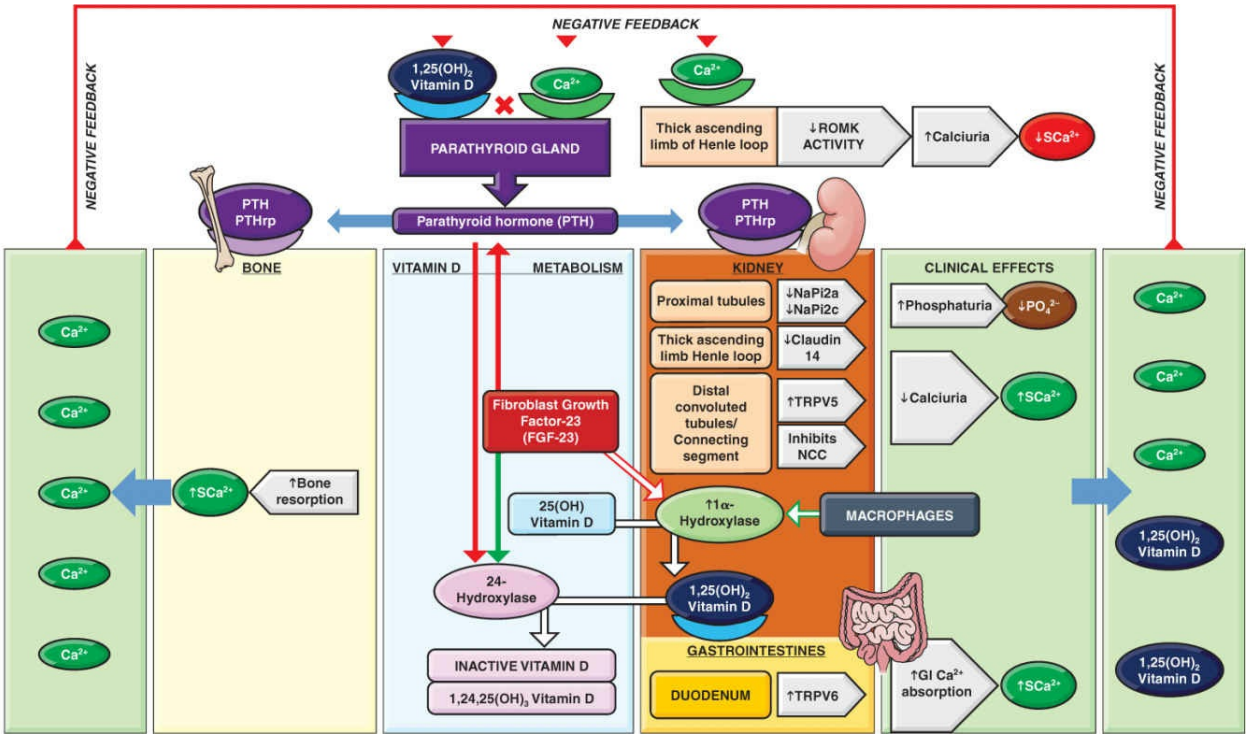

FIGURE 3.3 Calcium metabolism. Parathyroid hormone (PTH) released from parathyroid gland binds to its receptor PTH1R in the bones and kidneys. In bones, this leads to increased bone resorption. In kidneys, there is reduced calciuria in the thick ascending limb of Henle loop and distal convoluted tubules/connecting segment. Additionally, PTH stimulates 1α-hydroxylase, which increases the hydroxylation of 25(OH)D to $1,25(OH)_2D$. The latter increases gastrointestinal Ca^{2+} absorption. All effects driven by PTH lead to increased serum Ca^{2+} level. The resulting increase in $1,25(OH)_2D$ and Ca^{2+} in turn bind to their respective receptors in the parathyroid gland as negative feedback to reduce PTH synthesis and release. Of note, the fibroblast growth factor (FGF-23) reduces $1,25(OH)_2D$ levels via inhibition of 1-α hydroxylase while stimulating 24-hydroxylase activity. The latter deactivates $1,25(OH)_2D$ into $1,24,25(OH)_2$-vitamin D. FGF-23 also exerts an inhibitory effect on the parathyroid gland. Abbreviations: GI, gastrointestinal; Na-Pi, sodium phosphate cotransporter; NCC, sodium chloride transporter; PTHrp, parathyroid hormone–related peptide; ROMK, renal outer medullary potassium channel; SCa^{2+}, serum calcium level; TRPV5, transient receptor potential calcium channel. Red arrows, inhibitory; Green solid arrows, stimulatory; Black open arrows, enzymatic transformation; Unidirectional blue arrows, Systemic effects; Double headed blue arrow, End organ effect of PTH or PTHrp; Red X, negative feedback on PTH gland.

Parathyroid hormone

- PTH is the key regulatory hormone to maintain calcium homeostasis.
- PTH binds to its receptor PTH1R and exerts its physiologic effects via

bones and kidneys.

- PTH effects on bones:
  - **Chronic/prolonged** PTH exposure increases bone resorption via increasing the bone resorption mediator *R*eceptor *A*ctivator of *N*F-κB *L*igand (RANKL) level while suppressing the secretion of the anti-osteoclastogenesis factor OPG. RANKL is normally secreted by osteoblasts to stimulate osteoclastic proliferation and activity (increase bone resorption).
  - **Intermittent** increase/administration of PTH increases bone mass via increasing osteoblast proliferation and survival.
- PTH effects on kidneys:
  - TAL: PTH enhances TAL paracellular Ca^{2+} reabsorption via inhibition of claudin 14 expression.
  - DCT/CN: PTH increases DCT/CN transcellular Ca^{2+} reabsorption by increasing apical expression of the calcium channel TRPV5 and reducing NCC activity.
  - Increase 1α-hydroxylase activity: The resultant increase in $1,25(OH)_2D$ level [via hydroxylation of 25(OH)D] leads to increased intestinal calcium absorption.
- Regulators of PTH:
  - Inhibitory factors:
    - $1,25(OH)_2D$ inhibits parathyroid cells via binding to vitamin D receptor (VDR).
    - Extracellular ionized calcium (iCa^{2+}) inhibits parathyroid cells via binding to CaSR.
    - Fibroblast growth factor (FGF-23) inhibits PTH transcription and secretion.
  - Stimulatory factors:
    - Hypocalcemia
    - Hypovitaminosis D
    - Hyperphosphatemia

Vitamin D Metabolism (Fig. 3.4)

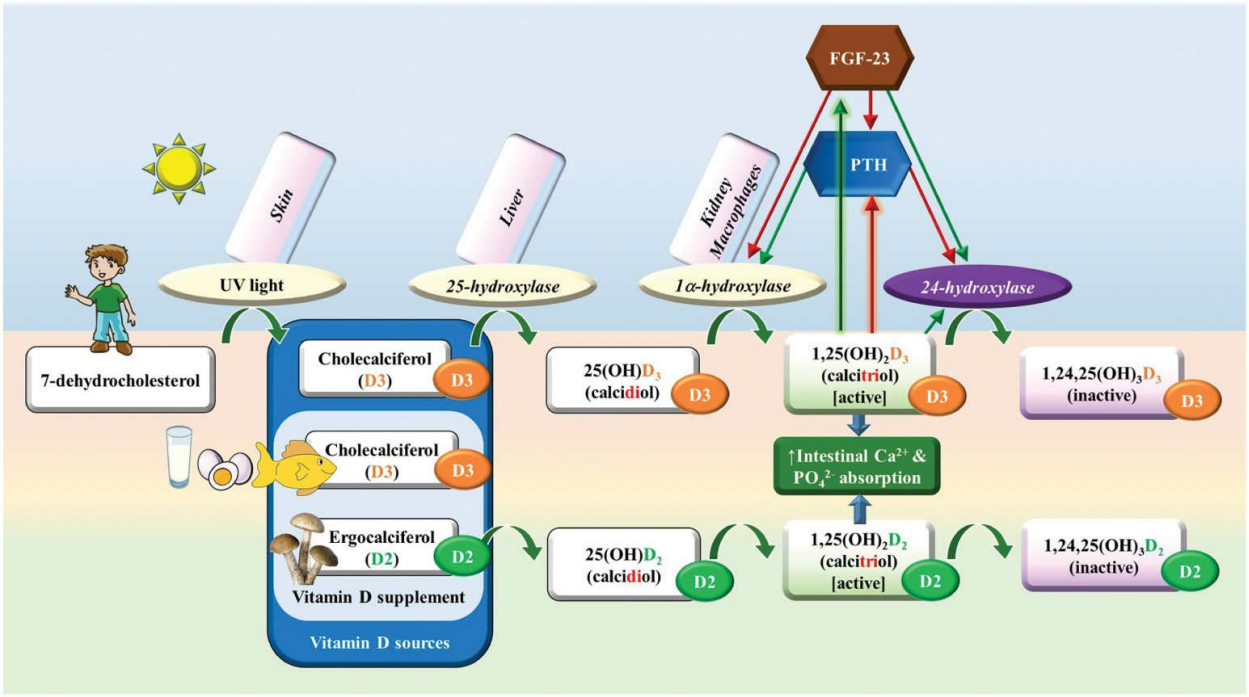

FIGURE 3.4 Vitamin D metabolism. *Red arrows*: inhibitory effect; *Green arrows*: stimulatory effect. D_2 and D_3 refer to the source of vitamin D: D_2 is plant based, whereas D_3 is animal or human derived. "Diol" and "triol" refer to the number of OH groups present on vitamin D. Both cholecalciferol and ergocalciferol have one existing OH group prior to the 25-hydroxylation step. 25-Hydroxylation by the liver converts these molecules into "diol" and subsequent 1α-hydroxylation by the kidneys converts them into "triol." Abbreviations: 1,25(OH)$_2$D, 1,25-dihyroxy-vitamin D; 25(OH)D, 25-hydroxy-vitamin D; FGF-23, fibroblast growth factor 23; NCC, sodium chloride transporter; PTH, parathyroid hormone; UV, ultraviolet.

- Ultraviolet (UV) light (skin exposure) converts 7-dehydrocholesterol to *cholecalciferol.*
- Liver hydroxylates cholecalciferol at the 25-carbon to 25(OH)D.
- Kidney hydroxylates 25(OH)D (via 1α-hydroxylase) to 1,25(OH)$_2$D. This is calcitriol, the most biologically active form of vitamin D.
- 24-Hydroxylation of 1,25(OH)$_2$D (by 24-hydroxylase) to 1,24,25(OH)$_3$—vitamin D renders vitamin D inactive.
  - Overactivity of 24-hydroxylase leads to 1,25(OH)$_2$D deficiency.
  - Underactivity of 24-hydroxylase (e.g., loss-of-function mutation of the enzyme) leads to 1,25(OH)$_2$D excess.
  - Regulation of 24-hydroxylase:
    - PTH decreases 24-hydroxylase activity.
    - Vitamin D receptor agonist (VDRA), that is, 1,25(OH)$_2$D, increases

24-hydroxylase activity.
    - The fibroblast growth factor 23 (FGF-23) increases 24-hydroxylase activity while decreasing 1α-hydroxylase activity. The former results in increased inactivation of $1,25(OH)_2D$, whereas the latter results in reduced $1,25(OH)_2D$ formation. Essentially, FGF-23 is "anti" $1,25(OH)_2D$.
- Of note, $1,25(OH)_2D$ synthesis increases during puberty, pregnancy, and lactation.
- Physiologic effects of $1,25(OH)_2D$:
    - Increases intestinal absorption of calcium and phosphate
    - Stimulates FGF-23 and 24-hydroxylase
    - Provides negative feedback on PTH via:
        - Reducing PTH gene transcription
        - Increasing VDR and CaSR expressions on parathyroid cells
        - Reducing parathyroid cell proliferation
    - Maintains healthy bone formation and mineral homeostasis
    - Regulates various cellular functions involving the immune and cardiovascular systems and the differentiation, proliferation, and apoptosis of normal and malignant cells

Parathyroid Hormone

- Primary function is to increase ionized calcium level in response to hypocalcemia
    - Increases $1,25(OH)_2D$ level via:
        - Stimulation of 1α-hydroxylase activity
        - Inhibition of 24-hydroxylase activity
    - Increases calcium reabsorption at TAL and DCT/CN
- PTH also induces phosphaturia by suppressing the transcriptions of genes encoding proximal tubular sodium phosphate transporters NPT2a and NPT2c that normally function to reabsorb luminal phosphate.
- FGF-23 has an inhibitory effect on PTH synthesis and secretion. However, this effect is blunted in advanced CKD.

Fibroblast Growth Factor 23

- FGF-23 is a peptide produced by osteocytes and osteoblasts.
- Functions of FGF-23:
  - Induces phosphaturia by suppressing proximal tubular NPT2a and NPT2c expressions
  - Reduces $1,25(OH)_2D$ activity via inhibition of 1α-hydroxylase and stimulation of 24-hydroxylase activity
  - Inhibits PTH
- Regulatory factors of FGF-23:
  - Factors that can increase FGF-23 level: $1,25(OH)_2D$, phosphate, PTH, calcium, inflammatory markers, angiotensin II and aldosterone, hypoxia, anemia, erythropoietin, magnesium deficiency, lithium, obesity, diabetes
  - Factors that can decrease FGF-23 level: insulin/insulin-like growth factor-1 (IGF1), hypocalcemia
  - FGF-23 is upregulated by increased phosphate "burden" (not necessarily actual hyperphosphatemia) and $1,25(OH)_2D$. In chronic kidney disease (CKD), FGF-23 level increases *before* PTH increase.
- Increased FGF-23 level has been shown to be associated with:
  - Increased mortality in critically ill patients with and without acute kidney injury (AKI)
  - Left ventricular hypertrophy, heart failure, volume status in patients with end-stage kidney disease (ESKD)
  - Bone loss
  - Infectious complications, increased inflammatory cytokines
  - Reduced erythrocytosis (anemia of CKD)

Calcium Intake and Cardiovascular Outcomes

- 2019 meta-analysis based on sources from PubMed, Cochrane Central, Scopus, and Web of Science, published from inception dates up to March 2019, involving 26 prospective cohort studies and 16 randomized controlled trials (RCTs) revealed:
  - Data from cohort studies revealed that **dietary calcium** intake ranging from 200 to 1,500 mg/d did not affect the risk of cardiovascular disease, coronary heart disease (CHD), or stroke.

- However, **calcium supplements** alone may raise CHD risk, especially myocardial infarction (MI).

HYPERCALCEMIA

Causes of Hypercalcemia

Pseudohypercalcemia

Pseudohypercalcemia refers to having elevated total serum calcium but with normal or low ionized calcium levels. Pseudohypercalcemia has been reported with hyperalbuminemia (excessive albumin infusion), prolonged use of tourniquet with venopuncture, dehydration, paraproteinemia/hyperlipidemia (interference with automated chemistry analyzers), abnormally elevated calcium-binding globulin in hypergammaglobulinemia, and thrombocytosis.

True hypercalcemia

- The differential diagnoses of true hypercalcemic disorders may be based on major levels involved in normal calcium regulation (**Fig. 3.5 and Table 3.1**).

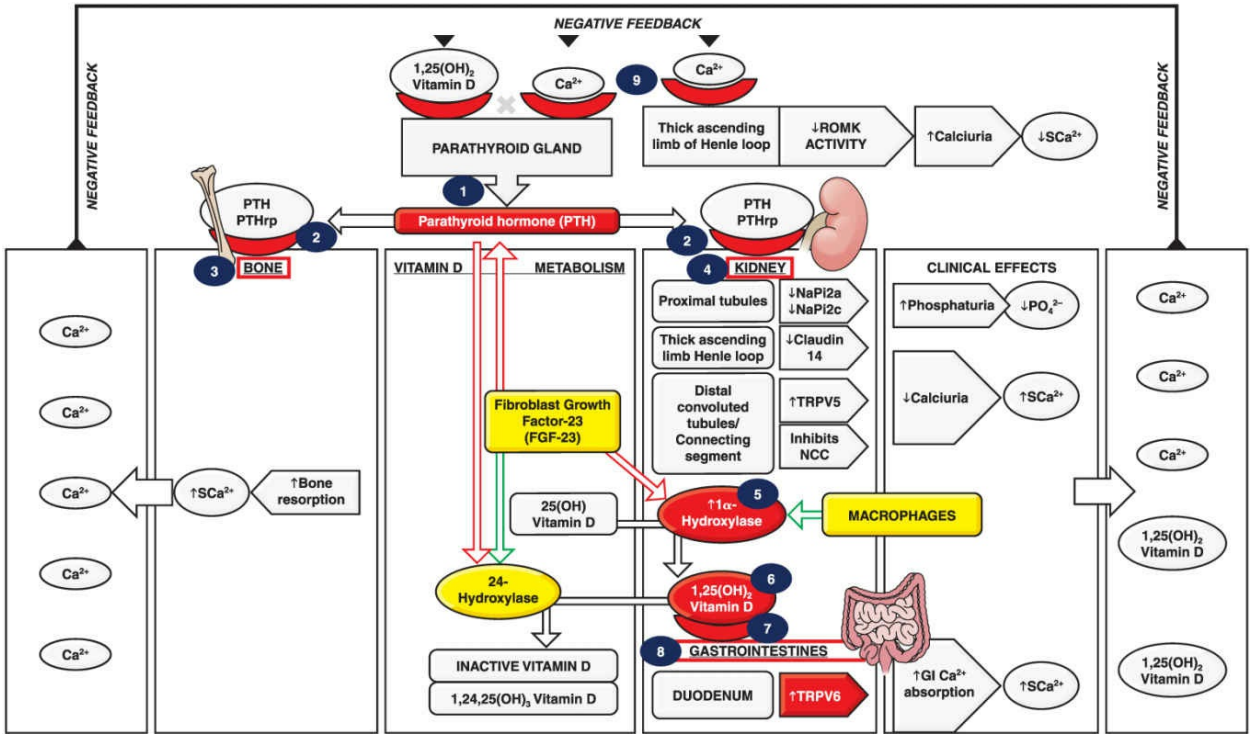

FIGURE 3.5 Calcium disorders may arise at different levels of calcium metabolism. **1:** Parathyroid

hormone; **2:** Parathyroid receptor; **3:** Bone metabolism; **4:** Renal calcium excretion; **5:** 1α-Hydroxylase; **6:** $1,25(OH)_2D$; **7:** Vitamin D receptor; **8:** Intestinal calcium absorption; and **9:** Calcium-sensing receptor. See Table 3.1 for hypercalcemic conditions that correspond to these 9 different levels of calcium metabolism. Abbreviations: GI, gastrointestinal; Na-Pi, sodium phosphate cotransporter; PTHrp, parathyroid hormone–related peptide; ROMK, renal outer medullary potassium channel; SCa^{2+}, serum calcium level; TRPV5, transient receptor potential calcium channel.

Table 3.1 Hypercalcemic disorders as they correspond to different levels of calcium metabolism

No.	Normal Calcium Regulation	Level of Pathology	Corresponding Hypercalcemic Conditions	Expected Laboratory Findings
1	Parathyroid gland	**PTH**	• Parathyroid hyperplasia, adenoma, carcinoma • PTHrp (paraneoplastic syndrome, pregnancy) • Drug-induced hyperparathyroidism: Lithium	• Serum: Hypercalcemia; hypophosphatemia; ↑PTH and ↑$1,25(OH)_2D$ levels • Urine: Hypercalciuria; phosphaturia
2	PTH binds to the receptor PTH1R	**PTH1R**	• Gain-of function mutation of PTH1R (Jansen disease)	• Serum: Hypercalcemia; hypophosphatemia; ↑$1,25(OH)_2D$ level, ↓PTH • Urine: Hypercalciuria; phosphaturia
3	PTH binding to PTH1R leads to: A. Increased bone resorption	**Bone**	• Metastatic malignancy • Presence of osteoclastic activating factors (multiple myeloma) • Drug induced (excess vitamin A) • Immobilization • Paget disease	• Serum: Hypercalcemia; normo- to hyperphosphatemia; ↓PTH and ↓$1,25(OH)_2D$ levels • Urine: Hypercalciuria
4	B. Reduced renal Ca^{2+} excretion	**Kidney**	• TAL: inactivating mutation of CaSR (familial hypocalciuric hypercalcemia [FHH])	• Serum: Hypercalcemia; normo- to hypophosphatemia; ↑PTH and ↑$1,25(OH)_2D$ levels • Urine: Hypocalciuria; phosphaturia • Serum: Hypercalcemia;

			• DCT/CN: • Thiazide diuretics; amiloride	↓PTH and ↓$1,25(OH)_2D$ levels; normo- to hyperphosphatemia • Urine: Hypocalciuria
5	C. Increased 1**α**-hydroxylase activity	**1α-Hydroxylase**	• Granulomatous disease • Inactivating mutation of 24-hydroxylase	• Serum: Hypercalcemia; normo- to hyperphosphatemia; ↑$1,25(OH)_2D$ level; ↓PTH level • Urine: Hypercalciuria
6	Increased $1,25(OH)_2D$ level	**1,25(OH)D**	• Tumor producing calcitriol (lymphomas, leiomyoblastoma) • Vitamin D ingestion	• Serum: Hypercalcemia; normo- to hyperphosphatemia; ↑$1,25(OH)_2D$ level, ↓PTH level • Urine: Hypercalciuria
7	$1,25(OH)_2D$ binds to its receptor VDR	**VDR**	• Gain-of-function mutations of VDR or its regulatory proteins*	• Serum: Hypercalcemia; normo- to hyperphosphatemia; ↓$1,25(OH)_2D$ level, ↓PTH
8	Binding of $1,25(OH)_2D$ to VDR leads to increased intestinal Ca^{2+} reabsorption	**GI tract**	• Excess calcium ingestion	• Serum: Hypercalcemia; normo- to hyperphosphatemia (milk-alkali); phosphate level may be low with calcium carbonate due to its phosphate-binding effect; ↓$1,25(OH)_2D$ and ↓PTH levels • Urine: Hypercalciuria
9	Ca^{2+} binds to its receptor CaSR: • at TAL to increase urinary Ca^{2+} excretion *and* • at PTH gland as negative feedback to reduce PTH	**CaSR**	• Inactivating mutation of CaSR (FHH) • Autoimmune disease with autoantibodies to CaSR	• Serum: Hypercalcemia; normo- to hypophosphatemia; ↑PTH and ↑$1,25(OH)_2D$ levels • Urine: Hypocalciuria; phosphaturia

Note: Refer to **Figure 3.5** for corresponding step numbers.

*Theoretical mutations/defects. Abbreviations: CaSR, calcium-sensing receptor; DCT/CN, distal convoluted tubule/connecting segment; GI, gastrointestinal tract; PTH, parathyroid hormone; PTH1R,

parathyroid hormone receptor 1; PTHrp, parathyroid hormone–related peptide; SCa^{2+}, serum calcium level; TAL, thick ascending limb of Henle loop; TRPV5, transient receptor potential calcium channel; VDR, vitamin D receptor.

- Classic primary hyperparathyroidism (PHPT), hypercalcemic PHPT:
  - Patients present with both elevated PTH levels and hypercalcemia.
  - Parathyroid adenoma (80%), diffuse hyperplasia (10% to 15%), or carcinoma (5%)
  - Multiple endocrine neoplasia type 1 (MEN-1):
    - Autosomal dominant inactivating germline mutation of a tumor-suppressor gene (*MEN-1* gene)
    - May involve parathyroid, anterior pituitary, enteropancreatic, other endocrine tumors
  - Multiple endocrine neoplasia type 2A (MEN-2A):
    - Autosomal dominant activating mutation of the RET proto-oncogene
    - May involve thyroid medulla, adrenal medulla, parathyroid with associated increase in calcitonin, catecholamines, and PTH

Normocalcemic PHPT

- Patients present with elevated PTH levels but normal serum calcium levels.
- Diagnosis of normocalcemic PHPT is a diagnosis of exclusion. The following secondary causes of hyperparathyroidism must be ruled out:
  - Conditions that could directly stimulate PTH secretion (e.g., vitamin D deficiency, malabsorptive disorders, primary hypercalciuria, CKD, metabolic bone diseases, lithium use, thiazide diuretics, tyrosine kinase inhibitors [sunitinib, imatinib can induce skeletal resistance to PTH, hence secondary hyperparathyroidism])
  - Conditions that could induce mild hypocalcemia and result in increased PTH secretion (e.g., use of bisphosphonate or denosumab)
  - Prevalence of clinical manifestations such as kidney stones, low bone mineral density, and hypertension (HTN) has been reported to be similar to those with hypercalcemic PHPT.

Nonhormonal PHPT

- Patients with PHPT who present with elevated S_{Ca} levels but normal PTH

level.

- Clinical manifestations have been reported to be similar to those with classic PHPT.

PTH-related peptides (PTHrp)

- Hypercalcemia of pregnancy:
  - PTHrp is produced from mammary and placental tissues in response to prolactin-receptor activation.
  - Treatment: bromocriptine
- Paraneoplastic syndromes associated with breast cancer and squamous cell lung carcinoma

Gain-of-function mutation of the PTH receptor (PTH1R): Jansen disease

- Rare hereditary condition due to activating mutations of the PTH receptor (PTH1R)
- Clinical manifestations: short-limbed dwarfism, severe hypercalcemia, hypophosphatemia, and metaphyseal chondrodysplasia

Increased bone resorption

- Malignancy:
  - Direct invasion (bone metastatic disease)
  - PTHrp
  - Osteoclastic activating factors (interleukins IL-1, IL-6), prostaglandins, transforming growth factors, tumor necrosis factor α
  - Immobilization (increased bone resorption)
- Paget disease with excessive bone resorption followed by increase in bone formation and sclerosis

Increased 1α-hydroxylase activity

- Granulomatous diseases (e.g., tuberculosis, sarcoidosis, berylliosis):
  - Due to increased 1α-hydroxylase activity in macrophages within granulomas
  - Sarcoid may increase plasma Ca^{2+} further with high sun exposure.
  - Laboratory findings: low PTH, high $1,25(OH)_2D$

- Reduced FGF-23 activity
  - Although reduced FGF-23 activity lifts its inhibitory effect on 1α-hydroxylase thereby increasing $1,25(OH)_2D$ levels, the latter inhibits PTH and results in calciuria. Plasma calcium level, therefore, may not be elevated.

Loss-of-function mutation of 24-hydroxylase

- Loss-of-function mutation of 24-hydroxylase leads to high levels of $1,25(OH)_2D$ and hypercalcemia (both of which suppress PTH).
- Resultant phenotype: hypercalcemia with associated nephrocalcinosis or nephrolithiasis
- Treatment: ketoconazole (inhibitor of 1α-hydroxylase) corrects hypercalcemia.

NOTE In contrast to patients with hypercalcemia secondary to excess $1,25(OH)_2D$, patients with inactivating 24-hydroxylase do not respond to corticosteroids.

Increased $1,25(OH)_2D$

- Tumor-associated: Hodgkin and non-Hodgkin lymphomas, ovarian dysgerminomas, leiomyoblastoma, among others. It has been suggested that cancer cells from these malignancies recruit and stimulate adjacent macrophages to express 1α-hydroxylase. Full mechanisms remain to be elucidated.
- Ingestion of vitamin supplements

Loss of function of CaSR

- Familial hypocalciuric hypercalcemia (FHH):
  - Rare autosomal dominant hereditary condition due to inactivating mutations of the gene encoding CaSR. Recall that in the TAL, CaSR senses hypercalcemia and inhibits ROMK, thereby reducing luminal K^+ recycling and loss of the positive luminal charge that normally facilitates paracellular calcium reabsorption. Whereas normal activation of CaSR induces calciuria, inactivating mutation of CaSR reduces calciuria by enhancing TAL paracellular Ca^{2+} reabsorption.
  - Laboratory findings:

- Moderate chronic hypercalcemia; normo- to hypophosphatemia due to elevated PTH levels; normo- to hypermagnesemia due to increased TAL paracellular reabsorption
- Plasma PTH is normal to moderately high. Inactivating mutation of CaSR allows for uninhibited PTH secretion, thus, elevated PTH levels. This explains why FHH may be mistaken for PHPT.
- $1,25(OH)_2D$ level may be high in response to elevated PTH levels.

NOTE Fractional calcium excretion is *low* (e.g., <0.01) in fhh, but *high* in PHPT. This is the differentiating point for FHH versus PHPT. Do *not* perform parathyroidectomy if hypercalcemia is due to FHH.

- Fractional excretion of calcium may be calculated as 24-hour calcium clearance divided by 24-hour creatinine clearance, which is referred to as "calcium-to-creatinine clearance ratio" (CCCR):
  - CCCR = UV/P of calcium ÷ UV/P of creatinine; Since V is the same for both,

$$\text{CCCR} = \text{U/P (calcium)} \div \text{U/P (creatinine)}$$

$$= ([\text{urine calcium}] \times [S_{Cr}])/([\text{urine creatinine}] \times [S_{Ca}])$$

  - CCCR < 0.010 indicates fhh, whereas cccr > 0.020 suggests PHPT.
- Treatment: The use of calcimimetics has been reported to be successful in a small case series.

- Some patients with the diagnosis of hyperparathyroidism have been found to have autoantibodies to CaSR. These patients may have similar presentations as those with FHH.

Ingestions

- Calcium-containing products (calcium carbonate, Nicorette gum, calcium-supplemented bottled carbonated water, etc.)
- Excessive vitamin D (over-the-counter vitamin supplements)
- Medications: lithium (may lead to hyperparathyroidism), thiazide diuretics, antacids (calcium carbonate—patients present with both hypercalcemia and metabolic alkalosis), vitamin A overload (increased bone resorption)

Clinical Manifestations, Complications of Hypercalcemia

- Fatigue, poor concentration, headaches, depression, anxiety
- Ocular: conjunctivitis, band keratopathy
- Cardiac: shortened QT, arrhythmias

NOTE An ST-like elevation may be seen on electrocardiogram (ECG) (as the T wave moves closer to the QRS wave) in patients with severe hypercalcemia and may be mistaken as acute MI.

- GI: constipation, nausea, vomiting, peptic ulcer disease, pancreatitis
- Kidney-related complications: polyuria, nephrogenic diabetes insipidus, kidney stones, medullary and cortical calcium depositions (nephrocalcinosis)

Management of Hypercalcemia

Volume repletion with normal saline as tolerated

Medical therapies

- **Loop diuretics** may be added if hypervolemic to enhance paracellular Ca^{2+} excretion from thick ascending loop of Henle.
- **Bisphosphonates:**
  - Inhibit bone resorption and calcitriol synthesis
  - Preferred agents for hypercalcemia associated with cancer
  - Commonly used agents:
    - Intravenous pamidronate, oral alendronate, clodronate
    - Calcitonin: rapid onset of action (within hours), but only short-term benefit due to tachyphylaxis
  - Zoledronic acid has been used successfully in patients with sarcoid-induced hypercalcemia and may become first-line agent for this indication (contraindicated for estimated GFR [eGFR] <35 ml/min/1.73 m^2).
  - Mithramycin: cytostatic drug
    - Potent inhibitor of bone resorption
    - Rapid onset of action, effect lasts days, but high adverse effects (transaminitis, thrombocytopenia)
    - Reserved for malignant hypercalcemia. Note that in malignant

hypercalcemia, prostaglandin antagonists (e.g., aspirin, indomethacin) may also be considered.

- **Corticosteroids:** 0.5 to 1.0 mg/kg prednisone daily
  - Reduces GI absorption of calcium
  - May be used in hypervitaminosis D (either endogenous source such as sarcoid/granulomatous diseases or exogenous vitamin D ingestion)
  - Corticosteroid is ineffective in patients with vitamin D-24-hydroxylase mutations. Ketoconazole is used instead (see below).
  - May be considered in lymphoproliferative malignancies such as lymphoma, multiple myeloma, or even solid organ malignancy such as breast cancer
- **Ketoconazole:**
  - Inhibits calcitriol synthesis via inhibition of 1-α hydroxylase
  - May be used for patients with vitamin D-24-hydroxylase loss-of-function mutation
- **Calcimimetics** (also see **Secondary Hyperparathyroidism, Calcimimetics** below):
  - CaSR agonists such as cinacalcet, etelcalcetide
  - May be used for hyperparathyroidism (primary, secondary, or even parathyroid carcinoma), particularly for nonsurgical candidates
- **Others:**
  - Propranolol for thyrotoxicosis-induced hypercalcemia
  - Estrogens in women with PHPT (Although estrogen increases GI calcium absorption, it also inhibits PTH-driven bone resorption. The net effect is reduction in hypercalcemia.)
- **Treatment consideration for malignancy-associated hypercalcemia:**
  - Denosumab (Prolia, Xgeva) is a human mAb that binds to and inhibits the bone resorption mediator RANKL. RANKL is normally secreted by osteoblasts to stimulate osteoclastic proliferation and activity (increase bone resorption). Inhibition of RANKL by denosumab thus inhibits osteoclastic activity.
  - Denosumab may ameliorate malignancy-associated hypercalcemia due to bone involvement.

- May cause severe hypocalcemia in patients with ESKD and should be avoided

Parathyroidectomy for PHPT

Indications (2016 American Association of Endocrine Surgeons Guidelines)

- Age <50 years old regardless of clinical manifestations due to the eventual development of significant complications if left untreated over lifetime
- Serum calcium level >1.0 mg/dL above normal range (or ionized calcium > 0.12 mmol/L above normal range).
- Marked bone density reduction with T-score ≤−2.5 at lumbar spine, femoral neck, total hip, or the one-third radius for postmenopausal women or men >50 years old
- Objective evidence of kidney involvement (e.g., stones, hypercalciuria >400 mg/d, reduced kidney function attributable to PHPT)
- Other considerations
  - Presence of severe symptoms: neurocognitive and/or neuropsychiatric symptoms attributable to PHPT, underlying cardiovascular disease with potential disease acceleration, fibromyalgia, gastroesophageal reflux, reduced functional capacity, altered sleep patterns
  - Patient surgical preference due to difficult/impossible follow-up

Presurgical considerations for PHPT

- Localization with imaging studies to allow minimally invasive surgery may be preferred over four-gland exploration without presurgical imaging.
- Localization studies: combination ^{99m}Tc-sestamibi scintigraphy and/or single-photon emission computed tomography (SPECT) and ultrasound
  - If positive for adenoma → focused surgery
  - Otherwise, consider four-dimensional computed tomography (CT), exploratory surgery

Hungry bone syndrome

- Definition: profound (S_{Ca} < 6 mg/dl) and prolonged (>4 days postoperative) hypocalcemia along with hypophosphatemia and hypomagnesemia following parathyroidectomy for severe hyperparathyroidism

- Risks: severe hyperparathyroidism with associated skeletal manifestations, preoperative indices of high bone turnover, osteitis fibrosa cystica, and/or "brown tumors"
- Pathogenesis:
  - Continuing high skeletal calcium uptake for bone formation without the opposing calcium leak from bone resorption due to the acute fall in PTH following parathyroidectomy
- Management:
  - Intravenous calcium supplement (6 to 12 g/d), followed by oral therapy when safe, plus
  - Calcitriol (2 to 4 μg/d), plus
  - Correction of hypomagnesemia (Magnesium serves as a cofactor for vitamin D-binding protein, 25-hydroxylase, 1α-hydroxylase, and 24-hydroxylase enzymes. Optimal vitamin D activity requires magnesium.)
  - Preoperative repletion of vitamin D and use of bisphosphonates (e.g., intravenous administration of pamidronate 30 mg daily × 2 consecutive days or single dose of 60 mg) have been suggested to ameliorate postoperative hungry bone syndrome.

HYPOCALCEMIA

Causes of Hypocalcemia (Table 3.2)

Table 3.2 Hypocalcemic disorders as they correspond to different levels of calcium metabolism

No.	Normal Calcium Regulation	Level of Pathology	Corresponding Hypocalcemic Conditions	Expected Laboratory Findings
1	Parathyroid gland	**PTH**	• Parathyroidectomy • Resistance to PTH (Albright renal osteodystrophy, magnesium deficiency, tyrosine kinase inhibitors [sunitinib, imatinib])	• Serum: ↓PTH level (↑PTH if PTH resistance); ↓1,25$(OH)_2$D level; hypocalcemia; normo- to hyperphosphatemia
2	PTH binds to the receptor PTH1R	**PTH1R**	• Loss-of-function mutation of PTH1R (Blomstrand chondrodysplasia,	• Serum: ↑PTH level; ↓1,25$(OH)_2$D level; hypocalcemia

			primary failure of tooth eruption)	
3	PTH binding to PTH1R leads to: A. Increased bone resorption	**Bone**	• Increased bone formation (Hungry bone syndrome)	• Serum: Hypocalcemia; normo- to hypophosphatemia; Abrupt lowering of PTH level

4	B. Reduced renal Ca^{2+} excretion	**Kidney**	• Increased renal Ca^{2+} excretion:
			  • TAL:
			  ◦ Gain-of-function mutation of CaSR
			  ◦ CaSR agonists (cinacalcet, etelcalcetide)
			  • DCT/CN:
			  ◦ Loss-of-function mutation of TRPV5
				• TAL-activating mutation of CaSR:
				  • Serum: Hypocalcemia; ↓PTH level (due to continuing negative feedback); ↓$1,25(OH)_2D$ level
				  • Variable phosphate level
				  • Urine: Hypercalciuria
				• DCT/CN:
				  • Serum: Hypocalcemia; ↑PTH and ↑$1,25(OH)_2D$ levels; hypophosphatemia
				  • Urine: Hypercalciuria; phosphaturia

5	C. Increased 1α-hydroxylase activity	**1α-Hydroxylase**	• Reduced 1α-hydroxylase activity:
			  • Gain-of-function mutation of 24-hydroxylase
			  • Any mutation leading to increased FGF-23 activity
				• Serum: ↓$1,25(OH)_2D$ level; hypocalcemia; ↑PTH level; hypophosphatemia

6	Increased $1,25(OH)_2D$ level	**$1,25(OH)_2D$**	• Reduced $1,25(OH)_2D$ levels:
			  • Severe malnutrition and/or malabsorption
			  • Kidney failure
			  • Deficiency of
				• Serum: ↓$1,25(OH)_2D$ level; hypocalcemia; ↑PTH level; hypophosphatemia

			$1,25(OH)_2D$ precursors: ◦ Severe lack of sun exposure ◦ Liver failure	
7	$1,25(OH)_2D$ binds to its receptor VDR	**VDR**	• Loss-of-function mutation of VDR or its regulatory proteins	• Serum:↑$1,25(OH)_2D$ level; hypocalcemia; ↑PTH level; normo- to hypophosphatemia
8	Binding of $1,25(OH)_2D$ to VDR leads to increased intestinal Ca^{2+} reabsorption	**GI tract**	• Severe malnutrition and/or malabsorption	• Serum: Hypocalcemia; ↑PTH and ↑$1,25(OH)_2D$ levels; hypophosphatemia
9	Ca^{2+} binds to its receptor CaSR: at TAL to increase urinary Ca^{2+} excretion *and* at PTH gland as negative feedback to reduce PTH	**CaSR**	• Gain-of-function mutation of CaSR • CaSR agonists (cinacalcet, etelcalcetide)	• Urine: Hypercalciuria • Serum: Hypocalcemia; ↓PTH and ↓$1,25(OH)_2D$ levels; hyperphosphatemia
		Other	• Systemic tissue calcifications: • Acute pancreatitis • Rhabdomyolysis	• Serum: Hypocalcemia; ↑PTH and $1,25(OH)_2D$ levels; • Hypophosphatemia (likely due to compensatory hyperparathyroidism) • Hyperphosphatemia with rhabdomyolysis

Note: Refer to **Figure 3.5** for corresponding step numbers.

Abbreviations: CaSR, calcium-sensing receptor; DCT/CN, distal convoluted tubule/connecting segment; GI, gastrointestinal tract; PTH, parathyroid hormone; PTH1R, parathyroid hormone receptor 1; PTHrp, parathyroid hormone–related peptide; SCa^{2+}, serum calcium level; TAL, thick ascending limb of Henle loop; TRPV5, transient receptor potential calcium channel; VDR, vitamin D receptor.

Pseudohypocalcemia

- Acute respiratory alkalosis or severe metabolic alkalosis: Clinically significant reduction in ionized calcium (iCa^{2+}) may occur due to increased Ca^{2+} complexing to the increased levels of organic anions associated with alkalemia. Free iCa^{2+} is low, but total serum calcium levels remain the same.

- Hypoalbuminemia: low total serum calcium with normal iCa^{2+} levels due to reduced albumin-bound calcium fraction

True hypocalcemia

- Similar to hypercalcemia, the differential diagnoses of true hypocalcemia may be based on the levels outlined for normal serum calcium metabolism. In narrowing down the differential diagnoses, consider how vitamin D and serum phosphorus are affected at each level. See Figure 3.5 and Table 3.2**.**

Hypoparathyroidism

- Causes: Neck irradiation, amyloid infiltration of parathyroid glands, idiopathic, sporadic, or postoperative hypoparathyroidism

Resistance to PTH

- Resistance to PTH leads to high PTH levels.
- Laboratory findings: hypocalcemia, high phosphorus level, low $1,25(OH)_2D$, high PTH levels
- Notable conditions:
  - Albright hereditary osteodystrophy:
    - Hereditary condition linked to dysfunctional G-proteins that fail to mediate intracellular signaling by PTH.
    - Patients present with short fourth and fifth metacarpals and rounded facies.
  - Magnesium deficiency reduces PTH synthesis and release and induces skeletal resistance to PTH.
  - Drug induced: tyrosine kinase inhibitors sunitinib, imatinib

Inactivating mutation of PTH1R (very rare)

- Reported conditions include lethal Blomstrand chondrodysplasia and primary failure of tooth eruption.

Increased bone formation

- Hungry bone syndrome: reduced bone resorption relative to bone formation due to the abrupt lowering of PTH level following parathyroidectomy

Increased renal calcium excretion

- Activating mutation of CaSR (see below)
- Loss-of-function mutations of TRPV5
- Use of loop diuretics

Reduced 1,25(OH)$_2$D activity

- Notable laboratory findings: hypocalcemia, elevated PTH, hypophosphatemia due to reduced intestinal absorption of both Ca^{2+} and PO_4^{2-} and PTH-induced phosphaturia
- Vitamin D resistance due to mutations of VDR
- Kidney failure (labs as above, except PO_4^{2-} level is normal to high)

Reduced intestinal calcium absorption

- Malabsorptive syndromes
- Malnutrition

Activating mutation of CaSR

NOTE CaSR is present in both the kidneys and parathyroid gland. Any mutation or agent affecting CaSR will affect both organs. Clinical manifestations must be considered for both.

- Renal effect: hypercalciuria, followed by hypocalcemia
- Parathyroid gland effect: PTH cellular proliferation and activity are suppressed. Reduced PTH secretion leads to hyperphosphatemia and reduced 1,25(OH)$_2$D level. The latter also leads to hypocalcemia.

Systemic tissue calcium sequestration

- Acute pancreatitis: This results in compensatory hyperparathyroidism and associated phosphaturia.
- Rhabdomyolysis (calcium is sequestered into injured tissue, thus hypocalcemia): In this condition, intracellular phosphate is released from injured muscle cells, leading to hyperphosphatemia.
- Treatment of rhabdomyolysis-induced hypocalcemia is not recommended unless neurologic symptoms or ECG changes (i.e., prolonged QT, tetany) because:
  - Hypocalcemia associated with rhabdomyolysis is transient as

sequestered calcium will be released back into circulation with recovery.
  - PTH is stimulated during the initial hypocalcemic phase and can contribute to recovery-phase "overshoot" hypercalcemia.
  - Calcium infusion in the presence of hyperphosphatemia may facilitate intravascular and soft-tissue calcifications.

Diagnosis of Hypocalcemia, Notable Laboratory Findings

- Calcium-to-creatinine clearance ratio (CCCR):
  - High ratio >0.020 in all forms of hyperparathyroidism or conditions with elevated PTHrp, renal calcium wasting conditions (e.g., activating mutation of CaSR, post-AKI diuresis, diuretics, and severe CKD)
  - Low in other etiologies of hypocalcemia
- Urinary calcium excretion *during treatment with calcium and vitamin D derivatives*:
  - Increased in the treatment of hypoparathyroidism and renal calcium wasting conditions and may lead to nephrocalcinosis
  - Decreased in other causes of hypocalcemia
- Urinary phosphate excretion:
  - Increased in vitamin D deficiency (due to increased PTH), CKD, active phosphate infusion
  - Low in hypoparathyroidism (recall that the opposite is true in PHPT), pseudohypoparathyroidism, magnesium deficiency
- Intracranial calcifications, particularly within basal ganglia, are observed more frequently in idiopathic hypoparathyroidism compared with other forms of hypoparathyroidism.

Management of Hypocalcemia

NOTE In the case of concurrent acidemia and severe hypocalcemia, correct hypocalcemia *first*. Do *not* correct acidemia prior to the correction of hypocalcemia. Alkalinization reduces iCa^{2+} levels and may precipitate life-threatening neurologic complications and/or arrhythmias.

Calcium *cannot* be given in the same intravenous line as sodium bicarbonate due to calcium precipitation as calcium carbonate.

- Correct underlying etiology

- Calcium supplement:
  - Calcium gluconate is generally preferred over calcium chloride ($CaCl_2$) because it is less irritating to blood vessels and tissue.
  - Calcium chloride may be used if there is central venous access.
  - **Note:** One gram of $CaCl_2$ contains 272 mg (13.2 mEq) of elemental calcium, whereas 1 g of calcium gluconate contains 94 mg (4.7 mEq). *Thus*, 1 ampule of calcium chloride = 3 ampules of calcium gluconate in terms of elemental calcium content.
  - In severe cases of hypocalcemia where there are neurologic complications (i.e., tetany, seizures, arrhythmias), administer calcium gluconate as:
    - Intravenous bolus: 10 mL of 10% diluted in 50 mL of either 5% dextrose water or isotonic saline, followed by
    - Continuous infusion of a solution mixture containing 8 to 10 ampules of calcium gluconate in 1 L of normal saline or 5% dextrose water to run over the next 24 hours
- Thiazide diuretics may be used concurrently with calcium supplementation in patients with hypoparathyroidism to reduce urinary calcium excretion and nephrocalcinosis. As with calcium stone management, high fluid intake and low sodium intake should be advised.
- Vitamin D supplement: calcitriol, 1α-hydroxycholecalciferol, or paricalcitol is the treatment of choice for idiopathic or acquired hypoparathyroidism because they can minimize large calcium supplement.
- Correct hypomagnesemia if applicable

DISORDERS OF PHOSPHATE METABOLISM

Phosphate Background

- 99% of total body phosphates (700 g) exist intracellularly and in bones.
- 1% of total body phosphates exist extracellularly as HPO_4^{2-} and $H_2PO_4^-$ in a 4:1 ratio, with normal serum phosphate concentrations of 2.8 to 4.5 mg/dL.
- Daily phosphate intake is approximately 1 to 1.5 g/d, where 60% to 80% is absorbed by the GI tract and 10% is secreted back into the GI tract.

- Kidneys excrete 60% to 70% of dietary intake.
- Less than 1% of total body phosphate is involved in constant bone turnover.
- Physiologic roles of phosphate: bone mineralization, phospholipid bilayers, adenosine triphosphate (ATP), DNA/RNA synthesis, glycolysis, cell function, unloading of O_2 via 2,3-bisphoglycerate

Phosphate Metabolism (Fig. 3.6)

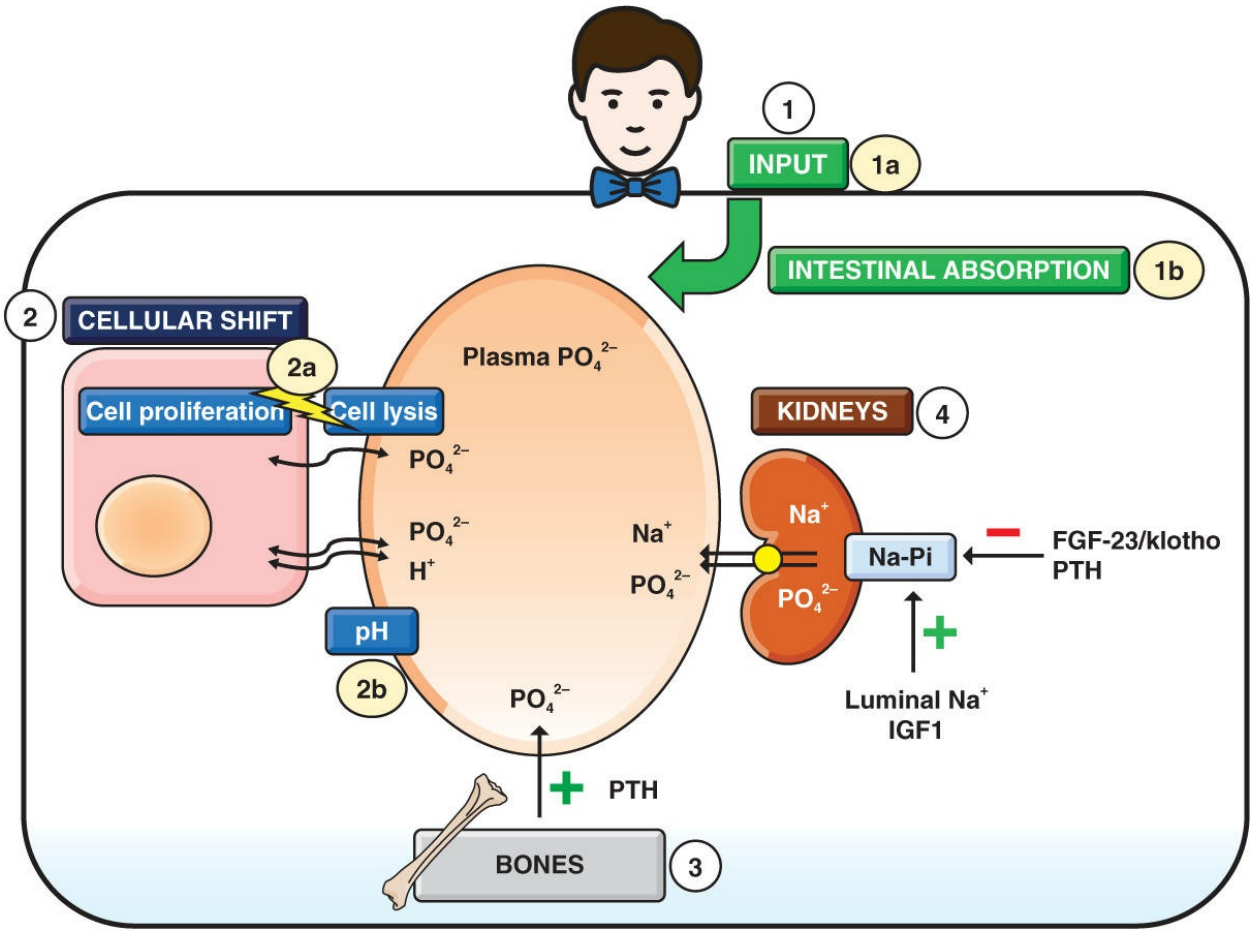

FIGURE 3.6 Phosphate metabolism. Plasma phosphate level is dependent on **(1)**. Input—**1a:** Ingestion, **1b:** intestinal absorption. **2**—Cellular shift: **2a:** Cell proliferative or lytic state, **2b:** acid–base status, **3:** net bone formation/resorption, and **4:** sodium phosphate cotransporter activity in the kidneys. Abbreviations: FGF-23, fibroblast growth factor 23; IGF1, insulin-like growth factor-1; Na-Pi, sodium phosphate cotransporter; PTH, parathyroid hormone.

GI tract

- GI phosphate absorption is a linear and nonsaturable function of phosphate intake.
- Absorption occurs via both paracellular and transcellular pathways.
- Transcellular absorption occurs via sodium phosphate (Na-Pi) cotransporters, type 2b, in the small intestines.
  - *NPT2b*, the gene encoding Na-Pi 2b, is upregulated by calcitriol.
  - Niacin inhibits Na-Pi 2b and has been used to reduce GI phosphate absorption. Niacin may reduce phosphate by 0.4 mg/dL.
  - Deletion of NPT2b has no phosphate phenotype in humans. It is possible that paracellular absorption alone may be sufficient to maintain

phosphate levels.

Kidney

- Phosphate is minimally protein bound and freely filtered in the glomeruli.
- Total renal reabsorption is approximately 85% to 90%, leaving the fractional excretion of phosphate to be 10% to 20%.
- Proximal tubules:
  - Absorption of phosphate occurs via Na-Pi, types 2a and 2c, at the brush borders of proximal tubules.
  - In the presence of increased plasma phosphate level, FGF-23 and PTH downregulate *NPT2a* and *NPT2c* (genes encoding Na-Pi 2a and Na-Pi 2c, respectively), thereby increasing phosphaturia.
  - FGF-23 requires the cofactor klotho for optimal function. Mutations of either FGF-23 or klotho can lead to hypophosphaturia thus hyperphosphatemia.
  - Insulin-like growth factor is associated with Na-Pi cotransporter stimulation, thus reducing phosphaturia.
  - Typically, kidneys excrete 5% to 20% of the filtered phosphate load to maintain phosphate balance, that is, fractional excretion of phosphate ($FePO_4$) is 5% to 20%.
  - In CKD, when GFR is reduced, each of the remnant nephrons will have to excrete more phosphate per filtered load to maintain balance. $FePO_4$ can exceed 50%.

Indices used to assess renal phosphate excretion

- $FePO_4 = (U_{PO_4} \times S_{Cr})/(S_{PO_4} \times U_{Cr})$, where U_{PO_4} = urine phosphate concentration, S_{Cr} = serum creatinine, S_{PO_4} = serum phosphate concentration, U_{Cr} = urine creatinine concentration.
- Fractional tubular reabsorption of $PO_4 = 1 - FePO_4$: A level <0.86 suggests phosphaturia.
- Tubular maximum reabsorption of PO_4 to GFR ratio (TmP/GFR): an index that may be determined using a monogram after measuring fasting serum and urine concentrations of phosphate and creatinine. A low number

indicates PO_4 wasting.

HYPERPHOSPHATEMIA

Causes of Hyperphosphatemia (Fig. 3.7)

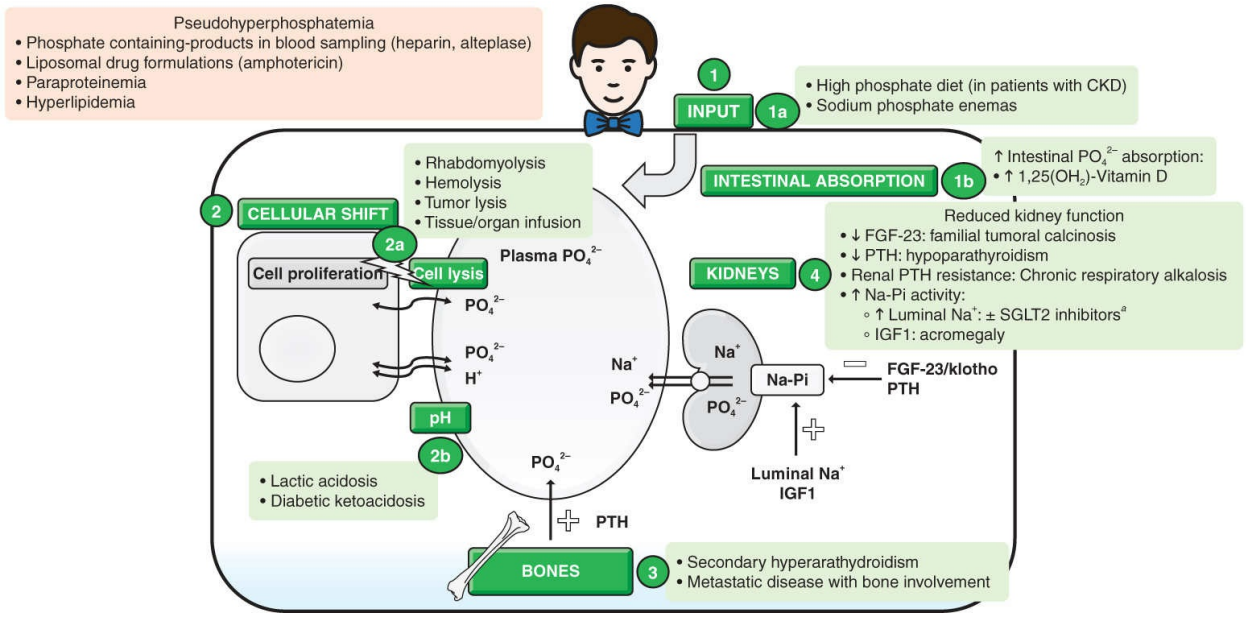

FIGURE 3.7 Etiologies of hyperphosphatemia.

[a]See text for SGLT2 inhibitors and fracture risks.

Abbreviations: FGF-23, fibroblast growth factor 23; IGF1, insulin-like growth factor-1; Na-Pi, sodium phosphate cotransporter; PTH, parathyroid hormone; 1, input; 1a, phosphorus ingestion; 1b, increased intestinal absorption of phosphorus; 2, cellular shift; 2a, conditions leading to extracellular shifts of phosphorus; 2b, acid-base disorders leading to extracellular phosphorus shifts; 3, conditions leading to phosphorus shifts from bones; 4, factors reducing kidney excretion of phosphorus.

Pseudohyperphosphatemia

- Heparin and alteplase contaminated blood sampling: These solutions may contain phosphoric acid as a buffer solution.
- Liposomal-coated drugs such as liposomal amphotericin: The phosphate hydrolyzed from liposomal phospholipid bilayer at the low pH used in the assay to measure serum phosphorus is falsely read as part of serum phosphate.
- Paraproteinemia (multiple myeloma, Waldenström macroglobulinemia, monoclonal gammopathy of undetermined significance):
  - Precipitation of paraproteins and associated turbidity may interfere with

light absorbance by UV spectrophotometry.
    - Excess binding of phosphate to certain paraproteins
    - Specific physiochemical characteristics of paraproteins per se may interfere with phosphate measurements.
- Hyperlipidemia: presumed associated turbidity

Exogenous sources

- Ingestion of phosphate salts such as accidental ingestion of phosphate-containing enemas. Of interest, data from the Veterans Affairs database revealed that the use of sodium phosphate enemas prior to colonoscopy increased the likelihood of having long-term eGFR decline compared with the use of polyethylene glycol (odds ratio 1.4).
- Treatment with calcitriol (increase GI absorption of phosphates)
- Hyperphosphatemia from exogenous sources usually only occurs in association with reduced kidney function.

Extracellular shift

- Cell death, extracellular release of phosphate: rhabdomyolysis, hemolysis, malignant hyperthermia, heavy tumor burden with necrotic cell death, tumor lysis syndrome, bowel infarction
- Acid–base status:
    - Lactic acidosis
    - Diabetic ketoacidosis
    - Chronic respiratory alkalosis (associated with prolonged hyperventilation) may lead to renal resistance to PTH, hyperphosphatemia, hypocalcemia, and, possibly, reduced PTH secretion.
- Increased bone resorption (in association with poor renal phosphate excretion):
    - SHPT (PHPT is usually associated with hypophosphatemia.)
    - Metastatic disease with bone involvement

Reduced kidney excretion

- Reduced glomerular filtration (typically with eGFR < 25 to 30 ml/min/1.73

m^2)

- Hypoparathyroidism (idiopathic, postsurgical, pseudohypoparathyroidism, PTH resistance, abnormal forms of plasma PTH)
- Drug induced:
  - Bisphosphonates may cause a transient rise in serum phosphate level due to increased renal tubular reabsorption. This effect, however, is normally overridden by the secondary increase in PTH induced by bisphosphonates. Sustained increase in serum phosphate may occur in patients with underlying hypoparathyroidism.
  - SGLT2 inhibitors:
    - It is presumed that the inhibition of sodium glucose reabsorption by the SGLT2 inhibitor increases luminal Na^+, thereby providing the electrochemical gradient favorable for sodium phosphate reabsorption via Na-Pi cotransporters. The resulting increased phosphate reabsorption leads to elevated serum phosphate levels, followed by increased FGF-23 secretion → reduced $1,25(OH)_2D$ → increased PTH. The compensatory increase in FGF-23 and PTH corrects the initial rise in serum phosphate but has been implicated in increased bone loss and fracture risks.
    - Reported adverse skeletal effects with SLGT2 inhibitors:
      - Dapagliflozin: dose-dependent increase in bone fractures
      - Canagliflozin: increased incidence of fractures
      - Empagliflozin: doubling in incidence in upper extremity fractures
- Acromegaly:
  - Increased IGF1 in acromegaly is thought to increase tubular reabsorption of phosphate via stimulation of Na-Pi cotransporters.
  - Increased calcitriol with increased intestinal phosphate absorption may also be contributory.
- Familial tumoral calcinosis:
  - Rare autosomal recessive disorder affecting Middle Eastern or African ancestries
  - Thought to involve inactivating mutations of *GALnt3*, *FGF-23*, or *klotho* genes, all of which are necessary for optimal FGF-23 activity. *GALnt3*

encodes glycosyltransferase, an enzyme necessary for posttranslational processing and stabilization of FGF-23.

- The lack of active FGF-23 (low FGF-23) leads to:
  - Hyperphosphatemia
  - Loss of FGF-23 inhibitory effect on 1,25 vitamin D synthesis → elevated $1,25(OH)_2D$ (increased GI calcium absorption) → reduced PTH → hypercalciuria
  - Ectopic calcifications due to combination of net positive calcium balance and hyperphosphatemia
  - Serum calcium however, tends to be normal.

Clinical Significance of Hyperphosphatemia

- Soft-tissue and vascular calcium phosphate depositions
- Hyperphosphatemia inhibits the conversion of 25-vitamin D to $1,25(OH)_2D$ (calcitriol).
- Data from the Third National Health and Nutrition Examination Survey (1988 to 1994) revealed that fasting, but *not* nonfasting, elevated serum phosphorus levels were associated with increased mortality.

Management of Hyperphosphatemia

- Dietary restriction: Avoid food with preservatives.
- Fluid resuscitation to ensure good renal excretion
- Use of phosphate binders with meals to reduce GI absorption of dietary phosphates (see **Secondary Hyperparathyroidism** section)
- Administration of intravenous dextrose and insulin to increase intracellular phosphate shift if clinically indicated

HYPOPHOSPHATEMIA

Causes of Hypophosphatemia (Fig. 3.8)

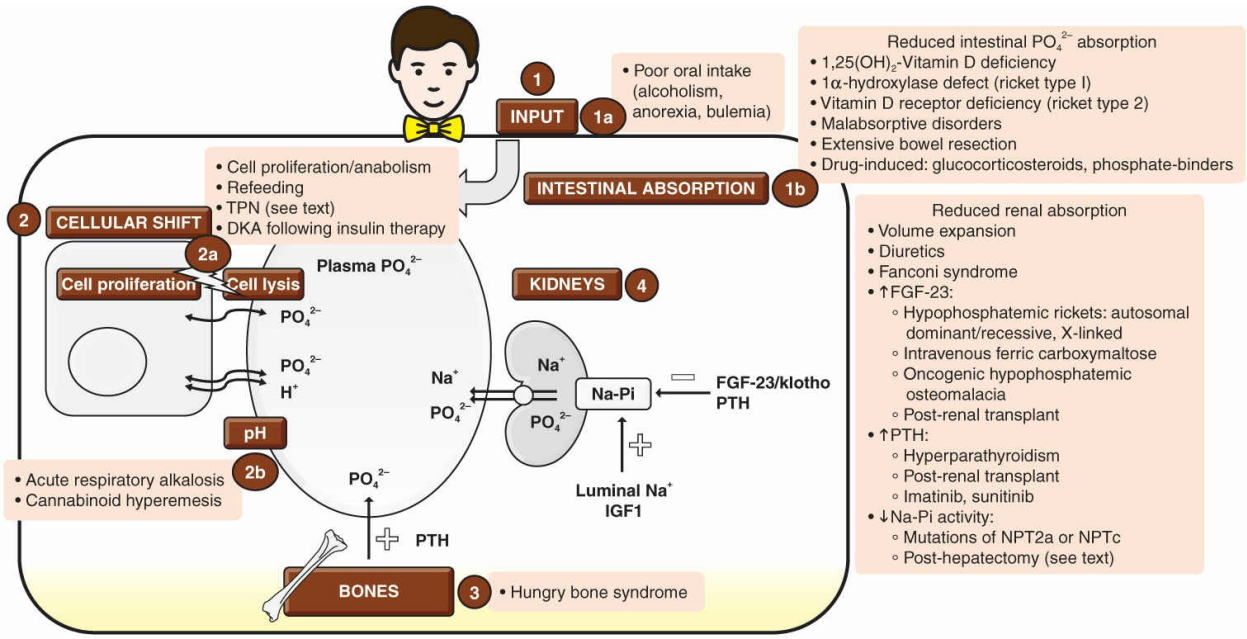

FIGURE 3.8 Etiologies of hypophosphatemia. Abbreviations: DKA, diabetic ketoacidosis; FGF-23, fibroblast growth factor 23; IGF1, insulin-like growth factor-1; Na-Pi, sodium phosphate cotransporter; PTH, parathyroid hormone; TPN, total parenteral nutrition; 1, input; 1a, low phosphorus ingestion; 1b, conditions leading to reduced intestinal absorption; 2, cellular shift; 2a, conditions leading to intracellular shifts of phosphorus; 2b, acid-base disorders leading to intracellular phosphorus shifts; 3, conditions leading to phosphorus shifts into bones; 4, factors that increase phosphaturia.

Reduced input

- Reduced intake: alcoholics, eating disorders (anorexia, bulimia), old/debilitated/poor patients with poor access to high phosphate-containing food
- Reduced GI absorption:
  - Vitamin D deficiency
  - Vitamin D–dependent rickets:
    - Defect in renal 1α-hydroxylase (vitamin D–dependent rickets type 1)
      - Laboratory findings: low $1,25(OH)_2D$, hypocalcemia, SHPT, hypophosphatemia
      - 50% of patients may have alopecia.
      - Treatment: low-dose calcitriol
    - VDR deficiency (vitamin D–dependent rickets type 2):
      - Laboratory findings: high $1,25(OH)_2D$ level
      - Treatment: high-dose calcitriol

- Malabsorptive GI disorders, extensive bowel resection

Cellular shift

- *Acute* respiratory alkalosis:
  - *A*cute respiratory alkalosis (hyperventilation) leads to extracellular CO_2 diffusion, which, in turn, leads to a rise in intracellular pH. The increased intracellular pH increases glycolysis, a process where phosphates are needed to produce ATPs. The required cellular phosphate uptake leads to hypophosphatemia.
  - Cannabinoid hyperemesis syndrome may present with hypophosphatemia. Hyperventilation-induced cellular uptake of phosphate is thought to be contributory.
- **Note:**
  - Acute metabolic alkalosis does *not* cause hypophosphatemia because bicarbonate cannot freely cross cell membranes to cause a rapid rise in intracellular pH.
  - *Chronic* respiratory alkalosis is associated with *hyper*phosphatemia due to renal resistance to PTH and/or reduced PTH secretion.
- Refeeding syndrome
- Total parenteral nutrition (TPN) due to low phosphate content or endogenous insulin-mediated intracellular phosphate shift following TPN infusion
- Diabetic ketoacidosis following insulin administration

Increased kidney excretion

Volume expansion

Mutations leading to increased FGF-23 levels

- Autosomal dominant hypophosphatemic rickets:
  - Mutation in FGF-23 that renders FGF-23 resistant to proteolysis/degradation.
  - Associated skeletal abnormalities: bowing of long bones and widening of costochondral joints
- Autosomal recessive hypophosphatemic rickets: Mutations in *DMP1* can lead to increased FGF-23 levels. *DMP1* is a gene that encodes the dentin

matrix protein 1, a molecule thought to normally suppress bone secretion of FGF-23.

- X-linked hypophosphatemic rickets:
  - Mutations of the *PHEX* gene encoding the phosphate-regulating endopeptidase (on X chromosome). PHEX is thought to play a role in the proteolysis of FGF-23.
  - Associated skeletal deformities: short stature, osteomalacia

Drug-induced increase in FGF-23

Intravenous ferric carboxymaltose administration in patients *with iron deficiency* can lead to severe hypophosphatemia (even to level <1 mg/dl). the mechanism is not clear but thought to be due to increased fgf-23 levels. it has been suggested that the drug can inhibit the cleavage and inactivation of fgf-23 within osteocytes, resulting in increased levels of active fgf-23, phosphaturia, and hypophosphatemia and decreased $1,25(oh)_2d$ level. hypophosphatemia typically nadirs at approximately 2 weeks and resolves within 3 months following a single intravenous dose but may last over a year with repeated doses.

Intrinsic renal defect leading to reduced tubular phosphate reabsorption

- Fanconi syndrome
- Mutation of NPT2a: autosomal recessive Fanconi syndrome with associated hypophosphatemic rickets and kidney failure
- Mutation of NPT2c: hereditary hypophosphatemia with rickets and hypercalciuria (HHRH)
  - Phenotype: hypophosphatemia, low FGF-23, elevated $1,25(OH)_2D$, normal serum calcium, low to normal PTH, and hypercalciuria
  - Hypophosphatemia is independent of FGF-23 or PTH.

Oncogenic hypophosphatemic osteomalacia

- Mostly associated with benign mesenchymal tumors of mixed connective tissue type (e.g., hemangiopericytoma, fibroma, angiosarcoma, metastatic prostate carcinoma)
- Malignant tissue secretion of phosphatonins (i.e., FGF-23 and other

phosphaturic factors)

- Clinical manifestations:
  - Affected individuals present with impaired bone mineralization and hypophosphatemia caused by reduced renal phosphate reabsorption
  - Bone pain, muscle weakness, difficulty walking, pathologic fractures, height loss
- Laboratory findings:
  - Elevated FGF-23, hypophosphatemia, low $1,25(OH)_2D$, elevated PTH, normal to low serum calcium.
    - Calcitriol is inappropriately low to normal in this condition due to reduced 1α-hydroxylase activity with increased FGF-23 levels.
    - Intact PTH (iPTH) may be elevated due to low $1,25(OH)_2D$ levels.
  - Alkaline phosphatase levels are often elevated.
- Diagnosis: clinical manifestations above, markedly elevated FGF-23, hypophosphatemia, increased serum alkaline phosphatase, reduced TmP/GFR

Post-kidney transplant hypophosphatemia (also see Chapter 9)

- Persistent SHPT in new functioning allograft
- Persistently high circulating levels of FGF-23—although this is more commonly seen in patients with markedly elevated pretransplant FGF-23 levels
- Persistent hypophosphatemia beyond 1 year posttransplant is thought to be due to persistent hyperparathyroidism rather than increased FGF-23 levels.

Other conditions associated with hypophosphatemia

- Drugs: glucocorticosteroids, phosphate binders, diuretics, imatinib, sunitinib (tyrosine kinase inhibitors associated with secondary hyperparathyroidism due to skeletal resistance to PTH with normal to low calcium and hypophosphatemia)
- Alcoholism: malnutrition, hypovitaminosis D, hypomagnesemia-associated renal phosphate wasting, intracellular shift due to hyperventilation or glucose infusion
- Hungry bone syndrome (discussed under parathyroidectomy section)

- Hypophosphatemia following hepatectomy: This is thought to be due to increased proximal tubular expression of nicotinamide phosphoribosyltransferase (Nampt), a protein associated with reduced renal expression of Na-Pi cotransporters.

Clinical Manifestations of Hypophosphatemia

- Muscle weakness:
  - Increased risk for rhabdomyolysis, particularly among alcoholics with underlying alcoholic myopathy
  - Respiratory distress/arrest due to poor functioning/weak diaphragm, presumably because of inability to produce adequate ATPs
  - Cardiomyopathy
- Metabolic encephalopathy
- Hemolysis, red and white blood cell dysfunction
- Symptoms are typically not evident unless serum phosphate level is <1.5 to 2.0 mg/dl.

Management of Hypophosphatemia

- Phosphate supplementation: Estimating phosphate deficit (i.e., repletion dose):

  Phosphate dose (mmol) = 0.5 body weight (kg) × (1.25 − [serum phosphate mmol/L]).

- Treatment of underlying etiology whenever possible
- Anti–FGF-23 antibodies (KRN23): Monthly administration to patients with X-linked hypophosphatemia has been shown to increase serum phosphorus concentrations, TmP/GFR, and $1,25(OH)_2D$.

SECONDARY HYPERPARATHYROIDISM

Clinical Implications of SHPT

Also see **Chapter 4**

- Renal osteodystrophy with increased risk of fractures:
  - Osteomalacia

    - Osteopenia
    - Adynamic bone disease
    - Mixed bone disease
- Calcific uremic arteriolopathy (i.e., calciphylaxis)
- Accelerated atherosclerosis
- Refractory anemia
- Tertiary hyperparathyroidism
- Increased morbidity and mortality: 1% increase in relative risk of all-cause mortality per 100 pg/mL increase in PTH and a 2% increase in cardiovascular mortality

Diagnosis of SHPT

- SHPT may be diagnosed in patients with CKD and is characterized by elevated serum PTH levels with associated normal to high serum phosphate and normal to low serum calcium (prior to the administration of calcium-containing agents and/or vitamin D supplementation).
- Measurements of PTH:
    - Clinical significance (e.g., regarding bone health) and treatment of SHPT should depend on "trending" of PTH levels, *not* on a single value.
    - Clinical assays for measuring PTH levels are not standardized and may give a wide range of values. This variation is thought to be due to the ability of some assays to measure more (or less) circulating PTH fragments than others.
    - Current commercially available PTH measurements cannot differentiate biologically inactive oxidized forms of PTH from active nonoxidized forms.

Pathogenesis of SHPT

The pathogenesis of CKD-associated SHPT involves a complex interplay of multiple factors, as illustrated in **Figure 3.9**.

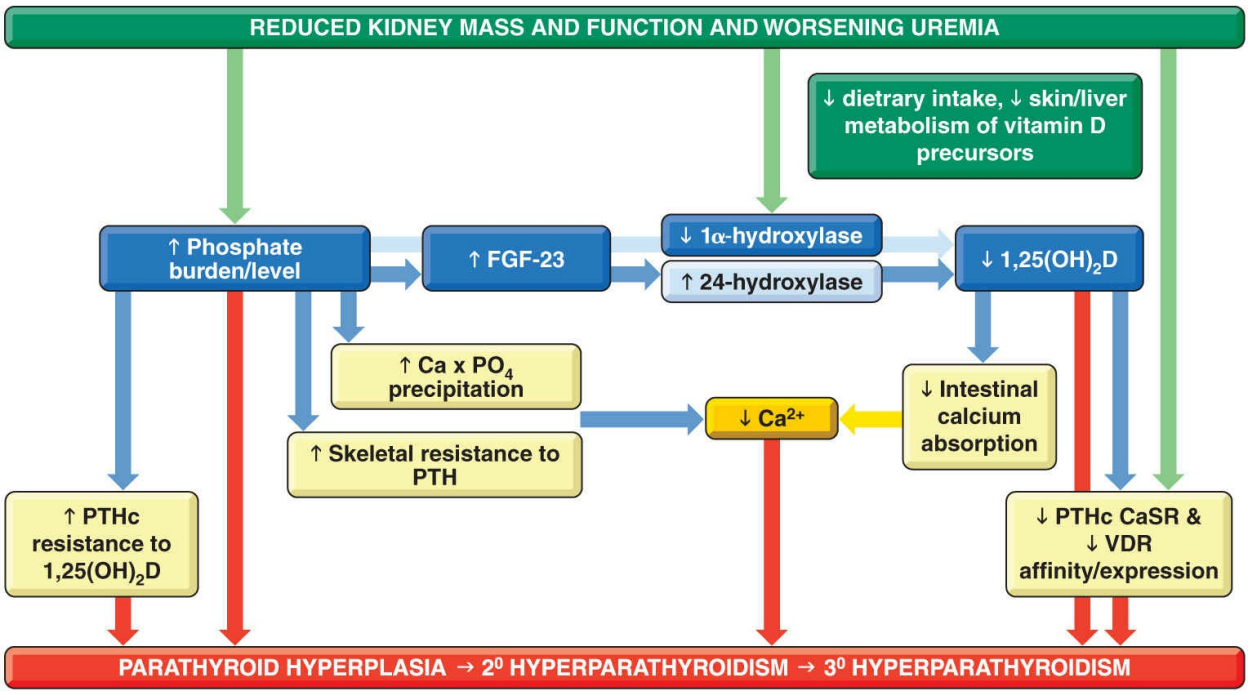

FIGURE 3.9 Pathogenesis of secondary hyperparathyroidism in patients with chronic kidney disease. All arrows indicate causal effects. Red arrows indicate direct effects on hyperparathyroidism. Abbreviations: $1,25(OH)_2D$, $1,25(OH)_2$-vitamin D; CaSR, calcium-sensing receptor; FGF-23, fibroblast growth fa ctor 23; PTH, parathyroid hormone; PTHc, parathyroid cell; VDR, vitamin D receptor.

- ***Reduced kidney mass and function*** **results in**:
  - Reduced 1-α hydroxylase activity, thus reduced $1,25(OH)_2D$ levels. **Note:** Reduced 1-α hydroxylase activity is only partially due to reduced kidney mass. Elevated FGF-23 level is thought to play a critical role in reducing 1-α hydroxylase activity in CKD. See below.
  - Reduced glomerular filtration, thus phosphate retention
- ***Phosphate retention*** **leads to:**
  - Direct stimulatory effects on the parathyroid gland to increase PTH secretion and parathyroid cell growth
  - Increased parathyroid cell resistance to calcitriol
  - Skeletal resistance to PTH
  - Reduced calcitriol synthesis (feedback phenomenon: calcitriol increases phosphate level, whereas high phosphate level reduces calcitriol synthesis)
  - Increased synthesis of FGF-23 (FGF-23 level is thought to be increased

prior to "overt" hyperphosphatemia)

- ***Increased FGF-23* leads to:**
  - Phosphaturia via suppression of Na-Pi 2a and Na-Pi 2c expressions in the brush border of proximal tubules. FGF-23 has low affinity for its receptor (FGFR1) and requires the cofactor klotho to effectively bind and activate the receptor. Of interest, klotho expression is reduced early in the course of CKD. This is thought to be the reason for reduced phosphaturia in patients with CKD. Reduction of klotho has also been implicated in inducing a more rapid progression of CKD.
  - Reduction in *1,25(OH)$_2$D* synthesis via FGF-23 inhibitory effect on 1α-hydroxylase and stimulatory effect on 24-hydroxylase
  - Inhibition of parathyroid gland via:
    - Reduction in PTH synthesis and secretion and PTH proliferation
    - Increasing expression of CaSR and VDR
- ***Reduced 1,25(OH)$_2$D level* leads to:**
  - Reduced intestinal absorption of calcium
  - Increased PTH synthesis transcription and parathyroid cell proliferation
  - Reduced expression of parathyroid VDR and CaSR , thus reduced negative feedback to parathyroid gland
  - Increased set point for calcium-regulated PTH secretion, all leading to hyperparathyroidism
- ***Other factors contributing to CKD-associated SHPT:***
  - Patients with kidney disease may also have reduced skin conversion of 7-dehydrocholesterol to cholecalciferol and liver hydroxylation of cholecalciferol to *1,25(OH)$_2$D*.
  - Hypocalcemia unrelated to vitamin D deficiency:
    - Poor dietary intake, malnutrition
    - Systemic $CaPO_4$ precipitation
- ***Notes* regarding FGF-23 in CKD:**
  - FGF-23 level is increased early in CKD, even before the rise in PTH levels. The elevated FGF-23 level is thought to be associated with the increased phosphate “burden” alone and not necessarily high serum phosphate levels.

- FGF-23 is an independent predictor of mortality, progression of kidney disease, left ventricular hypertrophy, vascular dysfunction, and kidney transplant outcomes.
- FGF-23 levels may remain increased post-kidney transplant (typically within the first year only) with resultant hypophosphatemia and relative $1,25(OH)_2D$ deficiency.

Management of SHPT

- Consistent control of mineral biochemical profile (PTH, calcium, phosphorus) is associated with improved survival.
- See Table 3.3 for a summary of 2017 Kidney Disease: Improving Global Outcomes (KDIGO) CKD-mineral and bone disorder (CKD-MBD) guidelines.

Table 3.3 Summary of KDIGO 2017 CKD-MBD guidelines

		G3a–5	Dialysis	Kidney Transplant
Bone health	BMD testing	Patients with evidence of CKD-MBD and/or risks for osteoporosis, **BMD testing is suggested** if it impacts treatment decisions		BMD testing is suggested in patients with osteoporotic risks
	Bone biopsy	Performing a bone biopsy is reasonable if type of renal osteodystrophy impacts treatment decisions		It is reasonable to consider a bone biopsy to guide treatment
		In patients with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, treatment choices accounting for the magnitude and reversibility of biochemical abnormalities with consideration of a bone biopsy is suggested.		In patients with eGFR >30 mL/min/1.73 m^2 and low BMD in the first 12 mo after transplant, treatment consideration with vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents is suggested.
CKD-MBD biochemical profile Treatments of CKD-MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered together.	Calcium	**Avoiding hypercalcemia** is suggested in adults. *Mild and asymptomatic hypocalcemia can be tolerated* in order to avoid inappropriate calcium loading.[a]		
			Use of D[Ca^{2+}] between 1.25 and 1.50 mmol/L is suggested.	
	Phosphate	**Lowering elevated phosphate levels toward normal range** is suggested.		
		Phosphate-lowering treatment should be based on **progressively or persistently elevated** phosphate level.[b]		
		Limiting dietary phosphate intake either alone or in combination with other treatments is suggested.[c]		
		Restricting dose of calcium-based phosphate binders is suggested.[a]		
	PTH	Optimal PTH level is not known. Evaluation for modifiable factors (e.g., hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency) in patients with **persistently elevated or progressively rising iPTH** is suggested.		
	Vitamin D	**Routine use of calcitriol and vitamin D analogs is not suggested** but reasonable for G4–G5 with severe and progressive hyperparathyroidism.[d]	In patients with CKD G5D requiring PTH-lowering therapy, calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analog is suggested.[e]	

[a]Higher calcium concentrations have been linked to increased mortality and nonfatal cardiovascular events. Individualized approach to the treatment of hypocalcemia should be considered because mild and asymptomatic hypocalcemia may be well tolerated and not known to be harmful.
[b]Phosphate-lowering treatment includes dietary phosphate restriction, phosphate binders, and dialysis.
[c]For dietary phosphate restriction, consider (1) fresh and homemade foods without inorganic phosphate–containing additives and (2) plant-based versus animal-based phosphate sources for lower bioavailability, 20% to 50% in the former versus 40% to 60% in the latter. Care must be taken to avoid malnutrition.
[d]Randomized controlled trials of vitamin D analogs demonstrated increased hypercalcemia risks and

lack of clinically relevant benefits. Also note that the use of calcimimetics is not indicated for patients with CKD not on dialysis. In patients with secondary hyperparathyroidism and CKD not on dialysis, the long-term safety and efficacy of calcimimetics have not been established. Clinical studies indicate that cinacalcet-treated patients with CKD not on dialysis have an increased risk for hypocalcemia compared with those with CKD on dialysis, an effect attributed to lower baseline calcium levels in the former group. The use of etelcalcetide has not been studied in patients with CKD not on dialysis and cannot be recommended.

[e]Calcimimetics, calcitriol, or vitamin D analogs are all acceptable first-line options in G5D patients.

Abbreviations: BMD, bone mineral density; CKD, chronic kidney disease; D[Ca^{2+}], dialysate calcium concentration; eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone; KDIGO, Kidney Disease: Improving Global Outcomes; MBD, mineral and bone disorder; PTH, parathyroid hormone.

Management of CKD-MBD (2017 KDIGO suggestions)

- **CKD G3a to 5D**:
  - Bone health: Bone mineral density testing (e.g., dual-energy X-ray absorptiometry [DEXA]) *is now suggested* to assess fracture risk if results impact treatment decisions.
  - Treatments of CKD-MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered together.
  - Lowering elevated phosphate levels *toward normal range* (rather than maintaining serum phosphate in the normal range) is suggested.
  - *Avoiding hypercalcemia* (rather than maintaining serum calcium in the normal range) is suggested. Higher calcium concentrations have been linked to increased mortality and nonfatal cardiovascular events. Individualized approach to the treatment of hypocalcemia should be considered because mild and asymptomatic hypocalcemia, particularly in the setting of calcimimetic treatment, can be tolerated in order to avoid inappropriate calcium loading.
  - *Phosphate-lowering therapy* (which may include binders, diet, and/or dialysis rather than just “phosphate-binding agents”) should be based on *progressively or persistently elevated serum phosphate* (rather than a single value).
  - Considerations for dietary phosphate restriction:
    - Fresh and homemade foods without inorganic phosphate–containing additives are preferred.
    - Plant-based phosphate sources have lower bioavailability compared

with those from animal sources, 20% to 50% in the former versus 40% to 60% in the latter.
        - Care must be taken to avoid malnutrition.
    - Measurements of 25(OH)D (calcidiol) levels is suggested with repeated testing done per baseline values and therapeutic interventions. Treatment of vitamin D deficiency and insufficiency may be corrected using treatment strategies recommended for the general population.
    - Patients with iPTH levels that are progressively rising or persistently above normal range are suggested to undergo evaluation for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency.
- **CKD G3a to 5 (without dialysis)**: Routine *use of calcitriol and vitamin D analogs is not suggested* but reasonable to be reserved for G4 and G5 with severe and progressive hyperparathyroidism.
    - Randomized controlled trials involving vitamin D analogs demonstrated increased hypercalcemia risks and lack of clinically relevant benefits.
    - **Note:** The use of calcimimetics is not indicated for patients with CKD not on dialysis. In patients with SHPT and CKD not on dialysis, the long-term safety and efficacy of calcimimetics have not been established. Clinical studies indicate that cinacalcet-treated patients with CKD not on dialysis have an increased risk for hypocalcemia compared with those on dialysis, an effect attributed to lower baseline calcium levels in the former group. (Of note, calcimimetic use in predialysis patients may also increase serum phosphate level due to its inhibitory effect on PTH, thus phosphaturic effect. This hyperphosphatemic effect does not occur in anuric patients on dialysis.)
- **CKD G5D**:
    - In patients requiring PTH-lowering therapy, suggested therapeutic options include calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D. *All agents are considered acceptable first-line options*.
    - Maintaining iPTH within the range of two to nine times of upper normal limit is suggested.

Phosphate control

- Dietary phosphate restriction (typically 1,000 mg/d):
  - Of the 1,000-mg phosphate ingested daily, ~60% is absorbed (600 mg/d or 4,200 mg/wk). A typical hemodialysis session removes ~800 mg or 2,400 mg/wk, assuming three dialysis sessions per week. Removal of the weekly net gain of 1,800 mg requires the use of phosphate binders.
  - Dietary phosphate:
    - Organic phosphorus:
      - Found in protein-rich foods from both animal and vegetarian sources of protein
      - Organic phosphorus is highly protein bound, which limits absorption.
      - Phosphorus derived from plants (phytate) has lower bioavailability compared with that from animal source.
    - Inorganic phosphorus commonly found in food preservatives or flavor enhancers have 90% to 100% bioavailability because they are not protein bound.
    - **Note:** Calcitriol [$1,25(OH)_2D$] increases GI absorption of phosphorus.
- Phosphate binders:
  - Commonly used agents in the United States and their notable and important clinical findings are reviewed in Table 3.4.

Table 3.4 Characteristics of commonly used phosphate-binding agents used in the United States

Phosphate Binders	Comments
Calcium acetate Calcium carbonate	• Elemental calcium content: 400 mg/1 g of calcium carbonate; 169 mg/667 mg of calcium acetate • Efficacy of calcium carbonate is reduced with the use of PPI or H2-blockers • Vascular and coronary artery calcification has been shown to be greater compared to non–calcium-based agents including sevelamer and lanthanum carbonate.
Sevelamer	• Interferes with GI absorption of active vitamin D, vitamin K, and levothyroxine • Reduces serum C-reactive protein, glycated hemoglobin, total and low-density lipoprotein cholesterols • No effect on FGF-23, klotho, intact PTH, or vitamin D levels

	• May crystallize in gut and leads to GI mucosal injury • Lowers all-cause mortality in CKD stages 3–5D but not cardiovascular mortality compared to calcium-containing binders (meta-analysis 2016)
Lanthanum carbonate	• Although lanthanum can accumulate in various tissues including bones, data to date have not shown evidence for liver damage or increased bone fractures • May crystallize in gut and leads to GI mucosal injury • Lower all-cause mortality but not cardiovascular events compared to calcium-containing binders • Low pill burden
Ferric citrate	• Reduces FGF-23 levels and increases hemoglobin
Sucroferric oxyhydroxide	• Reduces FGF-23 levels • Allows for reduction in erythropoiesis stimulating agent and intravenous iron doses • Low pill burden

Abbreviations: CKD, chronic kidney disease; FGF-23, fibroblast growth factor 23; GI, gastrointestinal; PPI, proton-pump inhibitor; PTH, parathyroid hormone.

  - The use of >1.5 g/d of elemental calcium-based phosphate binders can lead to positive calcium balance and is not recommended.
- Dialysis removal:
  - Hemodialysis removes approximately 800 mg of phosphorus per treatment.
  - Peritoneal dialysis removes approximately 300 mg of phosphorus per treatment.
  - Because phosphorus is predominantly intracellular, there is a postdialysis- rebound phenomenon due to extracellular shift.
  - Prolonged and frequent dialysis (i.e., nocturnal or daily hemodialysis) is superior in phosphorus removal compared with conventional hemodialysis.
  - **Note:** Increasing blood flow rate in hemodialysis is not effective in increasing phosphorus removal.

Vitamin D supplementation

- "Vitamin D" refers to inert vitamin D (e.g., cholecalciferol) prior to hydroxylation at both carbons 1 and 25 to become active $1,25(OH)_2D$.
- The prevalence of vitamin D deficiency is high among patients with CKD,

up to 97% in those requiring hemodialysis. **Note:** 25(OH)D level is measured as a surrogate for low "vitamin D" because hepatic hydroxylation of the vitamin D precursor, ergocalciferol, occurs readily without any regulation. 25(OH)D level generally serves well as an index of vitamin D deficiency.

- Factors associated with vitamin D deficiency in CKD:
  - Low sunlight exposure
  - Uremia-associated blunting of the response of plasma vitamin D to UVB irradiation
  - Uremia-associated skin hyperpigmentation and reduced UVB exposure
  - Urinary loss of vitamin D–binding protein–vitamin D complexes due to proteinuria and reduced proximal tubular reabsorption
  - Loss of vitamin D–binding protein–vitamin D complexes in peritoneal dialysate among patients receiving peritoneal dialysis
  - Poor nutrition
- Rationale for (inert) vitamin D supplementation:
  - Potential benefits other than for CKD-MBD: endothelial function, immunity, anti-inflammatory effect, regulation of the renin–angiotensin–aldosterone system, cardiac function/ventricular mass, response to erythropoietin-stimulating agents, malignancy
  - KDIGO suggests a dose of 1,000 to 2,000 IU/d of vitamin D_3, with acknowledgment that a more aggressive therapeutic plan may be required.
  - Ergocalciferol (D_2) versus cholecalciferol (D_3):
    - D_2 is found in vegetables (e.g., mushrooms) and typically in "vitamin D fortified" foods.
    - D_3 is found in animal-based foods (e.g., fish, meat, egg, dairy) or cutaneous conversion of 7-dehydroxycholesterol by UV sunlight in human.
    - Both ergocalciferol and cholecalciferol require hydroxylation at carbons 1 and 25 to become active $1,25(OH)_2D$.
    - Suggested advantages of D_3 over D_2:
      - D_3 may have greater affinity for 25-hydroxylase, hence better

conversion to 25(OH)D.
    - D_3 may have greater affinity for VDR.
    - D_2 has been suggested to have lower affinity for vitamin D–binding protein compared with D_3, hence higher systemic clearance and lower half-life compared to D_3.
  - The use of either D_2 or D_3 may be based on potential benefits of D_3 (discussed above) or local resources and/or patients' preference (i.e., vegans may prefer D_2).
- Rationale for the concurrent use of vitamin D with calcitriol or active vitamin D analogs in advanced CKD:
  - Vitamin D supplementation improves CKD-MBD, but may be insufficient to reduce PTH levels, particularly in later CKD stages G4 and G5. In advanced CKD, D_2 or D_3 may only be converted to 25(OH)D, but not to $1,25(OH)_2D$. Although the former can bind to VDR to exert intended physiologic effects, its affinity is 100 times less than that of $1,25(OH)_2D$.
  - Low calcidiol (25(OH)D) levels are associated with increased mortality in patients receiving hemodialysis.
- **Note:** Prior to any vitamin D supplementation, serum phosphate levels should be reduced to below 5.5 mg/dL, because vitamin D does increase GI absorption of phosphate and may worsen existing hyperphosphatemia.

Active vitamin D therapy (also known as vitamin D receptor agonist [VDRA])

- VDRA formulations in the United States include calcitriol: $1,25(OH)_2D_3$, doxercalciferol (1α-$(OH)D_2$) and paricalcitol (19-nor-$1\alpha,25(OH)_2D_2$)
- Comparative clinical effects of commercially available VDRA:
  - Both doxercalciferol and paricalcitol are thought to confer lower rates of hypercalcemia and hyperphosphatemia compared to calcitriol. However, a 2017 meta-analysis comparing paricalcitol with other VDRA found no significant differences in the incidence of hypercalcemia and hyperphosphatemia.
  - Observational studies revealed that the use of parenteral non-calcitriol VDRA in dialysis patients is associated with decreased risk of

hospitalization and mortality.
    - The use of parenteral paricalcitol is associated with improved survival compared to calcitriol.
- VDRA use is associated with increased FGF-23 levels, an independent predictor of mortality among patients with CKD. Regardless, there have been no studies to date that have reported an association of VDRA use with increased mortality.
- **Note:** Doxercalciferol 1(OH)-vitamin D needs to be hydroxylated at the 25 position to 1,25$(OH)_2$D in the liver before it becomes an active vitamin D. Thus, the use of doxercalciferol may not be optimally effective in advanced liver patients.

Calcimimetics

- Calcimimetics available in the United States: cinacalcet and etelcalcetide

Cinacalcet

- Mechanism of action: Cinacalcet acts on CaSR as a positive allosteric modulator to increase cellular sensitivity to extracellular calcium, thereby inhibiting parathyroid gland activity.
- Cinacalcet (30 to 180 mg/d):
    - Indications: treatment of SHPT in adult patients with CKD G5D, parathyroid carcinoma, and PHPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels, but who are nonsurgical candidates
    - Adverse effects: hypocalcemia and/or prolonged QT, seizures; upper GI bleeding; hypotension and/or worsening heart failure and/or arrhythmias; adynamic bone disease; chondrocalcinosis pyrophosphate (acute pseudogout)
    - Cinacalcet-induced hypocalcemia:
        - Thought to be due to the equivalent of post-(hyper)parathyroidectomy hungry bone syndrome, albeit a milder form
        - This phenomenon is predominantly asymptomatic with high likelihood for spontaneous recovery.

        - Therapy may not be necessary unless severe and symptomatic.
        - Prescribing information for use in CKD G5D: (1) Monitor serum calcium monthly once maintenance dose has achieved. (2) For serum calcium between 7.5 and 8.4 mg/dL or symptomatic, calcium-containing phosphate binders and/or vitamin D sterols can be used to raise serum calcium. (3) If level falls below 7.5 mg/dL or if symptomatic despite being on optimal dose of vitamin D, withhold cinacalcet until serum calcium reaches 8.0 mg/dL and/or resolution of symptomatic hypocalcemia. Reinitiation of cinacalcet should be done at dose lower than the previous one.
- Effective in controlling difficult-to-treat SHPT in both hemodialysis and peritoneal dialysis patients
- Cinacalcet effects on morbidity and mortality:
    - Post hoc analysis of four RCTs (*n* = 1,184), with follow-up at 6 to 12 months, revealed a reduction in risk of parathyroidectomy, fractures, and hospitalization.
    - Effect of Cinacalcet Hydrochloride therapy to Lower Cardiovascular Events (EVOLVE) trial also suggested reduction in the rate of clinical fracture with cinacalcet among patients with SHPT.
    - Cinacalcet with low dose VDRA may better reduce vascular calcification progression compared to VDRA therapy alone (A Randomized Study to Evaluate the Effects of Cinacalcet Plus Low dose Vitamin D on Vascular Calcification in Subjects with CKD) study.
    - Cinacalcet has been suggested to reduce the incidence of calcific uremic arteriolopathy.
    - Mortality data are conflicting. EVOLVE trial suggested a potential benefit of cinacalcet in risk reduction for death and cardiovascular outcomes. Cochrane analysis revealed no survival benefit.

Etelcalcetide

- Indication: treatment of SHPT in adults with CKD on hemodialysis
- Mechanism of action: Etelcalcetide acts as a direct CaSR agonist. (**Note:** Unlike cinacalcet whose action is to change the conformation of CaSR to

better sense plasma calcium, etelcalcetide directly activates CaSR in the absence of calcium.)

- Adverse effects: similar to those observed with cinacalcet above
- Half-life of etelcalcetide is >7 days compared to 30 to 40 hours for cinacalcet.

NOTE Both cinacalcet and etelcalcetide reduce while VDRA increase FGF-23 levels. Etelcalcetide may induce a greater FGF-23–lowering effect compared to cinacalcet. Whether this effect translates to improved survival compared with cinacalcet remains to be proven.

Management of hypocalcemia

- Calcium supplement should not exceed 1,000 mg/d.
- Avoid excess calcium supplement due to concerns for increased vascular calcifications and increased cardiovascular and all-cause mortality.
- For hemodialysis patients, KDIGO 2017 suggests the use of dialysate calcium concentration between 1.25 and 1.50 mmol/L or 2.5 and 3.0 mmol/L.
- *Notes* regarding calcium intake in patients with CKD:
  - Patients with CKD stage 3 or 4 can develop positive calcium balance when consuming dietary calcium ≥2,000 mg/d or receiving calcium carbonate supplement containing ≥1,500 mg of elemental calcium daily. Positive calcium balance may contribute to accelerated vascular calcifications.
  - KDIGO suggests that a daily intake of 1,000 mg elemental calcium provides neutral calcium balance in patients with CKD stage 3 or 4.

Indications for parathyroidectomy in patients with CKD and SHPT (Table 3.5)

Table 3.5 Indications for parathyroidectomy in patients with CKD and secondary hyperparathyroidism due to kidney disease

CKD, Non-transplant Patients	Kidney Transplant Recipients

• Elevated intact PTH levels >800 pg/mL that are refractory to medical therapy and clinical signs and symptoms associated with refractory hyperparathyroidism:
  • Hypercalcemia
  • Uncontrollable hyperphosphatemia
	• Severe and persistent hypercalcemia ≥11.5 mg/dL for ≥6–12 mo and
	• Symptomatic/progressive hypercalcemia:

• Evidence of osteitis fibrosa by bone biopsy, classic radiologic findings, or bone metabolic markers • Enlarged and/or nodular parathyroid glands (>500 mg) • Calciphylaxis • Intractable pruritus • Progressive calcification of blood vessels • Severe skeletal deformity • Severe bone pain • Anemia resistance to erythropoietin • Peripheral neuropathy	• Nephrolithiasis • Persistent osteitis fibrosa • Progressive vascular calcification • Calciphylaxis • Calcium-related renal graft function deterioration
Sustained intact PTH levels >1,000 pg/mL refractory to medical therapies, regardless of symptoms	

Note: KDIGO 2017 suggests parathyroidectomy "in patients with CKD G3a–G5D with severe hyperparathyroidism who fail to respond to medical or pharmacologic therapy." Specific indications for parathyroidectomy listed are opinion based. Note that the indications for parathyroidectomy for SHPT are different from those for PHPT.

Abbreviations: CKD, chronic kidney disease; PTH, parathyroid hormone.

- KDIGO 2017: Parathyroidectomy is suggested in patients with CKD G3a to G5D with severe hyperparathyroidism who fail to respond to pharmacologic therapy.
- For kidney transplant candidates, decisions regarding the need for parathyroidectomy and extent of parathyroid resection should be jointly made with the transplant center as SHPT (but likely not tertiary HPT) may resolve following a successful transplant. Also see **Chapter 9**.

DISORDERS OF MAGNESIUM METABOLISM

Magnesium Background

- Magnesium is the second most abundant intracellular and fourth most abundant cation in the body.
- 99% of Mg^{2+} is stored in bones or within cells.
- In plasma, 70% to 80% of Mg^{2+} exists as free ionized Mg^{2+} and 20% to 30% as protein-bound or complexed.

Physiologic Roles of Magnesium

- Cofactor for all enzymatic reactions requiring ATP (ATPase), "kinases"
- Enzyme activator for neuromuscular excitability and cell permeability

- Regulator of ion channels and mitochondrial function
- Critical element in cellular proliferation and apoptosis
- Important factor in both cellular and humoral immune reactions
- Cofactor of enzymes involved in modulation of transcellular glucose transport (Magnesium deficiency may play a role in the development of glucose intolerance and diabetes mellitus type 2 and posttransplant diabetes mellitus.)

Magnesium Metabolism

Input: GI absorption

- Average daily intake ~300 mg/d
- Approximately 50% is absorbed from GI tract via:
  - Passive paracellular absorption when there is a high-concentration gradient between intestinal lumen and epithelial cells
  - Active transport via transient receptor potential melastatin channel TRPM6 in the large intestines where there is a low intraluminal magnesium content. TRPM6 is also present in the DCT in the kidneys where it determines the final urinary magnesium loss.

Cellular shift, redistribution

- Bones are the principal reservoirs of Mg^{2+} and do not readily exchange with extracellular Mg^{2+}. In negative Mg^{2+} balance, bone Mg^{2+} shifting into the plasma does not occur for weeks. Acute maintenance of plasma Mg^{2+} relies on renal reabsorption.
- Cellular influx increases with catecholamines, refeeding syndrome, treatment of metabolic acidosis, hungry bone syndrome seen after parathyroidectomy, or diffuse osteoblastic metastases.
- Redistribution: Mg^{2+} deposition in necrotic tissues, for example, acute pancreatitis

Output

- There is a physiologic GI magnesium loss of ~40 mg/d from pancreatic and salivary secretions.
- GI loss: chronic diarrhea, steatorrhea

- Renal loss

Renal Metabolism of Magnesium (Fig. 3.10)

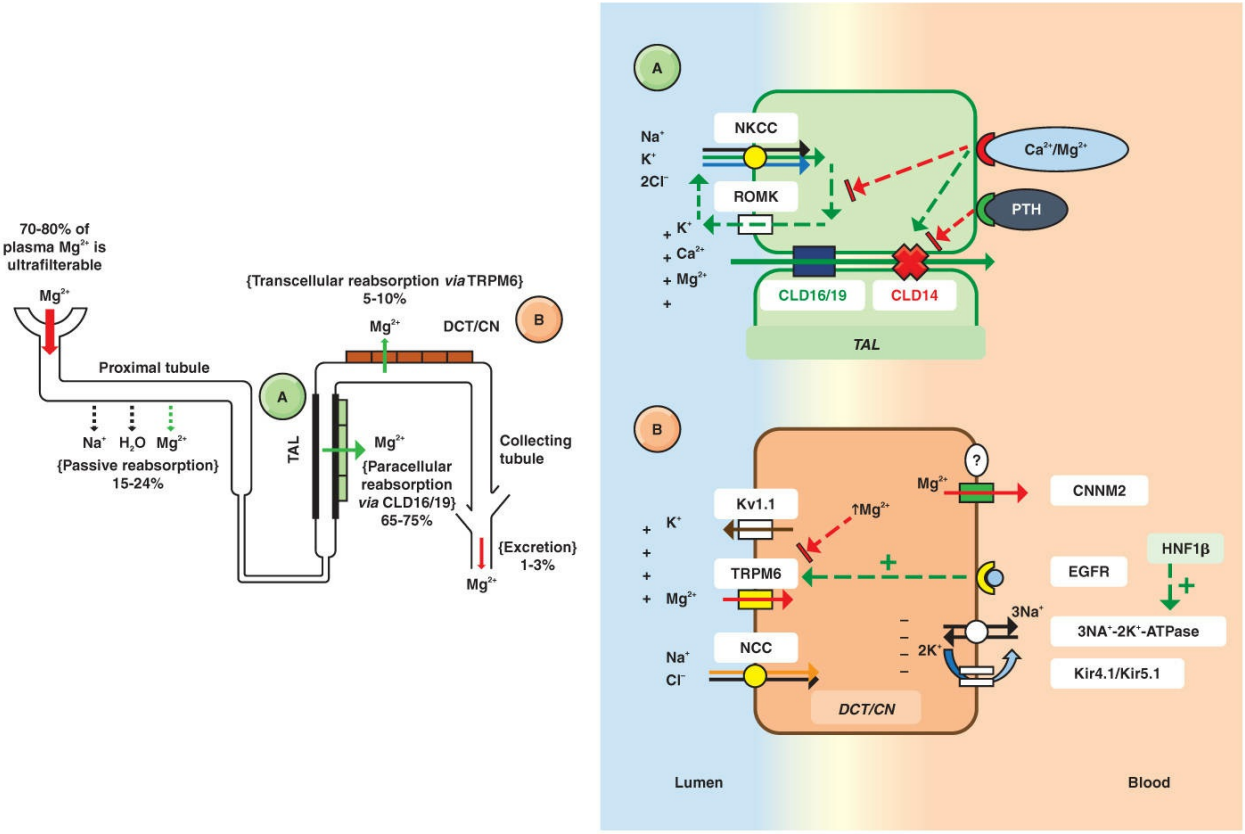

FIGURE 3.10 Renal handling of magnesium. A. Paracellular reabsorption of Mg^{2+} at TAL is similar to that for Ca^{2+}. B. The binding of either Ca^{2+} or Mg^{2+} to CaSR inhibits ROMK while stimulating CLD14. The former results in reduced intraluminal K^+ recycling, reduced positively charged lumen, thus increased calciuria/magnesiuria, while the latter results in inhibition of Ca^{2+}/Mg^{2+} paracellular reabsorption. In contrast, PTH inhibits CLD14 and results in increased paracellular reabsorption of Ca^{2+}/Mg^{2+}. B. In the DCT/CN, Kv1.1 and Kir4.1/Kir5.1 are thought to maintain the favorable transmembrane potential difference for Mg^{2+} reabsorption. Elevated serum Mg^{2+} level sensing by Ca^{2+}/Mg^{2+}-SR leads to inhibition of Kir4.1/Kir5.1; Epithelial growth factor binding to its receptor EGFR stimulates the shuttling of cytosolic TRPM6 to the apical surface for Mg^{2+} reabsorption. The molecular mediator of basolateral Mg^{2+} reabsorption remains unknown. Abbreviations: CaSR, calcium (magnesium) sensing receptor; CLD, claudin; CNNM2, divalent metal cation transporter; DCT/CN; distal convoluted tubule/connecting segment; EGFR, epithelial growth factor receptor; HNF-1β, hepatic nuclear factor 1β; Kir4.1/Kir5.1, inward rectifying potassium channel 4.1/5.1; Kv1.1, potassium voltage-gated channel; NCC, sodium chloride cotransporter; NKCC, sodium potassium 2 chloride cotransporter; PTH, parathyroid hormone; ROMK, renal outer medullary potassium channel; TAL, thick ascending limb of Henle loop; TRPM6, transient receptor potential melastatin channel 6.

Glomerular filtration

- 70% to 80% of plasma Mg^{2+} is ultrafilterable in the ionic form.
- Ultrafilterability of Mg^{2+} is dependent on glomerular filtration, volume and acid–base status, serum content of anions, glomerular basement membrane integrity.

Proximal tubules

15% to 25% is reabsorbed paracellularly, thought to be predominantly passive and proportional to Na^+ and H_2O reabsorption.

Thick ascending limb loop of Henle (TAL)

- 65% to 75% is reabsorbed paracellularly. Recall that both Ca^{2+} and Mg^{2+} reabsorption are facilitated by the positively charged lumen created via K^+ recycling through ROMK and the tight junction protein complex claudin 16/19 (see **Bartter and Gitelman Syndromes**).
- Claudin 14 reduces both Ca^{2+} and Mg^{2+} reabsorption.

DCT/CN

- 5% to 10% of total filtered Mg^{2+} (or 70% to 80% of Mg^{2+} delivered from TAL) is reabsorbed via TRPM6 (**Fig. 3.10**).
- The apical potassium voltage-gated channel Kv1.1 and basolateral potassium channel Kir4.1/Kir5.1 are thought to function to maintain the favorable transmembrane potential difference for Mg^{2+} reabsorption across TRPM6 in the DCT/CN.
- The basolateral (3)Na^+-(2)K^+-ATPase maintains the intracellular negative charge to promote intracellular Mg^{2+} uptake via TRPM6. The hepatic nuclear factor 1β (HNF-1β) regulates the transcription of Na^+-K^+-ATPase. Reduced HNF-1β expression or activity can lead to hypomagnesemia.
- The transport mechanism for basolateral Mg^{2+} extrusion remains to be defined.
- Regulation of TRPM6 activity and expression:
  - High intracellular Mg^{2+} reduces apical expression of TRPM6.
  - Epithelial growth factor (EGF) binding to its receptor (EGFR) increases activation and apical expression of TRPM6. This explains the reason for increased hypomagnesemia risk among patients receiving anti-EGFR monoclonal antibody therapy.
  - Other suggested regulators: PTH, aldosterone, low dietary magnesium intake

HYPOMAGNESEMIA

Clinical Manifestations of Hypomagnesemia

- Signs/symptoms (typically <1.2 mg/dl): muscular tremors, fasciculations, nystagmus, tetany, altered mentation, depression, psychosis, migraine, ataxia, vertigo, seizures, dysphagia, asthma, chronic fatigue syndrome
- Electrolyte disturbances associated with hypomagnesemia:
  - Hypokalemia:
    - This is thought to be due to impaired Na^+-K^+-ATPase at the DCT and ROMK at TAL (Mg^{2+} is a cofactor for the former and negative regulator for the latter—Mg^{2+} keeps ROMK closed. Reduced level of Mg^{2+} leads to K^+ leakage via ROMK.)
  - Hypocalcemia:
    - Hypomagnesemia is associated with impaired PTH secretion and tissue sensitivity to PTH, both leading to hypocalcemia.
    - Hypomagnesemia is also associated with reduced vitamin D metabolism.
  - Hypophosphatemia: Increased phosphaturia has been described with hypomagnesemia.
- ECG changes:
  - Prolonged QT and PR intervals
  - Flattening or inversion of precordial P waves
  - ST-depression
  - T-wave inversion
  - Widening of QRS
  - Torsades de pointes
  - Treatment-resistant ventricular fibrillation (and other arrhythmias)
  - Worsening of digitalis toxicity
- Other associated adverse effects: altered glucose homeostasis, increased insulin resistance, atherosclerotic vascular disease, HTN, MI, osteoporosis, worse GFR decline in patients with diabetes type 2 and CKD, worse recovery potential of AKI in intensive care unit (ICU) setting, asthma, osteoporosis
- The protective effects of magnesium are thought to be via its

anticalcification property, antioxidant activity on endothelial function, and mesangial smooth muscle relaxation effect, among others.

Causes of Hypomagnesemia

Reduced input

- Decreased intake: malnutrition, prolonged intravenous therapy without Mg^{2+} supplementation
- Decreased intestinal absorption: surgical resection of the small intestine, familial Mg^{2+} malabsorption (TRPM6)

Cellular shift/redistribution: see Magnesium Metabolism section above

Excessive urinary losses

- High-volume expansion, diuretics, postobstructive, posttransplant diuresis
- The use of proton-pump inhibitors has been reported to be associated with hypomagnesemia in some patients receiving concurrent diuretics. Single-nucleotide polymorphisms in TRPM6 have been attributed to the increased hypomagnesemic risk.
- Electrolyte disturbances: hypercalcemia, renal tubular acidosis (RTA), hypophosphatemia
- Drugs (aminoglycosides, amphotericin, cisplatin >> carboplatin, cyclosporine), EGF inhibitors (e.g., cetuximab, panitumumab, matuzumab), antituberculous drugs (e.g., capreomycin), ritodrine, β-adrenergic agonists (e.g., theophylline, salbutamol), other drugs (amphotericin B, pentamidine, foscarnet, pamidronate)
- Inherited disorders (refer to **Fig 3.10** to better understand the clinical effects of mutations involving various transporters/factors necessary for optimal magnesium reabsorption at the DCT):
  - Hypomagnesemia with secondary hypocalcemia: autosomal recessive mutation of TRPM6
    - Hypomagnesemia results from both poor GI absorption and urinary loss.
    - Affected individuals may present with seizures/tetany perinatally.
    - Treatment is high-dose oral administration of magnesium sulfate for absorption via passive paracellular pathway.

- Mutation affecting pro-EGF processing: normal EGF binding to its receptor is necessary for normal trafficking of TRPM6 to the apical surface in the DCT. Absence of EGF or presence of antibodies directed against EGFR (e.g., cetuximab, panitumumab, matuzumab) can lead to urinary magnesium wasting.
- Gitelman syndrome. NCC dysfunction/mutation may reduce TRPM6 expression.
- Familial hypomagnesemia with hypercalciuria and nephrocalcinosis: Mutation of claudin 16 or 19 (tight junction proteins), autosomal recessive, age of onset: children, renal Mg^{2+} and Ca^{2+} wasting, nephrolithiasis, and nephrocalcinosis
- Isolated dominant hypomagnesemia (IDH): Mutation of γ-subunit of Na^{+}-K^{+}-ATPase, autosomal dominant, urine Mg^{2+} wasting but hypocalciuria. Clinically, affected individuals have hypomagnesemia, but normal serum Ca^{2+} and K^{+}.
- HNF-1β mutation: HNF-1β regulates transcription of the gene encoding γ-subunit of Na^{+}-K^{+}-ATPase. Patients present similarly as IDH above.
- Potassium voltage-gated channel Kv1.1 mutation: reduces K^{+} exit into lumen, hence reduced positive voltage that would normally favor Mg^{2+} entry via TRPM6
- Inward rectifying potassium channel Kir4.1/5.1: loss of function reduces basolateral K^{+} recycling, hence reduced $3Na^{+}$-$2K^{+}$-ATPase activity that normally creates the negative intracellular voltage for Mg^{2+} apical entry

Other conditions associated with hypomagnesemia

- Acute pancreatitis, transfusion of citrated blood, severe burns, continuous ambulatory peritoneal dialysis, chronic alcoholism (multifactorial)
- Excessive GI fluid loss: prolonged nasogastric suction, ulcerative colitis, laxative abuse, intestinal and biliary fistulas
- Congenital causes of hypomagnesemia (Table 3.6)

Table 3.6 Congenital causes of hypomagnesemia

	Level of Defect	*Specific Defect	Condition
GI	Passive paracellular	TRPM6	Hypomagnesemia with secondary

absorption	transcellular via TRPM6		hypocalcemia
Cellular shift; tissue sequestration	—	—	—
Kidney handling	Glomerular filtration	—	—
	Proximal tubular reabsorption	—	—
	Thick ascending limb of Henle loop	Claudin 16/19	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis
		NKCC2	Antenatal Bartter syndrome type l with low to normal serum magnesium
		ROMK	Antenatal Bartter syndrome type 2 with low to normal serum magnesium
		CIC-Kb	Classic Bartter syndrome type 3, hypomagnesemia in ~20%
		*CaSR	Bartter syndrome type 5
	Distal convoluted tubule/connecting segment	TRPM6	Hypomagnesemia with secondary hypocalcemia
	Apical regulators/effects of TRPM6	Kvl.l	Isolated autosomal dominant hypomagnesemia
		Kir4.1/Kir5.1	Kir4.1 mutation: SeSAME/EAST syndrome; Kir5.1 mutation: hypomagnesemia, hypokalemia, hyperchloremic metabolic acidosis and hypercalciuria
		NCC	Gitelman syndrome
	Basolateral regulators/effectors of TRPM6	Na^+-K^+-ATPase	*FXYD2* (gene encoding Na^+-K^+-ATPase): autosomal dominant hypomagnesemia with hypocalciuria HNF-1β: Renal cysts and diabetes mellitus with renal magnesium wasting and hypocalciuria
		EGFR	Isolated recessive hypomagnesemia with normocalciuria
		CNNM2	Autosomal dominant hypomagnesemia
		Insulin	TRPM6 polymorphisms associated with reduced insulin activation of TRPM6, particularly if low dietary magnesium intake

*With the exception of CaSR, which is an activating mutation, all other mutations are loss of function mutations. Abbreviations: CaSR, calcium-sensing receptor; ClC-Kb, chloride channel; CNNM2, divalent metal cation transporter; EGFR, epithelial growth factor receptor; GI, gastrointestinal; HNF-

1β, hepatic nuclear factor 1β; Kir4.1/Kir5.1, inward rectifying potassium channel 4.1/5.1; Kv1.1, potassium voltage-gated channel; SeSAME/EAST syndrome, syndrome of seizures, sensorineural deafness, ataxia, intellectual disability (mental retardation) and electrolyte disturbances; NCC, sodium chloride cotransporter; NKCC2, sodium potassium 2 chloride cotransporter; ROMK, renal outer medullary potassium channel; TRPM6, transient receptor potential melastatin channel 6.

- Acquired causes of hypomagnesemia (Table 3.7)

Table 3.7 Acquired causes of hypomagnesemia

	Level of Defect	*Specific Defect	Condition
GI absorption	Passive paracellular transcellular via TRPM6	TRPM6	Malnutrition; prolonged nasogastric suction; malabsorptive conditions: short gut syndrome; alcoholism; use of proton-pump inhibitors
Cellular shift; tissue sequestration	—	—	Acute pancreatitis (Mg^{2+} and Ca^{2+} saponification in necrotic fat); hungry bone syndrome; refeeding; foscarnet (Mg^{2+} incorporation into bone matrix); massive blood transfusions; third-trimester pregnancy; lactation; parenteral alimentation; cardiopulmonary bypass
Kidney handling	Glomerular filtration	—	Hyperfiltration (DM, osmotic or postobstructive or ATN diuresis); volume expansion with fluid administration; increased filterable Mg^{2+} (e.g., metabolic acidosis, low serum organic anions)
	Proximal tubular reabsorption	—	Fanconi syndrome; drug toxicity (cisplatin, gentamicin, pentamidine); high dietary sodium intake
	Thick ascending limb of Henle loop	Claudin 16/19	—
		NKCC2	Loop diuretics; hypokalemia
		ROMK	Hypokalemia
		ClC-Kb	—
		*CaSR	Increased serum Mg^{2+} and Ca^{2+} levels; aminoglycosides; possibly calcimimetics
	Distal convoluted tubule/connecting segment	TRPM6	Calcineurin inhibitors: cyclosporine and tacrolimus reduce renal TRPM6 expression; rapamycin reduces TRPM6 stability
	Apical regulators/effects of TRPM6	Kvl.l	Hypokalemia
		Kir4.1/Kir5.1	Hypokalemia
		NCC	Thiazide diuretics; calcineurin inhibitors

	Basolateral regulators/effectors of TRPM6	Na^+-K^+-ATPase	Hypophosphatemia; cyclosporine has been shown to inhibit Na^+-K^+-ATPase; ethanol inhibits Na^+-K^+-ATPase
		EGFR	Anti-EGFR antibodies (cetuximab, panitumumab, matuzumab); cisplatin reduces EGF and TRPM6 mRNA; cyclosprine reduces TRPM6, NCC, and EGF mRNA
		CNNM2	—
		Insulin	Diabetes mellitus

*With the exception of CaSR, where the acquired conditions listed activate CaSR to cause hypomagnesemia, all other acquired conditions listed inhibit transporters/factors necessary for magnesium transport to cause hypomagnesemia. Abbreviations: ATN, acute tubular necrosis; CaSR, calcium-sensing receptor; ClC-Kb, chloride channel; CNNM2, divalent metal cation transporter; DM, diabetes mellitus; EGFR, epithelial growth factor receptor; GI, gastrointestinal; HNF-1β, hepatic nuclear factor 1β; Kir4.1/Kir5.1, inward rectifying potassium channel 4.1/5.1; Kv1.1, potassium voltage-gated channel; mRNA, messenger RNA; NCC, sodium chloride cotransporter; NKCC2, sodium potassium 2 chloride cotransporter; ROMK, renal outer medullary potassium channel; TRPM6, transient receptor potential melastatin channel 6.

Diagnosis of Hypomagnesemia

Total daily urinary magnesium loss

- Urinary magnesium > 20 mg/d indicates urinary Mg^{2+} wasting.
- Urinary magnesium < 10 mg/d indicates total body mg^{2+} depletion.

Fractional excretion of magnesium (FeMg)

- (FeMg) = $([U_{Mg} \times S_{Cr}]/[0.7 \times S_{Mg} \times U_{Cr}]) \times 100$
  - Factor of 0.7 indicates only ~70% of plasma Mg is filterable.
  - Equation should only be used in patients with relatively good kidney function.

Data interpretation

- For extra-renal causes of hypomagnesemia: FeMg <2.0% to 2.5% or 24-hour urine magnesium <20 mg
- For renal magnesium wasting: FeMg >2.0% to 4.0% or 24 hour urine magnesium > 20 mg
- **Note:** The site of renal magnesium loss may be determined based on urinary calcium.
  - Conditions involving defective magnesium reabsorption at the loop of Henle will have concurrent calcium wasting, that is, urinary calcium

>250 mg/d. Examples: loop diuretics, CaSR agonists (e.g., gentamicin, cinacalcet), familial hypomagnesemia with hypercalciuria and nephrocalcinosis (claudin 16/19 mutations).

- Conditions involving defective magnesium reabsorption at the distal tubules will have hypocalciuria, that is, urinary calcium <200 mg/d. examples: thiazide diuretics, gitelman syndrome, isolated dominant hypomagnesemia.

- See Table 3.8 for a summary of indices used in the diagnosis of magnesium disorders.

Table 3.8 Indices used in the diagnosis of magnesium disorders

Test	Description	Interpretation
24-Hour urine Mg^{2+} collection	• 24-Hour urine collection • Also check urine creatinine to assess collection adequacy	• >20 mg/d is considered high urinary Mg^{2+} excretion • <10 mg/d indicates total body mg^{2+} depletion • Examples for clinical application: • For hypomagnesemia, >20 mg/d may be consistent with renal wasting • For hypermagnesemia, >20 g/d may be consistent with excess intake

Percent fractional excretion of Mg^{2+} (FeMg)	• $FeMg = (U_{Mg} \times S_{Cr}) \div (0.7 \times S_{Mg} \times U_{Cr}) \times 100$
	  • The factor 0.7 indicates that only ~70% of plasma Mg^{2+} is filterable.
	  • Equation should only be used for patients with relatively good kidney function
		• FeMg >2%–4% is considered high urinary Mg^{2+} excretion
		• FeMg <2%–2.5% is considered low urinary mg^{2+} excretion
		• Examples for clinical application:
		  • For hypomagnesemia, <2% may be consistent with gastrointestinal loss and/or malnutrition
		  • For hypermagnesemia, >2% may be consistent with excess intake

Abbreviations: S_{Cr}, serum creatinine; S_{Mg}, serum magnesium concentration; U_{Cr}, urine creatinine; U_{Mg}, urine magnesium concentration.

Management of Hypomagnesemia

- Severe deficiency: Intravenous repletion for severe but non–life-threatening hypomagnesemia: 1 to 2 g/h for 3 to 6 hours, then 0.5 to 1 g/h as needed to correct deficiency

- Symptomatic deficiency: Intravenous: 1 to 2 g over 15 to 60 minutes; maintenance intravenous therapy may be required to correct deficiency (0.5 to 1 g/h).
- Severe or symptomatic
  - Infuse 1 to 2 g $MgSO_4$ (in 100 mL 5% dextrose water) over 15 minutes.
  - Torsades: Infuse 1 to 2 g $MgSO_4$ over 1 to 2 minutes.
  - Seizures: Infuse 2 g $MgSO_4$ over 10 minutes; administration of calcium may be necessary (separate line).
- Aldosterone has been suggested to induce renal Mg^{2+} wasting, an effect that may be ameliorated by aldosterone antagonists (e.g., spironolactone, eplerenone).

NOTE

- Intravenous magnesium supplementation causes an abrupt rise in serum Mg^{2+} level, which leads to reduced reabsorption of Mg^{2+} across the TAL. This limits efficient magnesium repletion with intravenous supplementation.

- *Caution* with excessive Mg^{2+} supplementation:
  - Drug interactions: central nervous system (CNS) depressants (barbiturates, hypnotics, narcotics, antihistamines, antidepressants); cardiac glycosides; neuromuscular blocking agents (pancuronium)
  - Side effects related to overdosing: flushing, sweating, hypotension, depressed reflexes, flaccid paralysis, hypothermia, circulatory collapse, cardiac and CNS depression proceeding to respiratory paralysis. Hypocalcemia with signs of tetany secondary to $MgSO_4$ therapy for eclampsia has been reported.

HYPERMAGNESEMIA

Clinical Manifestations of Hypermagnesemia

- Signs/symptoms: muscular weakness, paralysis, ataxia, drowsiness, confusion, paralytic ileus, bladder paralysis, nausea/vomiting, hypotension, bradycardia, absent tendon reflexes, hypoventilation—essentially, everything “slows down.”
- Associated electrolyte changes: hypocalcemia (due to suppressed PTH secretion and possible Mg^{2+} binding and activation of CaSR)

- ECG changes:
  - Increased PR and QT
  - Increased QRS duration
  - Variable decrease in P-wave voltage
  - Variable degree of T-wave peaking
  - Complete atrioventricular block
  - Asystole
- Other effects: hypoparathyroidism, vascular relaxation, interference with platelet adhesiveness, thrombin generation time, and clotting time
- Hyperkalemia may occur due to the suppression of K^+ secretion. This is possibly due to Mg^{2+} gatekeeping function in ROMK: Mg^{2+} normally keeps ROMK closed and limits K^+ wasting.

Causes of Hypermagnesemia

- Kidney failure, rhabdomyolysis, tumor lysis, tissue necrosis
- Excessive intake: oral, infusion, magnesium-containing enemas, Dead Sea water drowning (very high content of both calcium and magnesium), parenteral, urethral irrigation; use of common Mg^{2+}-containing medications, especially among patients with CKD: laxatives (milk of magnesia), antacids (extra-strength Rolaids, Mylanta)
- Redistribution: acute acidosis
- Others: Familial hypocalciuric hypercalcemia, diabetic ketoacidosis, lithium, milk-alkali syndrome, theophylline toxicity, adrenal insufficiency, hypothyroidism

Treatment of Hypermagnesemia

- Antagonizing magnesium:
  - Calcium is a natural antagonist of Mg^{2+}.
  - Calcium: ~100 to 200 mg *elemental* Ca^{2+} infused over 5 to 10 minutes
  - One 10 mL ampule of Ca^{2+} gluconate contains 90 mg of elemental calcium.
  - One 10 mL ampule of Ca^{2+} chloride contains 272 mg of elemental calcium.

- Removal of magnesium:
  - Dialysis
  - Diuresis with furosemide (**Note:** Loop diuretics can lower Ca^{2+}, which may precipitate arrhythmias in patients with hypermagnesemia.)
- Cardiopulmonary support

NOTE
- Magnesium can potentiate the hypotensive effect of CCBs and can cause severe hypotension in preeclamptic/eclamptic patients treated with both. Treatment of this complication is administration of calcium gluconate.
- Both hypomagnesemia and hypermagnesemia can reduce PTH secretion.

KIDNEY STONES

Definitions

- Nephrolithiasis refers to *intratubular* stone deposits.
- Nephrocalcinosis refers *to interstitial* stone deposits in cortex and medulla.
- Both may occur in the same patient.

Epidemiology

- Lifetime risks have been estimated to be ~5% to 10% of US women and 10% to 20% of US men.
- Prevalence based on the National Health and Nutrition Evaluation Survey (NHANES):
  - Prevalence of kidney stones has steadily increased for women from 4.1% in 1994 to 9.4% in 2014 and 6.3% to 10.9% for males over the same time period.
  - The prevalence from 2010 to 2014, however, was relatively stable for males, from 10.6% to 10.9%, but increased from 7.1% to 9.4% for females.
  - Kidney stone prevalence increased over every decade of life starting at age 20 in males, peaking at ~18% for age >60 years, but appears to peak and plateau to ~10% beyond the fourth decade for females.
  - The prevalence has increased at a greater rate among younger compared to older age groups:
    - Since 2007 to 2014, stone prevalence remained relatively stable for

males for each decade of life over the age of 20 but increased for females in the 20 to 39 and 40 to 59 age groups over the same period. The prevalence in females increased the most in the youngest age group of 20 to 39, from 3.9% in 2007 to 2008 to 7.5% in 2013 to 2014 and 7.4% to 10.8% for the 40 to 59 age group over 2007 to 2008 and 2013 to 2014, respectively.

    - Based on the US Census and South Carolina Medical Encounter database, which included younger individuals, the greatest increase in stone incidence from 1997 to 2012 was observed among 15- to 19-year olds.

- Geographic risk: more prevalent in Southeast US, presumably due to hot climate in association with inadequate fluid intake and/or increased sun exposure
- Recurrence rates depend on the number of stone episodes already experienced; younger age; male gender; higher body mass index (BMI); family history of stones; history of brushite, struvite, or uric acid stone; stone size; and the number of stones on imaging (based on 3,364 incident kidney stone formers in Olmsted County, MN).
- Association with HTN: The same study from Olmsted County, MN, revealed that the risk of HTN was higher after the first symptomatic kidney stone event. Kidney stone type, severity, and treatment were not associated with incident HTN.
- 2015 analysis from the Atherosclerosis Risk in Communities database did not find an association between kidney stone history and CKD risk. Regardless, close kidney function monitoring is warranted among individuals with complicated stone history.
- Associations with cardiovascular outcomes:
    - 2014 meta-analysis (*involving cohort studies from PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and conference proceedings through February 27, 2014*) reported increased risk for incident CHD (hazard ratio 1.19, $p = 0.05$) and stroke (hazard ratio 1.40, $p < 0.001$) among patients with kidney stones.
    - 2017 meta-analysis (*involving PubMed or EMBASE publications before*

May 31, 2016) similarly revealed increased risk of CHD and stroke.

Stone Types and Prevalence in the United States

- Calcium (70% to 90%): Of all calcium stones, most common type is mixed calcium oxalate and phosphate, followed by calcium oxalate and calcium phosphate.
- Uric acid (5% to 10%); The incidence of uric acid stone is on the rise in the United States and thought to be associated with the increased incidence of metabolic syndrome.
- Struvite (<10%)
- Cystine (<1%)
- Other (<1%)

Common crystals associated with kidney stones are shown in **Figure 3.11.**

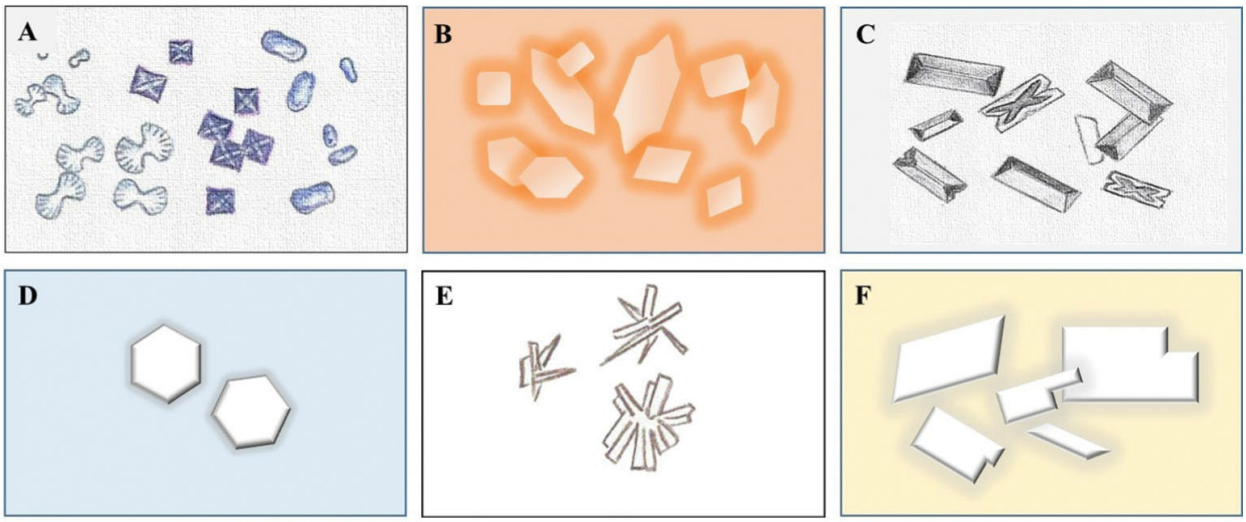

FIGURE 3.11 Stone crystals. **A.** Calcium oxalate crystals (octahedral, dumbbell, or picket fence shaped) may be seen with ethylene glycol toxicity or hypercalcemia. **B.** Uric acid crystals (plate like, rhomboid, or square shaped) may be seen in acidic urine pH <6.0 and tumor lysis syndrome. **C.** Struvite crystals, "coffin lid," or fern-leaf like if freshly formed; consist of ammonium, magnesium, and phosphate. **D.** Cystine crystals (perfect hexagonal shape) may be seen in cystinosis, but not in normal urine. **E.** Calcium phosphate crystals (blunt-ended needles, prisms, or rosette) may also appear amorphous as urate but calcium phosphates precipitate at basic urine pH >7.0 rather than low pH. Additionally, unlike the *pinkish* orange color with urate, calcium phosphate crystals are colorless or white. **F.** Cholesterol plates.

Stone Inhibitors and Promoters

Stone inhibitors

- Inorganic stone inhibitors:
  - Mg^{2+}
    - Mg^{2+} complexes with oxalate thereby decreases calcium oxalate supersaturation.
    - Mg^{2+} may also reduce gut oxalate absorption.
    - Higher dietary Mg^{2+} has been shown to be associated with a 30% lower risk of stone formation in men, but not in women.
  - Pyrophosphate: forms highly soluble complexes with Ca^{2+}
  - Citrate: binds to calcium to form a soluble complex in urine, thus effectively reduces Ca^{2+} availability for calcium phosphate/oxalate formation
- Organic stone inhibitors: nephrocalcin, urinary prothrombin fragment 1, protease inhibitor: inter-α-inhibitor, glycosaminoglycans
- High urine flow: *most* effective inhibitor/intervention in stone prevention
- Dietary factors associated with lower stone risks: dietary calcium (dairy and nondairy), dietary potassium, caffeine, DASH diet, Mediterranean diet (rich in fruits, vegetables, nuts, fish, and legumes; low in meats, saturated fats, and sugars; moderate alcohol), coffee (regardless of caffeine content), tea, beer, wine, orange juice (source of citrate), zinc (e.g., oysters, beans, mushrooms, cashews)

Stone promoters

- Randall plaque: subepithelial calcification in the renal papilla that act as an anchor for calcium oxalate crystals and are considered to be the initiating event in renal stone formation
- Urinary factors:
  - High Na^{+} diet reduces proximal tubular reabsorption of Na^{+} and passive Ca^{2+} reabsorption, thereby increases calciuria and risk for calcium stone formation.
  - High Na^{+} intake has also been reported to be associated with increased uricosuria.
  - High levels of stone substrates: calcium, oxalate, urate, phosphate, cystine

- Low urine pH facilitates uric acid, cystine precipitation.
- High urine pH facilitates calcium phosphate precipitation. **Note:** Although triple phosphate stones (i.e., magnesium ammonium phosphate or struvite) are seen in high urine pH, it is the ammonia concentration that is the primary factor for the triple phosphate crystal formation. Alkalinization of a urine specimen with ammonia generates triple phosphates, whereas alkalinization with sodium hydroxide does not.
- Low urine flow
- Bacterial products

Other factors associated with increased stone risk

- Overweight and obese individuals with BMI ≥25 and >30 kg/m^2, respectively, have been suggested to have increased incidence of uric acid, but not calcium stones. Urinary metabolic profiles have been reported to have higher sodium, calcium, uric acid, and oxalate, along with lower urine pH compared to those with BMI <25.
- Medical conditions: HTN, diabetes, obesity and recent weight gain (effect of obesity on stone risk is more evident in females than males), metabolic syndrome (BMI > 25 kg/m^2, diabetes mellitus, HTN, and dyslipidemia), gout, cholelithiasis
- Bariatric surgeries, 2016 meta-analysis:
  - Roux-en-Y is associated with increased risk for kidney stones: Patients have increased oxalate and calcium oxalate excretion at 6- and 12-month follow-up, presumably due to increased intestinal fat malabsorption. (Calcium preferentially binds to free fatty acids in the gut, thereby allowing free oxalate to be absorbed.)
  - Restrictive bariatric surgery was associated with decreased stone risk compared to control.
- Laboratory findings:
  - Higher 1,25$(OH)_2$D (even within normal range) and FGF-23 levels have been shown to be associated with increased incident symptomatic stone (Health Professionals Follow-up Study). Involved mechanisms remain unclear.

- Elevated serum uric acid level has been shown to be associated with increased stone risk (stone type not documented) in a dose–response association in men, but not in women (Korean cohort analysis 2017).

- Dietary factors associated with higher stone risks:
  - Supplemental (not dietary) vitamin C intake >1,000 mg/d is associated with increased incident kidney stones in men, but not in women (Nurses' Health Study I and II and Health Professionals Follow-Up Study). Vitamin C is converted to oxalate and renally excreted.
  - Supplemental (*not* dietary) calcium
  - Others: dietary oxalate, sucrose, fructose, sugar-sweetened soda, punch

Table 3.9 summarizes kidney stone promoters and corresponding management options for different stone types.

Table 3.9 Stone risks and management options

Stone Type	Risks	Management Options
All stones	Low urine volume	• Fluid intake to produce >2.5 L of urine volume daily • Protective fluids: coffee, tea, beer, wine, orange juice • Fluids with potential increased stone risks: sugar-sweetened sodas, fruit punch, grapefruit juice (increase in urinary citrate but also oxalate), cranberry juice (minimal increase in citrate but also urinary calcium and oxalate)
Calcium oxalate and calcium phosphate	Hypercalciuria	• Evaluate and treat primary hyperparathyroidism or granulomatous disease • Maintain *normal dietary* calcium intake (e.g., 900–1,000 mg/d)—Dietary calcium restriction is *not* recommended. • Low-normal protein diet • Thiazide diuretics and/or low-dose K^+-sparing amiloride • K-citrate or K-HCO_3 (10–20 mmol bid to tid) as safely tolerated. Do not use Na^+-alkali salts as Na^+ load can increase urinary Ca^{2+} excretion.[a] • Neutral orthophosphate (e.g., K-phos neutral, 1.0–2.5 g/d in divided doses tid to qid)[b]
	High urinary sodium	• Dietary sodium restriction to <100 mmol/d

		(<2.3 g/d)
	Hypocitraturia	• Encourage high citrate diet, citric fruit juices (orange juice > lemonade) • Consider K-citrate (10–20 mmol bid to tid) as safely tolerated. Do not use Na^+-alkali salts as Na^+ load can increase urinary Ca^2 excretion.
	Hyperuricemia	• Allopurinol if recurrent calcium oxalate stones in the absence of hypercalciuria or hyperoxaluria • Restriction of nondairy protein (high uric acid containing proteins)[c]
	Other	Replace magnesium if low serum magnesium level
Calcium oxalate	Hyperoxaluria	• Dietary oxalate restriction[d] • Continue dietary oxalate restriction only if it effectively reduces urinary oxalate concentration • Avoid ingestion of >500 mg/d of ascorbic acid
	Primary hyperoxaluria	• Pyridoxine (250–500 mg/d), orthophosphate (40–60 mg/kg/d), K-citrate (0.15 g/kg), and/or magnesium oxide (500 mg/d/m^2) • Combined liver and kidney transplant as clinically indicated
	Inflammatory bowels	Cholestyramine[e]
Calcium phosphate	Hyperphosphaturia	• Beneficial effect of dietary phosphate restriction has not been shown.
	High urine pH (e.g., >7.0)	Urine acidification is generally not done. Reduce K-citrate dose if this agent is being used
Uric acid	Hyperuricemia	• Allopurinol or febuxostat • Avoid high uric acid containing proteins[c]
	Low urine pH	• K-citrate 10–20 mmol bid to tid; uptitrate as needed and safely tolerated: Consider tid frequency instead of bid to reduce intermittent pH-lowering episodes when uric acid may precipitate.[a]
Triple phosphate (i.e., magnesium ammonium phosphate, struvite)	Genitourinary tract abnormality with recurrent urinary tract infections	• Correction of anatomic tract abnormality if possible • Treatment of underlying infection • Stone removal • Urease inhibitor acetohydroxamic acid (Lithostat) 250 mg tid to qid[f]

Cystine	High urine cystine level	• High fluid intake 3.5–5.0 L/d[g] • Dietary restriction • Use of drugs that can form soluble heterodimers with cysteine as last resort (D-penicillamine, tiopronin. captopril)[h]
	Low urine pH	• K-citrate 40–80 mmol/d in divided doses tid to qid to achieve urine pH >7.0.
2,8-Dihydroxyadenine	Adenine phosphoribosyltransferase deficiency	• Xanthine oxidase inhibitors: Start low dose of either allopurinol or febuxostat and uptitrate as needed to achieve disappearance of 2,8-dihydroxyadenine crystals in the urine.

[a]Avoid urine pH above 7.0 because alkaline urine favors calcium phosphate precipitation.
[b]Orthophosphates can increase serum phosphate and reduce 1,25$(OH)_2$D level.
[c]Proteins with high uric acid content: anchovies, sardines, herring, mackerel, scallops and mussels, waterfowl, organ meats, glandular tissue, and meat juice drippings or extracts.
[d]High oxalate diet: dark green leafy vegetables such as spinach and rhubarb, Swiss chards, nuts, chocolate.
[e]Cholestyramine binds both bile acids and oxalate, but its gastrointestinal side effects may limit routine use.
[f]Acetohydroxamic acid is associated with significant side effects. Its use should be limited to patients who cannot or refuse to undergo stone removal.
[g]Patients with cystine stone require much higher urine volume compared to those with all other stone types to inhibit stone formation.
[h]Side effects may limit medical therapy in patients with cystine stone.
Abbreviations: bid, twice; qid, four times daily; tid, three times daily.

Clinical Manifestations

- Pain depends on stone location:
  - Intrarenal stone: asymptomatic unless pyelonephritis or obstruction with distention of renal capsule
  - Proximal ureter: colicky flank or anterior abdominal pain
  - Distal third ureter: flank pain radiating to groin/genitals
  - Ureterovesicular junction: suprapubic pain, urgency, dysuria
  - Bladder neck: suprapubic pain, anuria, gross hematuria
- Hematuria: ranges from none to microscopic to gross hematuria
- Pyuria: may be sterile due to inflammation or associated with concurrent urinary tract infection/pyelonephritis

General Dietary Advice for Kidney Stones

General Dietary Advice for Kidney Stones

- Fluid intake to ensure *urine volume* ≥2.0 to 2.5 L/d
  - Protective fluids: coffee, tea, beer, wine, orange juice
  - Fluids that can increase stone risks: sugar-sweetened sodas, fruit punch, grapefruit juice, cranberry juice. Sugar-sweetened drinks containing sucrose or fructose can increase stone risk possibly via increased urinary calcium, uric acid, and/or oxalate excretion.
- Sodium restriction to 2 to 2.3 g or 88 to 100 mmol daily; low sodium delivery to proximal tubules increase both sodium and calcium reabsorption, thus lower luminal calcium content for stone formation.
- *Dietary* calcium intake from either nondairy or dairy sources is protective against stones, but not calcium *supplement* given in between meals. The former can bind and eliminate intestinal phosphate or oxalate from the diet, thereby reducing phosphate/oxalate absorption. The latter predominantly increases intestinal calcium absorption without the benefit of reducing any phosphate/oxalate absorption that occurs during meals.
- Increase fruits, vegetables, and fruit juice intake to increase citrate excretion to increase urine pH and luminal citrate concentration. This is beneficial to patients with uric acid and calcium stone.
- Avoid high animal protein intake due to:
  - High acid load that reduces citrate excretion
  - Increased calcium excretion secondary to increased calcium removal from bone
  - Increased urinary oxalate and uric acid excretion
- Dietary oxalate restriction if calcium oxalate stones *and continue only if* urine excretion of oxalate is effectively reduced (e.g., avoid dark green leafy vegetables such as spinach, rhubarb, nuts, chocolate). If not effective, discontinue dietary oxalate restriction.

Specific Stones

Calcium stones

Background

- Mixed calcium oxalate and phosphate is the most common stone, followed by calcium oxalate, then calcium phosphate.

- When calcium phosphate is the main constituent (i.e., >50% of stone composition is calcium phosphate):
  - Urine pH is higher than that observed with calcium oxalate.
  - Types of calcium phosphate stones:
    - Calcium apatite (main constituents of bones/teeth)
    - Calcium brushite (calcium monohydrate phosphate): physically resistant to extracorporeal shock-wave lithotripsy (ESWL); repeated treatments may be necessary.

Metabolic risk factors for calcium stones

- Hypercalciuria (most common risk for calcium stones):
  - Idiopathic
  - Absorptive hypercalciuria (increased GI calcium absorption): autosomal dominant, jejunal mucosa is hyperresponsive to vitamin D.
  - PHPT
  - Medullary sponge kidney (see **Chapter 6**)
  - Distal RTA (Nephrocalcinosis associated with distal RTA (type 1) is predominantly composed of calcium phosphates (**Fig. 3.12**).)

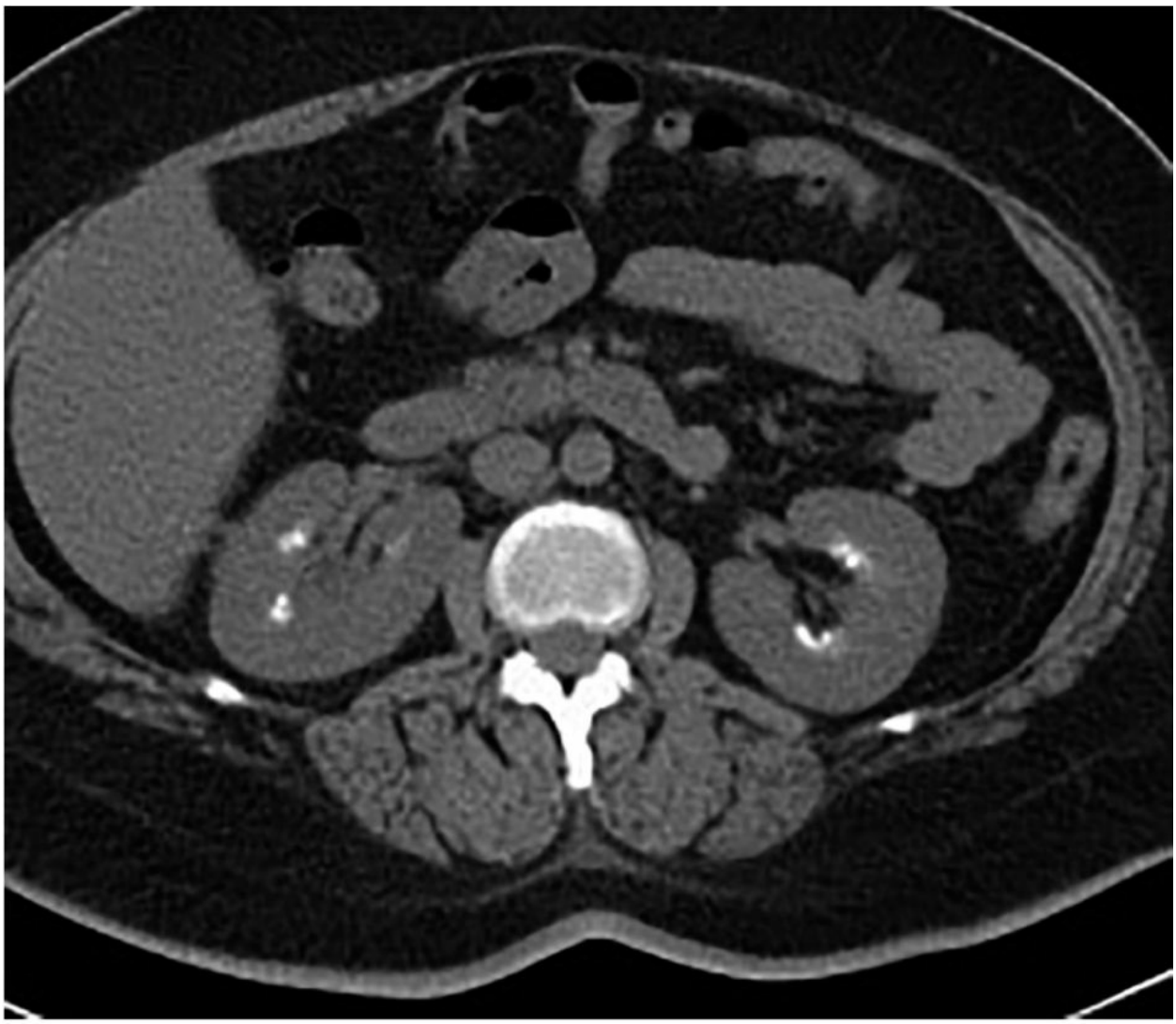

FIGURE 3.12 Medullary nephrocalcinosis. Axial and coronal noncontract computed tomogram showing amorphous and course pyramidal calcifications in both kidneys consistent with medullary nephrocalcinosis.

- Horseshoe kidney is associated with increased risk for calcium oxalate >> calcium phosphate stones, and abnormalities in metabolic profile including hyperparathyroidism, hypercalciuria, hyperoxaluria, hyperuricosuria, and hypocitraturia.
- Loss-of-function mutation of 24-hydroxylase, the enzyme that inactivates $1,25(OH)_2D$. Recall that treatment for this mutation is ketoconazole.
- Activating CaSR mutation leading to reduced Ca^{2+} reabsorption at TAL
- Others: Bartter syndromes, Dent disease (hypercalciuria with

nephrocalcinosis), familial hypomagnesemia with hypercalciuria and nephrocalcinosis (mutation of claudin 16/19)
    - Resorptive hypercalciuria: increased bone resorption secondary to PHPT
- Hyperuricosuria: Dissolved uric acid salts appear to increase calcium oxalate precipitation via unclear mechanism(s).
- Phosphaturia: “renal phosphate leak” due to:
    - Mutations involving proximal tubular Na-Pi cotransporters
    - Increased FGF-23 or presence of an allelic variant (FGF23716T)
- Hyperoxaluria
    - Dietary causes of hyperoxaluria:
        - Low calcium in diet allows free oxalate to be absorbed readily in the intestines, which is then eliminated in the urine. In contrast, high dietary calcium intake such as dairy products can bind to dietary oxalate to form intestinal calcium oxalate and effectively eliminate dietary oxalate.
        - High intake of protein, oxalate, or its precursors (ethylene glycol, methoxyflurane anesthesia, or large doses of ascorbic acid in susceptible individuals)
    - Enteric causes of hyperoxaluria:
        - Fat malabsorption (e.g., inflammatory bowel disease/resection/bypass, exocrine pancreatic insufficiency). Undigested fatty acids bind calcium within the GI tract, hence less calcium availability to bind oxalate in the gut for elimination. This leads to increased intestinal oxalate absorption and urinary oxalate excretion.
        - Malabsorptive bariatric surgeries
        - Slc26a6 variant has been suggested to be associated with increased stone risk. *Slc26a6* is a gene encoding a multifunctional anion transporter responsible for oxalate transport in both the intestines and the kidneys.
        - Presence of gut *Oxalobacter formigenes is thought to be protective against kidney stones: O. formigenes* is a gram-negative bacteria that degrade gut oxalate. Colonized patients have been shown to have

reduced oxaluria under controlled, standardized diet. An association between *O. formigenes* colonization and reduced number of stone episodes (recurrence) has also been shown.

- Primary hyperoxaluria (PH):
  - Autosomal recessive disorders (types 1, 2, and 3 or PH1, PH2, and PH3, respectively) due to mutations of enzymes involved in hepatic glyoxylate metabolism, resulting in excessive production and urinary excretion of oxalate. Deposition of oxalate in the bones, joints, and bone marrow defines "oxalosis."
  - There is wide outcome variability for PH patients. Nonetheless, without aggressive therapy, death from kidney failure and oxalosis may occur. PH1 typically presents with ESKD in early adulthood if undiagnosed and untreated.
  - Diagnosis is based on significantly elevated urine oxalate levels (i.e., >two to three times upper normal limit) and genetic analysis. The presence of urinary glycolate is suggestive of PH1, whereas elevated urinary levels of L-glyceric acid may be suggestive of PH2.
  - Management involves high fluid intake and administration of calcium oxalate inhibitors, including neutral phosphate (orthophosphate 40 to 60 mg/kg/d), potassium citrate (0.15 g/kg), and/or magnesium oxide (500 mg/d/m^2). A 3-month trial of pyridoxine (250 to 500 mg/d) may be considered in patients with PH1. Combined kidney liver transplant is suggested in PH1, whereas kidney-alone transplant in PH2 is preferred.

- Hypocitraturia:
  - Citrate forms *soluble* complexes with calcium in tubular lumen, thereby lowers calcium availability for calcium stone formation. Hypocitraturia predisposes patients to calcium stones.
  - Conditions associated with chronic metabolic acidosis such as RTA can reduce intraluminal citrate and, thus, increased stone risk.

NOTE Citrate metabolism

- Citrate exists as a divalent (citrate^{2-}) or trivalent (citrate^{3-}) anion.
- Citrate^{2-} + HCO_3^- → Citrate^{3-} + CO_2 + H_2O

In metabolic acidosis (i.e., lack of HCO_3^-), there are more citrate^{2-} than citrate^{3-}. Proximal tubular reabsorption of citrate^{2-} occurs more readily than that of citrate^{3-}, leaving less citrate in tubular lumen.

- Intracellular acidosis associated with metabolic acidosis also promotes citrate mitochondrial uptake and metabolism, hence lowering cytoplasmic concentration. This results in a more favorable chemical gradient for tubular citrate reabsorption, leaving less citrate in tubular lumen.

- Inflammatory bowel disease
- Idiopathic

- Others: vitamin A deficiency (associated with reduced urinary concentration of stone inhibitors glycosaminoglycans and citrate and increased urinary calcium and oxalate excretion), hot climates, immobilization, urinary tract anomalies
- Medications:
  - Consider medical therapy if dietary trial × 3 to 6 months does not improve urine chemical profile or if there is evidence of increasing stone formation (increase in size and/or number of stones).
  - If hypercalciuria is present:
    - Thiazide (watch for hypokalemia and treat as needed) and/or low-dose K^+-sparing amiloride to increase Ca^{2+} reabsorption. Avoid triamterene due to possible crystallization and precipitation of the drug.
    - If thiazide/amiloride intolerance:
      - 40 to 60 mmol of K-HCO_3 or K-citrate daily in divided doses (bid to tid).
        - Alkalinization may improve citrate excretion. Avoid alkalinization with Na^+-alkali salts as Na^+ load increases urinary Ca^{2+} excretion.
        - Must monitor urine pH and serum K^+ with K-salt alkalinization. pH >7.0 may facilitate calcium phosphate precipitation.
      - Administration of neutral orthophosphate reduces Ca^{2+} excretion and increases excretion of calcium stone inhibitors (pyrophosphate).
        - Examples of neutral orthophosphates: K-phos neutral, 1.0 to 2.5

g/d in divided doses (bid to qid)
    - May be considered for hyperabsorptive hypercalciuria due to high 1,25$(OH)_2$D state because phosphate reduces 1,25$(OH)_2$D level and may also bind to intestinal calcium
- If hyperoxaluria is present:
  - Dietary restriction of fat and oxalate (if effective in reduction of oxaluria)
  - Consider pyrophosphate
  - High-dose pyridoxine of 150 to 500 mg every day (vitamin B_6), particularly if pPH1: Vitamin B_6 may reduce oxalate production and urinary oxalate excretion.
- For enteric hyperoxaluria:
  - Low-fat/oxalate diet
  - Consider oral calcium carbonate or citrate (1 to 3 g daily) with meals to bind oxalate in intestinal lumen.
  - Cholestyramine binds both bile acids and oxalate, but its GI side effects may limit routine use.
  - Oral oxalate decarboxylase in enteric hyperoxaluria: Reloxaliase, oral capsule to be taken with food to degrade oxalate—under phase 3 trial
- If hypocitraturia is present:
  - Consider fruit juice and/or K-citrate (monitor K level in patients with advanced CKD)
  - Urine alkalinization to increase intraluminal citrate levels:
    - Lumen $Citrate^{2-}$ + HCO_3^- (from alkalinization) → $Citrate^{3-}$ + CO_2 + H_2O. Reabsorption of $citrate^{3-}$ at proximal tubules (via Na-citrate cotransporter in luminal membrane) is lower than that for $citrate^{2-}$. The higher concentration of luminal citrate facilitates the formation of soluble calcium citrate complexes, thereby effectively reduces calcium availability for calcium stone formation.
    - Alkalinization also reduces intracellular citrate metabolism, resulting in higher intracellular citrate concentration. The higher intracellular citrate concentration leads to less favorable chemical gradient for tubular citrate reabsorption, hence higher luminal

citrate availability. **Note:** Hypokalemia induces intracellular acidosis and associated increased intracellular citrate metabolism, leading to lowering of intracellular citrate levels and formation of a favorable chemical gradient for tubular citrate reabsorption.

- Magnesium supplement: Supplement only if serum magnesium is also low. Treatment with magnesium has not been shown to reduce stone recurrence.
- Allopurinol: Consider allopurinol if there is hyperuricosuria in the absence of hypercalciuria or hyperoxaluria in patients with calcium oxalate stones. The use of allopurinol in these patients has been shown to reduce the likelihood of calcium oxalate stone recurrence.

Uric acid stones

Risks for uric acid stones

- Low urine pH
- Defect in ammoniagenesis: NH_3 buffers urine pH. The lack of NH_3 results in low urine pH.
- Conditions associated with hyperuricosuria:
  - Gout
  - Purine overproduction: myeloproliferative disorder, acute leukemia, glycogen storage disease, malignancy
- Metabolic syndrome, obesity, diabetes mellitus, insulin resistant:
  - Excessive dietary acid ingestion and/or increased endogenous acid production
  - Defective NH_4^+ excretion
  - Absence of inhibitors or presence of promoters of uric acid precipitation

Management of uric acid stones

- Urine alkalinization:
  - K-citrate 10 to 20 mmol bid to tid. **Note:** This is the *most* important intervention for uric acid stones in addition to maintaining urine volume >2.5 L/d. Urinary alkalinization with citrate is thought to be more important than reducing uricosuria.
  - For uric acid stone formers who do not respond to alkali therapy,

increase a morning or add a mid-day dose of alkali to correct the urinary pH fall that may occur late afternoon and evening.
    - K-citrate is more effective in reducing calcium oxalate supersaturation than sodium bicarbonate. Sodium bicarbonate increases urine sodium excretion and associated urine calcium excretion, whereas K-citrate increases urinary K excretion and reduces urine calcium excretion.
- Reduction in uricosuria:
    - Xanthine oxidase inhibitors (e.g., allopurinol, febuxostat) reduce urinary uric acid excretion.
    - Reduction of purine dietary intake
- Reversal of metabolic syndrome if applicable/possible

Struvite stones (i.e., triple phosphate stones)

Background

- Composition: magnesium ammonium phosphate (struvite) and calcium carbonate apatite. Also known as “triple phosphate”: Phosphate is present in its trivalent form and combines with three cations: NH_4^+, Mg^{2+}, Ca^{2+}. Struvite stone formation requires high NH_4^+ level and high urine pH, where the high NH_4^+ arises from urinary tract infection with urea-splitting organisms.
- The inciting urinary tract infection is commonly associated with anatomic abnormalities, obstruction of pelviureteric junction, calyceal diverticulum, horseshoe kidney, tubular ectasia (medullary sponge kidney), ureterocele, vesicoureteral reflux, ureteral stricture
- Urinary infection with urea-splitting organisms (urease producing organisms): *Proteus*, *Haemophilus*, *Yersinia*, *Klebsiella*, *Serratia*, *Citrobacter*, *Staphylococcus epidermidis*, *Ureaplasma urealyticum*, *Pseudomonas*

Management of struvite stones

- Treatment of underlying infections (culture specific)
- Stone removal: percutaneous nephrolithotomy > combination shock-wave lithotripsy and percutaneous lithotomy > open surgery
- 4 to 6 months of suppressive low-dose antibiotics (nitrofurantoin or

sulfamethoxazole–trimethoprim) - Note, however, the use of nitrofurantoin is contraindicated for creatinine clearance < 60 ml/min (dr ugs.com, updated aug 1, 2019).

- Medical therapy: urease inhibitor acetohydroxamic acid (Lithostat) 250 mg three (tid) to four times daily (qid)
  - Reserve for patients who cannot or refuse to undergo stone removal
  - Inadequate urinary drug level if S_{Cr} > 2 mg/dL
  - Significant side effects (40% to 60%): headaches, hemolytic anemia (15% to 20%), depression, dyspepsia, diarrhea, hallucination, palpitations, sweating, deep vein thrombosis, pulmonary embolism
  - Mandatory follow-up of stone size in 3 to 4 months
  - Correction of anatomic abnormality whenever possible

2,8-Dihydroxyadenine stone

Background

- Adenine phosphoribosyltransferase (APRT) deficiency is a rare autosomal recessive disorder of purine metabolism that leads to kidney stones and CKD.
- APRT deficiency prevents adenine recycling (from the purine nucleotide salvage pathway) and leads to adenine accumulation. Xanthine oxidase metabolizes the accumulated adenine to 2,8-dihydroxyadenine (2,8-DHA), which is insoluble in the urine and can cause kidney injury with or without stone formation.
- 2,8-DHA stone is radiolucent and may be mistaken as uric acid stone.

Management

- Either allopurinol or febuxostat can prevent stone formation and CKD. Optimal dosing has not been defined. Initiation of low-dose allopurinol or febuxostat with uptitration as needed for disappearance of 2,8-DHA crystals in the urine sediment has been suggested.

Cystine stones

Background

- Causes of cystine stones/crystalluria:
  - Hereditary:

        - Mutation of renal epithelial cell transporters resulting in reduced reabsorption of dibasic amino acids, including cysteine, ornithine, lysine, arginine (COLA). Cysteine dimerizes to form cystine, which is highly insoluble.
        - Genetic inheritance: predominantly autosomal recessive but may be autosomal dominant with incomplete penetrance
    - Renal tubular immaturity in infants, Wilson disease, and Fanconi syndrome are other causes of elevated urinary cystine levels.
- Clinical manifestations:
    - ~20% to 40% are mixed stones.
    - Homozygous cystinuria:
        - Lifelong, recurrent urolithiasis that is difficult to manage surgically or medically
        - >50% of asymptomatic homozygotes develop kidney stones.
        - 75% present with bilateral calculi.
        - Typical age of onset is in the second or third decade of life; 25% in the first decade; 30% to 40% in teenage years.

Management

- High fluid intake, 3.5 to 5.0 L/d. Note that this is much higher than that required other types of stones. Monitor for hyponatremia.
- Alkalinization of urine with 40 to 80 mmol of K-citrate daily (urine pH > 7.0)
- Reduction of sodium and protein intake to reduce urinary cysteine excretion
- Last resort: Use drugs that form heterodimers with cysteine, thus competing for cysteine–cysteine disulfide bond formation, the insoluble cystine.
    - D-Penicillamine
    - α-Mercaptopropionylglycine (tiopronin); both D-penicillamine and tiopronin have significant side effects, including loss of taste, fever, proteinuria, serum sickness–type reactions, nephrotic syndrome.
    - Captopril (side effect: hypotension)

Drug-associated stones/urinary crystallizations

- Calcium stone formation: loop diuretics (increase urinary calcium excretion); vitamin D (GI absorption of calcium); glucocorticoids (bone resorption); calcium-containing antacids; theophylline (interferes with pyridoxine metabolism and worsens oxaluria in primary oxaluria type 1); acetazolamide (alkalinize urine, increase risk for calcium phosphate stones), topiramate (antiepileptic, has significant carbonic anhydrase activity, thus alkalinization of urine), amphotericin B (alkalinize urine due to H^+ back-leak), high-dose (i.e., >>500 mg/d) vitamin C (metabolized to oxalate)
- Uric acid stone formation: probenecid (inhibits renal tubular reabsorption of uric acid)
- Medications that may crystallize: triamterene, acyclovir (high intravenous dose, e.g., treatment dose for encephalitis), indinavir, allopurinol (xanthine stones)

Stone Diagnosis

Imaging studies

- Ultrasound versus noncontrast CT:
  - Ultrasound may miss ureteral stones <3 mm.
  - Cost, availability
  - Radiation exposure with CT
  - Contrast-enhanced CT may be required to diagnose indinavir stones.
- Plain film (Kidney-Ureter-Bladder X-ray, KUB):
  - Detects calcium stones > 5 mm
  - Low dose of radiation
  - Inexpensive
- Magnetic resonance imaging: poor tool for visualizing stones
- Intravenous pyelogram: contrast dye exposure

  Note:

  - Radiolucent “stones” on plain X-ray film:
    - Uric acid and xanthine stones
    - 2,8-DHA stone

        - Case report of pseudoephedrine/guaifenesin stone
        - Cystine and struvite stones are often but not always radiopaque.
    - Staghorn-appearing stones are typically associated with struvite, but may be seen in other stone types: struvite >> calcium carbonate apatite > cystine, uric acid stones.

Biochemical evaluation

- First-time uncomplicated stone presentation: Minimal evaluation:
    - Basic chemistry, serum calcium, phosphorus, uric acid
    - Routine urinalysis; consider: 24-hour urine for volume, creatinine, pH, calcium, oxalate, citrate, uric acid
    - Complete metabolic profile evaluation outlined below is optional.
- Indications for complete metabolic profile evaluation:
    - Recurrent stone or bilateral stone disease
    - Family history of stones
    - Presence of inflammatory bowel disease, malabsorption
    - Past medical history with any of gout, RTA, PHPT, osteoporosis or pathologic skeletal fractures, nephrocalcinosis, or bariatric surgery
    - Struvite, cystine, uric acid, or calcium phosphate
    - Patient is a child.
- Complete metabolic profile evaluation:
    - Analysis of stone composition if available
    - Two 24-hour urine collections (one during usual daily activities and diet, i.e., work-day, and one during resting day, i.e., weekend to evaluate for work-related factors) for: volume; creatinine (to determine collection adequacy), pH (hint to type of stone); Na^+ (relevant in calcium stones); stone substrates: Ca^{2+}, oxalate, uric acid, cystine (if young age or strong family history of cystine stones), ammonium; stone inhibitors: citrate, Mg^{2+}, K^+; dietary protein intake: SO_4^{2-} (high content of sulfate-containing amino acids reflects animal protein intake), urea nitrogen
        - Laboratory calculations of urinary supersaturation of stone substrates if available
        - Serum: full chemistry panel including at minimum potassium, total

CO_2, creatinine, glucose, calcium, uric acid, phosphate, and magnesium

- If serum calcium is high or high-normal or phosphorus is low or low-normal, obtain PTH, $1,25(OH)_2D$, chest X-ray (sarcoidosis). Consider urine evaluation for mycobacterium tuberculosis in endemic areas.

Management of Kidney Stones: General Considerations

Stone passage depends on stone location and stone size

- Stone location: Proximal stones are less likely than distal stones to pass spontaneously.
- Stone size:
  - <5 mm, spontaneous passing rate up to 95%
  - 5 to 8 mm, spontaneous passing rate 60% to 70%
  - ≥8 mm, spontaneous passing rate ~10% to 20%

Pain control

- Nonsteroidal anti-inflammatory drugs (NSAIDs) may be preferred if there is no volume depletion, kidney disease, GI bleed, or contraindications:
  - Low cost
  - Inhibit prostaglandin-mediated pain pathways
  - Decrease ureteral contractility
  - Stop NSAIDs at least 3 days prior to shock-wave lithotripsy to minimize bleeding risks.
- Otherwise use opioids: faster onset of pain relief compared with NSAIDs but concerns for abuse potential
- Combination of NSAIDs and opioids may be also considered.

Urologic Management Options (American Urological Association: Evidence-Based Recommendations to Guide Choice of Modality)

- <10 mm: observation if pain is controlled and no evidence of obstruction or infection. initiate medical expulsion therapy below.

Medical expulsion therapy (MET)

- 4 to 6 weeks trial of α-blockers (e.g., tamsulosin) or CCBs (e.g., nifedipine only if hypertensive) and/or low-dose glucocorticoid (e.g., prednisone 20 to 25 mg daily × 10 days)
- Rationale for α-blockers:
  - Inhibit basal ureteral tone and peristaltic frequency and decrease intensity of ureteral contractions, thereby facilitating stone passage
  - Slightly faster stone passage compared with CCB

Urology consult if MET fails

- Smaller stones that do not pass: ESWL and/or ureteroscopy. ESWL has been linked to a small increased risk of HTN.
- Larger or more complex stones, impacted stones in proximal ureter: percutaneous nephrolithotomy
- Altered anatomy (previous surgeries, malignancy, etc.): open/laparoscopic surgery

Indications for urgent urologic consult

- Presence of infection with urinary tract obstruction
- Urosepsis
- Intractable pain or vomiting or both
- Acute kidney failure
- Obstruction in solitary or transplanted kidney
- Bilateral obstructing stones

Monitoring Response to Therapy

- 24-hour urine collection after 6 to 8 weeks for chemical profile, pH, and volume. Of note, follow-up measurements of urine calcium level may *not* be a reliable predictor of treatment effectiveness for reducing stone recurrence risk. Increased fluid intake, however, has been shown to significantly reduce risk of stone recurrence over 5-year follow-up.
- Imaging studies: helical CT or ultrasound at 1 year. If negative, repeat in 2 to 4 years depending on findings and risks.

Access the eBook for self-assessment questions.

CHAPTER 4

Chronic Kidney Disease

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Chronic kidney disease (CKD) is classified based on (1) cause, (2) glomerular filtration rate (GFR) category, and (3) albuminuria category.

Assessment

Glomerular Filtration Rate

- GFR is used to define CKD, guide routine care, evaluate and manage expected complications of CKD, assess CKD progression, determine drug dosing, and assess prognosis.
- GFR may be estimated as the clearance rate of a solute that is 100% filtered.
- Clearance of any solute "X" equals [Ux]V/[Px], where [Ux] and [Px] represent the concentrations of solute "X" in the urine and plasma, respectively, and V represents the urine volume per unit time.

Creatinine Clearance

- Traditionally, creatinine (Cr) has been used as the "solute" of choice in estimating GFR because the kidney freely filters Cr.

$$\text{GFR} = \frac{[\text{urine creatinine concentration}] \times \text{urine output rate}}{[\text{plasma creatinine concentration}]}$$

- Limitations of using Cr as a marker of GFR:
  - Cr level may reflect muscle mass and dietary intake, independent of glomerular filtration.
  - Cr levels are typically in the low normal range for elderly patients or patients with malnutrition, limb amputation(s), or cirrhosis (reduced hepatic Cr synthesis, volume overload/dilutional). Cr levels may be in the high normal range despite having normal GFR in muscular young individuals.
  - Cr is also secreted by renal tubules, which leads to overestimation of GFR.
- The ideal solute for calculation of GFR should be:
  - Naturally made (endogenous) in the plasma
  - 100% freely filtered by the glomerulus
  - Not secreted by renal tubules
  - Not reabsorbed by renal tubules

NOTE

- A solute that is both filtered by the glomerulus and secreted by the tubules (e.g., Cr) will overestimate the GFR because there will be more solute in the urine than if the solute comes from filtration alone. Additionally, tubular Cr secretion is upregulated in advanced CKD, which can further overestimate GFR in this patient population.
- A solute that is both filtered by the glomerulus and reabsorbed by the tubules (e.g., urea) will underestimate the GFR because less solute will be seen in the urine than if the solute comes from filtration alone.
- For reasons above, GFR estimates from 24-hour urine collections in advanced CKD are typically calculated as the average of creatinine clearance (CrCl) and urea clearance.
- Alternatively, drugs that inhibit tubular secretion of Cr may be used during the 24-hour urine collection for a more accurate assessment of GFR. Traditionally, cimetidine may be used for this purpose. Of interest, other drugs that may inhibit proximal tubular secretion of Cr include dronedarone, trimethoprim, probenecid, pyrimethamine, salicylates, dolutegravir, cobicistat, ranolazine, and tyrosine kinase inhibitors, including imatinib.
- CrCl and urea clearance require a 24-hour urine collection and can be cumbersome.

Methods to Estimate GFR Other Than 24-Hour Urine Collection

- Use of exogenous filtration markers (in lieu of serum creatinine [SCr]): inulin, iothalamate, iohexol, ethylenediaminetetraacetic acid, and diethylenetriaminepentaacetic acid: These markers are chelated to radioisotopes for easy detection with nuclear scanning. In clinical settings

where determination of exact kidney function is necessary (i.e., evaluation of potential kidney donor's kidney function), GFR as measured by inulin or iothalamate may be obtained.

- Equations to estimate GFR (estimated GFR [eGFR]):

Cockcroft–Gault (CG) formula (dependent variables: age, gender, weight, SCr)

- Male: CrCl (mL/min) = ([140 − age] × weight [kg])/(72 × SCr [mg/dL])
- Female: same as formula for male above × 0.85 (empirical correction factor for presumed lower muscle mass in females)
- Note that CG formula is in mL/min. To normalize to 1.73 m^2 body surface area (BSA), multiply CrCl above by the ratio (1.73/patient's BSA).
- Limitations of CG formula:
  - CrCl is overestimated in patients with excessive weight due to adipose tissue or volume (weight is in the numerator).
  - Derivation of CG formula was based on old methods of SCr measurement and may not be accurate with modern SCr measurements.
  - Traditionally, CG formula has been used for drug dosing. With modern SCr measurements and new eGFR equations, clinicians must read package inserts for recommended methods of eGFR to be used for renal dose adjustments.

Modification of Diet in Renal Disease (MDRD) Study

- Derived from patients with CKD
- MDRD equations were derived based on urinary clearance of ^{125}I-iothalamate.
- MDRD-4 variables (age, gender, race [African American vs. non–African American], calibrated standardized SCr). SCr should be measured by specific assay traceable to the international standard reference materials and minimal bias compared to isotope dilution mass spectrometry (IDMS) reference methodology.
- MDRD-6 variables (age, gender, race [African American vs. non–African American], calibrated standardized SCr, albumin, blood urea nitrogen [BUN])
- Limitations of MDRD equations:

- *Underestimate* GFR in patients with GFR >60 mL/min/1.73 m^2, which over-reports the incidence of CKD. Many laboratories report eGFR greater than 60 as ">60 mL/min/1.73 m^2" rather than an actual calculated value due to inaccurate estimates in patients with higher GFR range.
- Not validated in geriatric patients, children, and pregnant women
- Not validated in nonsteady states such as acute kidney injury (AKI)
- Not derived for races other than "white" or "African American"
- Both MDRD-4 and CG overestimate true GFR in sick hospitalized patients.
- Incorporation of BUN and albumin (MDRD-6) partially improves GFR estimates at the expense of increasing complexity.

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)

- Derived from large database of research studies' participants with diverse characteristics, including those with and without CKD, diabetes mellitus (DM), and known organ transplantation
- Dependent variables are similar to those used in MDRD-4 and include age, gender, white or black race, SCr
- Derived based on either SCr-alone CKD-EPI(creat) or cystatin C (cys)-alone CKD-EPI(cys) or both SCr and cystatin C CKD-EPI(creat-cys)
- Compared to CKD-EPI(creat), CKD-EPI(cys) is not more accurate in estimating measured GFR, but is more accurate in estimating GFR in patients with low body mass index (BMI) and more accurate for risk predictions.
- Compared to either CKD-EPI(creat) or CKD-EPI(cys) alone, combined CKD-EPI(creat-cys) is more accurate for estimating GFR.
- Advantages of CKD-EPI over MDRD:
  - Similar accuracy as MDRD for GFR <60 ml/min/1.73 m^2
  - Better accuracy for eGFR >60 mL/min/1.73 m^2
  - Lower CKD prevalence (because CKD-EPI[SCr] is better at estimating higher GFR)
  - Better accuracy for risk predictions

- Applicable across more diverse population

- Advantages of MDRD over CKD-EPI: MDRD performs better and provides better accuracy in estimating GFR in severely obese individuals.
- The use of cystatin C in lieu of SCr:
  - Cystatin C is a cationic low-molecular weight (LMW) cysteine proteinase inhibitor that is produced at a constant rate by all nucleated cells. It is 99% filtered by glomeruli and metabolized by proximal tubular cells.
  - Serum cystatin C level reflects GFR well.
  - Normal range:
    - Both males and females: ages 20 to 50 years: 0.70 to 1.21 mg/L; age >50: 0.84 to 1.55 mg/L
    - Young healthy individuals: 0.53 to 0.95 mg/L
  - Advantages of using serum cystatin C compared to SCr:
    - Cystatin C may more accurately estimate GFR than SCr in patients with reduced muscle mass (e.g., liver disease, neuromuscular disease).
    - Cystatin C may detect AKI earlier than SCr.
    - Cystatin C has been reported to be a better predictor of deaths from cardiovascular causes and CKD complications.
    - Whereas cystatin C correlates linearly with cardiovascular risk (e.g., heart failure), SCr correlates in a J-curve relationship.
  - Limitations of using cystatin C:
    - There is evidence of tubular secretion of cystatin C and extrarenal elimination (15% to 20%); thus, GFR may be overestimated.
    - Cystatin C production and metabolism may be altered by various clinical conditions. Higher cystatin C levels may be seen in patients with older age, male gender, white race, obesity, DM, inflammatory state, and lower serum albumin level. Other factors that may alter cystatin C levels are thyroid disease, malignancy, and steroids.
    - Cystatin C measurement is expensive and not widely available.
    - Standardization of cystatin C measurement is still lacking.
    - Unless combined with SCr, eGFR formulas with cystatin C alone are

not more accurate in estimating GFR or predicting end-stage kidney disease (ESKD).

- Whereas cystatin C-alone–based eGFR appears to be a better biomarker for mortality and CKD complications, SCr-based eGFR serves as a better predictor of ESKD. This is thought to be due to the non-GFR determinants of cystatin C level, such as inflammation and vascular remodeling.

Full age spectrum (FAS)

- Equation derived based on three principles:
  - The average GFR for healthy populations (children, adolescents, and young adults) is 107.3 mL/min/1.73 m^2 after kidney function matures (around 2 years of age) until the age of 40 years.
  - The age decline in GFR begins at ~40 years.
  - GFR and population-normalized SCr (SCr/Qcrea) are inversely related, where Qcrea is the mean or median SCr concentration of the corresponding age-/sex-matched healthy population.
- The FAS equation has been reported to be valid even in patients with eGFR > 60 mL/min.

Limitations of eGFR formulas

- Less accurate in nonsteady state
- If SCr is used, accuracy may be compromised in the presence of factors other than GFR that alter SCr levels (e.g., extremes of muscle mass, presence of inhibitors of tubular secretion of Cr, dietary intake) or factors that interfere with Cr assay.

Kidney Disease: Improving Global Outcomes Recommendations

- Use SCr *and* a GFR-estimating equation for initial assessment (rather than using SCr alone).
- Clinical laboratories should measure SCr using a specific assay with calibration traceable to the international standard reference materials and minimal bias compared to IDMS reference methodology.
- Clinical laboratories should report eGFR in adults using the CKD-EPI

equation.

- Racial–ethnic and regional modifications to CKD-EPI Cr equations are required.
- Additional testing (e.g., cystatin C) or clearance measurement is suggested for confirmation when SCr-based eGFR is less accurate (e.g., patients with low muscle mass).
  - In adults with eGFR(Cr) of 45 to 59 mL/min/1.73 m^2 who have no other markers of kidney damage and confirmation is required, cystatin C measurement is suggested. If eGFR(cys) or eGFR(Cr-cys) is also <60 ml/min/1.73 m^2, the diagnosis of ckd is confirmed.
  - GFR measurement using an exogenous filtration marker is suggested under circumstances where more accurate ascertainment of GFR will impact treatment decisions (e.g., kidney donation).
- Categorization of eGFR:
  - G1: eGFR ≥ 90 mL/min/1.73 m^2
  - G2: eGFR 60 to 89 mL/min/1.73 m^2
  - G3a: eGFR 45 to 59 mL/min/1.73 m^2
  - G3b: eGFR 30 to 44 mL/min/1.73 m^2
  - G4: eGFR 15 to 29 mL/min/1.73 m^2
  - G5: eGFR < 15 ml/min/1.73 m^2
  - G5D: The letter D denotes dialysis dependent.
  - G1-5T: The letter T denotes kidney transplant.

Proteinuria

- Total proteinuria comprises LMW proteins, albumin, immunoglobulins (Igs), and Tamm–Horsfall proteins, among many others.
- Normal degree of proteinuria is generally <150 to 200 mg/d (or <0.2 g/g cr) but may be up to 250 to 300 mg/d (or <0.3 g/g cr) in normal pregnancy.

Increased proteinuria may be seen in the following conditions

Tubular injury (acute tubular injury, tubulointerstitial disease)

- LMW proteins are easily filtered but are also easily reabsorbed by proximal tubules daily. Proximal tubular injury leads to the loss of LMW

proteins.

- Proteinuria associated with tubular injury is referred to as “tubular proteinuria.”
- Tubular proteinuria is typically <1 to 2 g/d (or <1 to 2 g/g cr) and comprises predominantly lmw protein, *not* albumin.

Glomerular injury

- Proteinuria associated with glomerular injury (i.e., glomerular diseases) varies in range depending on the type of injury (nephrotic vs. nephritic glomerular disease).
- Glomerular proteinuria predominantly comprises of albumin.
  - Albuminuria is a marker of glomerular basement membrane (GBM) injury. Hence, albuminuria is used as a marker of early diabetic nephropathy.
  - The degree of albuminuria may be used as a marker of extent of GBM defect. The degree of albuminuria may be classified as:
    - A1: normal to mildly increased albuminuria: albumin excretion rate (AER) <30 mg/24 h or albumin-to-creatinine ratio (acr) < 30 mg/g
    - A2: moderately increased: AER 30 to 300 mg/24 h or ACR 30 to 300 mg/g
    - A3: severely increased: AER > 300 mg/24 h or ACR > 300 mg/g

Paraproteinemia

- The high production and glomerular filtration of LMW paraproteins (e.g., light chains with multiple myeloma) overwhelms the proximal tubular reabsorptive capacity and leads to proteinuria. This form of proteinuria is called “overflow proteinuria.”
- Overflow proteinuria may be >1 g/d depending on the amount of light chains produced and filtered. Albuminuria may be present if there is concurrent GBM injury due to paraprotein or associated amyloid depositions.

Methods to assess proteinuria

- Routine urinalysis (RUA) dipstick detects predominantly albuminuria

based on its ability to change pH.

- RUA does not detect tubular proteins or light-chain Igs well.
- The degree of proteinuria based on RUA must be correlated with hydration status.
- 24-hour urine proteinuria detects all types of proteins but is cumbersome to collect. Interpretation of proteinuria from a 24-hour collection requires confirmation of collection adequacy. An adequate collection should contain approximately 15 to 20 mg/kg/d for an "average" female and 20 to 25 mg/kg/d for an "average" male.
- Urine protein-to-creatinine ratio (uPCR) detects all types of proteins and reduces variations due to hydration status. It may be expressed as µg/mg Cr, mg/g Cr, g/g Cr, or mg/mmol Cr. For newly diagnosed CKD, obtain either uPCR or 24-hour urine collection for proteinuria. The latter may be collected for better accuracy.

NOTE

- Proteinuria comprised of <25% albuminuria may suggest either the presence of lmw proteins due to tubular injury and/or overflow proteinuria from monoclonal gammopathy.
- Significant proteinuria mismatch (i.e., high degree of proteinuria from either uPCR or 24-hour urine collection in association with minimal proteinuria from RUA) suggests the presence of free light chains (Bence Jones protein).
- Proteinuria selectivity refers to the ratio of clearance of immunoglobulins such as IgG (molecular weight of 160 kDa) to those of smaller proteins such as albumin (66.5 kDa) or transferrin (88 kDa). A value of <0.1 suggests highly selective proteinuria, which presumably reflects a lower degree of injury to the glomerular filtration barrier, hence lower disease progression risk, or, in the case of minimal change disease, better responsiveness to glucocorticoid compared to values >0.2.

- Microalbumin dipstick detects albuminuria, a marker of GBM defect.

CKD Epidemiology

- CKD definition (Kidney Disease Outcomes Quality Initiative or KDOQI):
  - Having kidney damage ≥3 months, as defined by *structural or functional abnormalities* of the kidney, with or without a decrease in GFR, manifest by either pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests, or having
  - GFR <60 ml/min/1.73 m^2 for ≥3 months with or without underlying

kidney damage (e.g., hepatorenal or cardiorenal syndrome)

- Overall lifetime risks for CKD stages 3a, 3b, and 4 and ESKD in the United States have been reported to be 59.1%, 33.6%, 11.5%, and 3.6%, respectively.
- Women have higher CKD risk but lower ESKD risk compared to men.
- Lifetime risks of CKD stages 4 and 5 and ESKD were higher in blacks and developed 10 to 15 years earlier than in whites.
- While the prevalence of CKD stages 1 to 4 remain relatively stable over the years, the prevalence for ESKD (stage 5) has increased at a much greater rate. The difference in the prevalence increase is referred to as the "CKD and ESKD paradox."
  - Theories for CKD and ESKD paradox:
    - Improved survival of CKD patients from cardiovascular events over the years
    - More rapid loss of kidney function over the years. This theory is less likely due to more aggressive blood pressure (BP) control and more use of angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker (ACEI/ARB).
    - Early renal replacement therapy (RRT) initiation
- DM is the leading cause of CKD in developed and many developing countries.

Predictors of CKD Progression

- Kidney Disease: Improving Global Outcomes (KDIGO) 2012: In predicting risk for outcome of CKD, identify the (1) cause of CKD, (2) GFR category, (3) albuminuria category, and (4) other risk factors and comorbid conditions.
- CKD progression (KDIGO):
  - Progression of CKD is defined as a drop in CKD category accompanied by ≥25% decline from baseline eGFR.
  - Rapid progression of CKD is defined as a sustained eGFR decline >5 mL/min/1.73 m^2/y.

Key predictors of CKD progression

Hypertension (HTN)

- MDRD participants assigned to lower mean arterial pressure (MAP) target <92 mm hg were 32% less likely to develop eskd compared with those assigned to “usual” bp target map of <107 mm hg.

Proteinuria

- Proteinuria comprising of nonspecific proinflammatory proteins can lead to direct tubular injury and/or complement activation with resultant tubulointerstitial inflammation.
- Exposure of tubular epithelial cells to a high-protein concentration can increase the synthesis of endothelin 1 (ET-1), a potent vasoconstrictor and a stimulator of renal cell proliferation and extracellular matrix, and transforming growth factor (TGF)-β synthesis. TGF-β is known to increase collagen and fibronectin production, both of which play a key role in tissue fibrosis.
- Higher degree of albuminuria is associated with an increased risk of ESKD.

Angiotensin II

- Increases plasma protein filtration via both hemodynamic effect and direct podocyte effect, the latter via stimulation of AT_1R
- Increases oxidative stress–associated injury, synthesis of cytokines, chemokines, TGF-β, connective tissue growth factor, chemotactic and cell adhesion molecules, all leading to increased plasma mesangial cell proliferation, extracellular matrix synthesis, and macrophage activation and infiltration
- Increases aldosterone synthesis. Aldosterone increases plasminogen activator–*inhibiting* factor I (PAI-I). Plasminogen activator normally induces proteolysis. Plasminogen activator *inhibitor* PAI-I reduces mesangiolysis and fibrinolysis, thus favoring mesangial expansion and fibrosis.

APOL1 gene variants

- The presence of ≥1 high-risk APOL1 variants (G1/G1, G2/G2, or G1/G2)

confers resistance to *Trypanosoma brucei* rhodesiense infection and improved survival in endemic areas.

- African Americans (with or without diabetes) with two APOL1 risk alleles develop more rapid CKD progression and increased risk of ESKD.
- Nonetheless, it should be noted that less than 40% of adults with two APOL1 risk alleles develop kidney disease. This observation suggests the interacting role of environmental factors with APOL1 variants to result in CKD.
- Fetal, but not maternal, APOL1 high-risk alleles have been shown to be associated with a 1.84-fold increased odd of preeclampsia.

Presence of cardiovascular or peripheral vascular diseases

Other possible predictors of CKD progression

- Presence of risk factors for cardiovascular disease: metabolic syndrome, elevated homocysteine, dyslipidemia, inflammatory prothrombotic and/or oxidative stress markers
- Illicit drug use (findings from the Chronic Renal Insufficiency Cohort Study)
  - The persistent use of cocaine, heroin, or methamphetamine was associated with increased risk for CKD progression and mortality among adults with CKD.
  - The use of marijuana was not associated with CKD progression.
- Tobacco smoking was not associated with CKD progression but with all-cause mortality.
- Environmental exposures: Lead and air pollution have been shown to be associated with increased incident CKD.
- High BMI: Obesity is thought to be associated with ESKD risk when accompanied by metabolic syndrome, diabetes, or HTN.
- Use of proton-pump inhibitors (PPIs)
  - Observational studies have reported the association of PPI long-term use and incident CKD.
  - Cause–effect relationship is not known but theorized to be related to associated hypomagnesemia. Unrecognized PPI-induced tubulointerstitial nephritis may also contribute.

- Dietary factors:
  - Water volume: High intake has not been shown to be renoprotective.
  - Sodium: High-sodium intake may increase CKD progression risk via exacerbation of existing HTN in salt-sensitive individuals and endothelial damage via oxidative stress and upregulation of TGF-β.
  - Coffee intake of ≥2 cups daily may be associated with a lower risk of ESKD in men (without polycystic kidney disease [PKD]).
  - Sodas: Sugar-sweetened drinks and diet sodas may be associated with increased CKD risk.
- Hyperuricemia, apolipoprotein E (APOE) genetic variation, increased pulse pressure >10 mm Hg, hypomagnesemia
- Accumulation of lipids in tissues such as that seen with nonalcoholic fatty liver disease is thought to induce worse outcomes via the release of inflammatory, profibrotic, coagulant, oxidative mediators.
- Fluid overload has been suggested to be a more important factor than DM for rapid progression and initiation of RRT in CKD stages 4 and 5.
- Of note, hypothyroidism is associated with decreased GFR, but not increased rate of CKD progression.

Kidney failure risk equation

- Tangri calculator (http://ckdpcrisk.org/lowgfrevents/) has been shown to accurately predict 2- and 5-year kidney failure risks as well as nonfatal cardiovascular events and death risk for adults with eGFR <60 ml/min/1.73 m^2. calculated risk is based on patient's age, gender, race (black on white), egfr, systolic blood pressure (sbp), history of cardiovascular disease, dm, urine albumin-to-creatinine ratio (uacr), and smoking history.

Slowing CKD Progression

Use of renin–angiotensin–aldosterone system (RAAS) inhibitors

- Renoprotective effects of ACEI and ARBs are beyond those of BP control.
- RAAS inhibition reduces intraglomerular pressure, hyperfiltration, and proteinuria
- Inhibits aldosterone-induced increase in PAI-I, the major inhibitor of fibrinolysis and proteolysis, thus reduction in extracellular

proteins/collagen accumulation

- Reduces TGF-β production
- Increases hepatocyte growth factor, a factor with antifibrotic potential
- Reduces albuminuria. Albuminuria has been shown to stimulate inflammatory response, vasoactive peptide production/release (endothelin), and fibrotic processes.

Combination RAAS (ACEI and ARB) inhibition therapy

- There may be synergistic reduction in proteinuria and BP control, but endpoints of renoprotection and cardiovascular mortality have not been proven.
- There may be increased risk for hyperkalemia and AKI.

Mineralocorticoid-receptor antagonists (MRAs)

- MRAs such as spironolactone or eplerenone mimic the molecular structure of the natural MR ligands.
- Either MRA above can decrease proteinuria (albuminuria) and BP when added to RAAS inhibition in patients with either diabetic or nondiabetic CKD.
- Adverse effects of current MRAs: hyperkalemia and metabolic acidosis for both agents; sex hormone–related side effects may also be problematic with spironolactone.
- Combined ACEI and MRA may reduce proteinuria more than combination of ACEI and ARB. Hyperkalemia, however, has been shown to be worse with the former combination.
- Finerenone represents a nonsteroidal compound designed to induce a conformational change to the MR complex to reduce its stability and nuclear translocation. Finerenone causes less hyperkalemia compared to traditional MRAs. Ongoing trials to test the efficacy and safety of finerenone in patients with diabetic kidney disease (DKD) include FIDELIO-DKD *and* FIGARO-DKD.

BP control

- 2017 Hypertension Clinical Practice Guidelines (American College of Cardiology/American Heart Association): Goal BP for everyone is

<130/80 mm hg except older fragile individuals with multiple comorbidities.

- For patients with glomerular disease and proteinuria, treat systolic blood pressure to goal <120 mm hg as safely tolerated.
- Note that BP goals tend to change over the years by different professional organizations. Readers are suggested to check with most current guidelines.
- Use an ACEI or ARB in diabetic adults with CKD *and* urine albumin excretion (UAE) ≥30 mg/24 h (or equivalent).
- Use an ACEI or ARB in nondiabetic adults with CKD and UAE > 300 mg/24 h (or equivalent).
- Clinical trials involving BP control versus GFR decline:
  - MDRD study involving patients with nondiabetic proteinuric renal disease: Strict BP control to target 125/75 mm Hg in patients with proteinuria > 1 g/d reduced GFR decline more than target 140/90 mm Hg. However, 48% of lower target BP group received ACEI compared with 28% in higher BP group.
  - African American Study of Kidney Disease and Hypertension (AASK) trial: Strict BP control to MAP 92 mm Hg (equivalent to 125/75 mm Hg) did not result in reduced GFR decline compared to higher MAP group of 102 to 107 mm Hg (equivalent to 135/85 to 140/90 mm Hg), unless significant proteinuria was present.
  - Ramipril Efficacy in Nephropathy 2 (REIN-2) trial involving patients with chronic, nondiabetic, proteinuric nephropathies: Addition of other agents to baseline ramipril to achieve tight BP control <130/80 mm hg did not confer additional benefits in terms of reduction in proteinuria or gfr rate of decline.
  - Keeping BP > 128/85 mm Hg may be advisable due to concerns for possible “J-curve” phenomenon of worse cardiovascular outcomes.
    - J-curve phenomenon observed (Farnett et al.): Literature review of 13 studies noted that lower diastolic BP (DBP) control was associated with worse cardiac events, but not with stroke. The beneficial DBP was thought to be 85 mm Hg.

    - Irbesartan Diabetic Nephropathy Trial (IDNT): DBP < 85 mm hg was associated with a trend for increase in all-cause mortality, a significant increase in myocardial infarction (mi), but decreased risk for strokes. goal bp 120/85 mm hg was recommended.
  - J-curve not observed:
    - Hypertension Optimal Treatment (HOT) trial: Patients assigned to DBP goal <80 mm hg had fewer cardiovascular outcomes compared with other bp groups. no j-curve effect was noted.
    - Appropriate Blood Pressure Control in Diabetes (ABCD) trial: no difference in cardiovascular outcome or benefit with BP target of 132/75 mm Hg versus 138/85 mm Hg

Reduction of proteinuria

- REIN study (ramipril): Baseline proteinuria correlated significantly with GFR decline.
- ARB was shown to be renoprotective (time to doubling of SCr, progression to ESKD, death): Reduction of End points in Non-Insulin Dependent Diabetes Mellitus with Angiotensin II Antagonist Losartan (RENAAL), IDNT (irbesartan 150 mg/300 mg vs. amlodipine).

Glycemia control in patients with DM

- KDOQI guideline: Target hemoglobin (Hb) A1C ~7% if safely tolerated to prevent or delay progression of microvascular complications of diabetes including DKD. Tighter control is not indicated.
- ADVANCE, ACCORD, VADT: Glycemic control reduced albuminuria, but no change in GFR.
- DCCT, EDIC, UKPDS: Glycemic control reduced both albuminuria and GFR decline.
- Intensive glycemic control led to increased hypoglycemic episodes.
- Sodium glucose transporter-2 inhibitors (SGLT-2is):
  - Empagliflozin and canagliflozin have been shown to reduce the risk of macroalbuminuria, doubling of SCr, ESKD, and renal death.
  - Dapagliflozin has been shown to reduce the risk of having >40% decrease in eGFR to <60 ml/min/1.73 m^2, eskd, and renal death.

- Mechanisms for the renoprotective effect of SGLT-2i include:
  - Reduction of glomerular hyperfiltration (via proximal tubular sodium wasting and tubuloglomerular feedback with afferent vasoconstriction to reduce GFR)
  - Reduction of renal hypoxia
  - BP-lowering effect via sodium wasting
- Glucagon-like peptide-1 (GLP1) analog:
  - Liraglutide has been shown to reduce new onset of persistent macroalbuminuria, change in UACR, doubling of SCr, ESKD, and renal death.
  - Semaglutide has been shown to reduce macroalbuminuria, doubling of SCr, ESKD, and renal death.
  - Mechanism for the renoprotective effect of GLP1:
    - Reduction of glomerular hyperfiltration (via proximal tubular sodium wasting and tubuloglomerular feedback with afferent vasoconstriction to reduce GFR)
    - However, this presumed beneficial effect may be counteracted by the direct nitric oxide (NO)–dependent vasodilatory effect of GLP1 on afferent arterioles.
    - BP-lowering effect
    - Other beneficial effects of GLP1: weight loss 0.8 to 1.4 kg, improvement in fasting and postprandial lipid profiles, modulation of tissue inflammation or fibrosis
- Dipeptidyl peptidase-4 (DPP4) inhibitors:
  - Saxagliptin and sitagliptin minimally reduced albuminuria.
  - Sitagliptin and linagliptin did not show any clinically significant beneficial renal effects.

Correction of metabolic acidosis

- Metabolic acidosis usually occurs at eGFR <30 ml/min/1.73 m^2.
- Adverse associated clinical effects:
  - Increased oxidation of branched chain amino acids (valine, leucine, isoleucine)

- Increased protein degradation, catabolic rate, muscle breakdown
- Decreased albumin synthesis
- Impaired vitamin D synthesis, bone metabolism, increased bone lysis
- Accelerated CKD progression
- Upregulation of ammonia, endothelin, and aldosterone production to promote tubular acid excretion
- Increased all-cause mortality

- KDIGO 2012: provide oral bicarbonate supplement to keep serum HCO_3^- ≥22 mmol/L
- Alkalinization does not worsen BP but may reduce CKD progression.
- Of note, HCO_3^- > 24 mmol/L may be associated with higher rate of heart failure, independent of alkali supplementation. Mechanism is unclear but thought to be unrelated to volume.

Albuminuria reduction

- See SGLT-2i, GLP1, DPP4 inhibitors above
- Pentoxifylline (PTF):
  - Methylxanthine derivative that acts as a phosphodiesterase inhibitor with anti-inflammatory, antiproliferative, antifibrotic properties
  - Effect of PTF on renal function and albuminuria in DKD: PREDIAN trial 2014:
    - Open-label, prospective, randomized trial designed to determine whether the addition of PTF to RAAS blockade slows CKD progression in DM2 and CKD stages 3 and 4
    - PTF (1,200 mg/d) (n = 82) versus control (n = 87) × 2 years. All received similar doses of RAAS inhibitors.
    - eGFR had decreased by 2.1 ± 0.4 mL/min/1.73 m^2 in PTF versus 6.5 ± 0.4 mL/min/1.73 m^2 in control (p < 0.001). albuminuria was +5.7% in control versus −14.9% in ptf (p = 0.001).
    - PTF plus RAAS inhibitors led to smaller decline in eGFR and greater reduction in albuminuria.
  - 2017 meta-analysis involving 11 randomized controlled trials (RCTs) (n = 705) on the efficacy and safety of PTF (400 to 1,200 mg/d) plus

ACEI/ARB in patients with CKD stages 3 to 5 revealed reduction in UAE from 900 to 791 mg/d and alleviation in eGFR decline.

Statins

- Data on the renoprotective effects of statins have been mixed:
- Studies revealing improvement in GFR:
  - ASCOT trial: 10,305 subjects with HTN and >3 cardiovascular risk factors: Atorvastatin significantly improved eGFR compared to placebo.
  - Effect of Statins on Renal Function in Chronic Kidney Disease Patient: Hu et al. (2018): The renoprotective effect of statins was significant in patients with CKD stages 3b to 5 (odd ratio [OR] 0.68, 95% confidence interval [CI] 0.48 to 0.95), but not statistically significant in those with CKD stages 1 to 3a (OR 0.97, 95% CI 0.68 to 1.38). The renoprotective effect of statins was significant in patients with proteinuria ≥1,000 mg/d (OR 0.63, 95% CI 0.43 to 0.92), but not in those with proteinuria <1,000 mg/d (or 1.02, 95% ci 0.74 to 1.41).
- Studies not revealing improvement in GFR:
  - SHARP trial:
    - Combination of simvastatin and ezetimibe conferred a 17% cardiovascular risk reduction in patients with CKD.
    - Renoprotective effect not proven.
  - PLANET trial: Atorvastatin versus rosuvastatin in patients with diabetic and nondiabetic CKD:
    - Atorvastatin improved proteinuria, not eGFR.
  - Rosuvastatin was associated with a fall in eGFR.
  - Fluvastatin RCT: No improvement in proteinuria.
- There is currently no guideline regarding the use of statins for the sole purpose of renoprotection.
- KDIGO general lipid guidelines (2013):
  - Initial assessment of lipid status with a lipid profile is *recommended* for adults with CKD, but follow-up measurements are not required for the majority of patients.
  - In adults with dialysis-dependent CKD, it is *suggested* that initiation of

statins or statin/ezetimibe combination ***not*** *be done*.

- In patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, continuation of these agents is *suggested*.
- In adults ≥50 years old with eGFR < 60 ml/min/1.73 m^2 (gfr categories g3a to g5), but not treated with chronic dialysis, treatment with a statin or statin/ezetimibe combination is *recommended* (regardless of lipid profile).
- In adults ≥50 years old with CKD and eGFR ≥60 mL/min/1.73 m^2 (GFR categories G1 to G2), treatment with a statin is *recommended*.
- In adults aged 18 to 49 years with CKD, treatment with a statin is *suggested* for those with one or more of the following: known coronary artery disease (CAD), DM, prior ischemic stroke, or estimated 10-year incidence of coronary death or nonfatal MI >10%.
- In adult with kidney transplant recipients, treatment with a statin is *suggested*.

- Efficacy and Safety of Evolocumab (proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitor) in CKD in the FOURIER trial revealed benefits extending to patients with CKD stages G2, G3a, and 3b.
  - Low-density lipoprotein cholesterol (LDL-C) lowering and relative clinical efficacy and safety of evolocumab versus placebo were consistent across CKD groups.
  - Absolute reduction in the composite of cardiovascular death, MI, or stroke with evolocumab was numerically greater with more advanced CKD (hazard ratio [HR] 0.82, 95% CI 0.72 to 0.93 for CKD stage G2, HR 0.65, 95% CI 0.65 to 0.95 for CKD stage ≥3).

Uric acid (UA)-lowering therapy

- Presumed pathogenesis involved in kidney injury with elevated UA levels:
  - RAAS activation, oxidative stress, mitochondrial dysfunction, epithelial–mesenchymal transition, endothelial dysfunction, vascular smooth muscle proliferation
- Clinical complications attributed to hyperuricemia: arteriosclerosis, glomerular HTN, glomerulosclerosis, interstitial disease, AKI, metabolic syndrome, nonalcoholic fatty liver disease, HTN, DM

- Clinical trials involving UA-lowering therapy:
  - Meta-analysis 2018 (Liu et al.): 12 RCTs, total *n* = 832: UA lowering was associated with reduced risk of worsening kidney function, ESKD, or death.
  - Japanese HTN Evaluation with ARB Losartan Therapy (J-HEALTH) study: *n* = 7,629 HTN patients: Change in serum UA inversely correlated with change in eGFR. Lower serum UA levels are associated with lower cardiovascular events. (Losartan has a uricosuric effect that can lower serum UA levels.)
  - Vascular Function and Uric Acid-Lowering in stage 3 CKD, 2017 RCT, Jalal et al., involving 80 adults with CKD stage 3 and asymptomatic hyperuricemia (≥7 mg/dL in men and ≥6 mg/dL in women), treated with allopurinol versus placebo: There were no significant between-group differences in BP or serum markers of inflammation and oxidative stress.
  - Large high-quality RCTs are still needed.
- KDIGO 2012:
  - "There is INSUFFICIENT EVIDENCE to support or refute the use of UA-lowering agents in CKD and either symptomatic or asymptomatic hyperuricemia in order to delay progression of CKD."
  - Treatment of hyperuricemia is "not benign."
    - Stevens–Johnson syndrome may occur with allopurinol therapy.
    - Both allopurinol and febuxostat (xanthine oxidase inhibitors) can increase urinary xanthine levels, which can be nephrotoxic.

Sodium restriction

- See Table 4.1. Note that there are concerns for strict sodium dietary restriction due to possible associated activation of RAAS and SNS, higher risks for CKD progression and odds of death. Two to 3 g daily sodium intake may be a more prudent approach. Lower sodium intake in patients with proteinuria >1 g/d may be associated with increased AKI events and excessive stimulation of RAAS.

Table 4.1 Nutrition guidelines for patients with chronic kidney disease

Daily Intake	Pre-ESKD	Pre-ESKD With DM	Hemodialysis	Peritoneal Dialysis	HD or PD With DM
Energy (kcal/kg) < 60 y	35	35	35	35	
Energy (kcal/kg) > 60 y	30–35	30–35	30–35	30–35	
*Protein (g/kg dry BW)	0.55–0.60 or 0.28–0.43 dietary protein/kg/d with additional keto acid analogs to meet protein requirements of 0.55–0.60 g/kg/d	0.8–0.9	1.0–1.2	1.2–1.3	1.0–1.2
Sodium	<100 mmol/d (2.3 g) to reduce blood pressure and minimize volume overload (proteinuria may also be reduced with low-sodium intake)				
Potassium	Adjust dietary intake as needed to maintain normal serum potassium level				
Phosphorus	Adjust dietary intake as needed to maintain normal serum phosphate level Consider bioavailability of phosphorus sources (e.g., animal, vegetable, versus additives)				
Calcium	Total elemental calcium intake of 800–1,000 mg/d (including dietary calcium, calcium supplementation, calcium-based phosphate binders) to maintain neutral calcium balance		Adjust calcium intake to maintain normocalcemia (given possibility of concurrent use of vitamin D analogs or calcimimetics)		
Dietary patterns	Prescribing a Mediterranean diet in adults with CKD 1–5 (nondialysis) and posttransplant with or without dyslipidemia may improve lipid profiles In adults with CKD 1–4, a diet with increased fruit and vegetable may decrease body weight, blood pressure, and net acid production				
Others	LC n-3 PUFA ~2 g/d may be prescribed to improve triglyceride levels		LC n-3 PUFA 1.3–4 g/d may be prescribed to reduce triglycerides and LDL cholesterol and raise HDL levels		
Multivitamins			It is reasonable to consider supplementation with MVI to adults with CKD 5D who have evidence of prolonged inadequate dietary intake		
Folic acid	Routine supplementation with or without B-complex is not recommended due to lack of benefits in cardiovascular outcomes.				

Vitamin C	It is reasonable to consider supplementation to meet recommended intake of >90 mg/d for men and 75 mg/d for women Avoid excessive intake due to risk of calcium oxalate precipitation in at-risk individuals
Vitamin D	Vitamin D supplementation with cholecalciferol or ergocalciferol to correct 25(OH)D deficiency/insufficiency is suggested
Vitamins E and A	Routine supplementation is not suggested due to potential for vitamin toxicity. If supplementation is necessary, monitor for toxicity.
Selenium and zinc	Routine supplementation is not suggested due to lack of evidence to support benefits.

Nutrition guidelines per Kidney Disease Outcome Quality Initiatives.

*For patients with glomerular disease and nephrotic range proteinuria, advise 0.8 to 1 g/kg ideal body weight/d; Add an additional 1 g per gram of urinary protein losses (up to 5 g/d). For those with non-nephrotic range proteinuria and eGFR < 60 ml/min/1.73 m^2, advise 0.8 g/kg/d.

Abbreviations: BW, birth weight; CKD, chronic kidney disease; DM, diabetes mellitus; ESKD, end-stage kidney disease; HD, hemodialysis; HDL, high-density lipoprotein; LC n-3 PUFA, long-chain ω-3 polyunsaturated fatty acid; LDL, low-density lipoprotein; PD, peritoneal dialysis.

Antifibrotic agents: Pirfenidone

- Oral agent that can inhibit various cytokines, including TGF-β, tumor necrosis factor-α, platelet-derived growth factor, and epithelial growth factor
- Proved effective in reducing injury in cyclosporine and tacrolimus nephrotoxicity, anti-GBM glomerulonephritis, doxorubicin toxicity in experimental models
- Clinical trials proving renoprotective effects of pirfenidone are still lacking.

Endothelin antagonists

- ET-1 mediates secretion of proinflammatory cytokines, growth factors, TGF-β.
  - Type A receptor (ET_AR) mediates vasoconstriction, sodium retention, podocyte dysfunction.
  - Type B receptor (ET_BR) mediates vasodilatation, sodium excretion.
    - Clinical study involving avosentan (nonselective ET-1 inhibitor) was terminated early due to excess congestive heart failure (CHF) complications (ASCEND trial).
    - Clinical studies on ET_AR-selective antagonism with atrasentan:
      - Phase 2 trial (RADAR trial): Atrasentan reduced albuminuria.

- Phase 3 trial (SONAR) was stopped prematurely due to a lower-than- expected number of renal events.

Nonrenal biomarkers in CKD

- Troponin:
  - Increased troponin level is associated with a two- to fourfold increased risk of all-cause mortality and major cardiovascular events.
  - In asymptomatic CKD patients, elevated troponin levels may indicate chronic structural heart disease (e.g., left ventricular hypertrophy, diastolic dysfunction, reduced ejection fraction) rather than acute coronary syndrome (ACS).
- Brain natriuretic peptide (BNP):
  - BNP is a less reliable marker of volume overload in CKD patients. Interpret with caution in patients with eGFR <60 ml/min/1.73 m^2.
  - However, BNP levels provide a good index for left ventricular mass and dysfunction.
- D-Dimer level can be elevated in CKD. A higher cutoff value may be needed in patients with advanced CKD to rule out pulmonary embolism.
- Acute-phase reactants associated with cardiovascular risk that may be elevated in CKD: fibrinogen, ceruloplasmin

Reversal of CKD

- Reversal of CKD remains to be a challenge.
- Pancreas transplant in eight type 1 diabetic patients with DKD revealed regression of glomerular lesions. However, full functional recovery was not achieved.
- Targets to consider for possible reversal: PAI-I, angiotensin II, TGF-β

Diabetic Kidney Disease

See **Chapter 7**.

Nondiabetic Kidney Disease

See **Chapters 6 and 7**.

Nephrosclerosis With Aging

- Structural changes with aging:
  - Reduction in kidney mass: 250 to 270 g kidney mass in 40 to 50 years old becomes 180 to 200 g by the age of 70 to 90.
  - Cortical thinning with relative medullary sparing (likely due to increased glomerulosclerosis)
- Histologic changes with aging:
  - Focal global glomerulosclerosis, thickening of GBM, mesangial expansion, ischemic changes with segmental adhesion to Bowman capsule
  - Tubular atrophy with cystic formation, interstitial fibrosis
  - Arteriolar intimal fibrosis—may be associated with thinning of media; hyaline arteriosclerosis seen in smaller vessels
- Functional changes with aging:
  - GFR reduction of 0.8 mL/min/1.73 m^2/y after age 40 may be observed.
  - GFR decline of 7 to 8 mL/min/1.73 m^2/y in those with underlying CKD
  - Albuminuria in 30% among patients ≥70 years old
  - Reduced concentrating and diluting capacities, which explains the propensity for increased nocturia and hyponatremia, respectively, in the elderly
  - Normal renal reserve

CKD and Pregnancy

Effects of pregnancy on volume homeostasis and the kidneys in women with *normal* kidney function

Volume and electrolytes

- Total Na^+ retention 950 mmol = 22 g
- Total water retention 6 to 8 L
- Plasma volume increases by 30% to 45% (up to 1.25 L) by the second trimester.
- Electrolyte changes:

Lower serum osmolality: 270 to 275 mOsm/kg versus nonpregnancy range of 280 to 290 mOsm/kg
- Lower S[Na^+]: 132 to 135 versus nonpregnancy range of 138 to 142 mmol/L

Kidney function

- Kidney length increases by 1 cm.
- Renal plasma flow and GFR increase by 50% by the second trimester.
- Glomerular hyperfiltration causes the midterm SCr to be as low as 0.4 to 0.6 mg/dL. A SCr ≥1.0 mg/dL is most likely abnormal.
  - Hemodynamic changes made by the kidneys during pregnancy are essential for normal fetal growth and development. Reduced renal function can adversely affect fetal outcomes.
  - Hyperdynamic changes and glomerular hyperfiltration in pregnancy accelerate progression of CKD.
- Increased loss of water-soluble vitamins, hence the need for prenatal vitamins.
- Increased proteinuria up to 300 mg/d or uPCR up to 0.3 g/g Cr is normal (predominantly tubular [nonalbumin, LMW] proteinuria).
    - Glucosuria is considered physiologic for later stages of pregnancy, which may be due to reduced tubular reabsorption or hyperfiltration overflow. However, early glucosuria requires testing for glucose intolerance or undiagnosed DM.

Hemodynamic changes

- Reduced vascular resistance:
  - Systemic arterial vasodilation mediated by NO and relaxin
  - Relative resistance to vasoconstrictors such as angiotensin II
  - Antidiuretic hormone (ADH) and RAAS are increased to counteract changes above, but the net effect is still reduction in vascular resistance.
- Increased cardiac output, increased thirst
- Decreased systemic BP:
  - DBP decreases by 7 to 10 mm Hg in early pregnancy, by as much as 20 mm Hg in mid-pregnancy, and returns to baseline by the third trimester.

- SBP only decreases slightly due to increased cardiac output (which offsets the reduction in peripheral resistance).

NOTE Poorly controlled HTN exaggerates kidney injury and GFR decline in pregnancy.

Management of CKD patients during pregnancy

General considerations

- Discontinue ACEI/ARB and statin (If patient is on immunosuppressive therapy, see **Chapter 8**.)
- Monitor Cr and proteinuria (uPCR)
- For chronic HTN BP goals in pregnancy, see **Chapter 5**.
- Initiate low-dose aspirin 81 mg after 12 weeks of pregnancy, preferably prior to 16 weeks, and continue until delivery for women with high risk for preeclampsia.
  - High preeclampsia risks: chronic HTN or kidney disease prior to pregnancy, obesity, women >40 years of age, multiple gestation, African American ethnicity, family history of preeclampsia, history of preeclampsia and preterm delivery at <34 weeks, history of preeclampsia in >2 pregnancies
- Nutritional support (avoid protein restriction), vitamins, folate supplements
- Iron supplement to keep serum ferritin levels of 200 to 300 µg/mL
- Maintain Hb 10 to 11 g/dL with erythropoiesis-stimulating agent
- Supplement calcium 1.5 to 2.0 g/d

Renal replacement therapy (RRT)

- RRT initiation is generally recommended at eGFR <20 ml/min/1.73 m^2 or bun >50 mg/dL.
- Increasing dialysis dose improves gestational age, live birth rates, and birth weight and lowers the rates of polyhydramnios and maternal HTN.
- Hemodialysis (HD):
  - Increase weekly sessions to achieve at least 20 h/wk (ideally 36 h/wk); this may require at least 5 days of dialysis treatments weekly.
  - Avoid rapid fluid shifts and volume removal.
  - Tight control of maternal weight and optimize ultrafiltration (UF) to

keep constant maternal/fetal hemodynamics to avoid growth retardation or poor outcomes. Consider intradialytic fetal monitoring.
  - BUN goal < 45 to 50 mg/dl

CKD and pregnancy outcomes

- Cr < 1.5 mg/dl:
  - Permanent loss of GFR in <10% of women
  - Live births in >90% of women
- Cr 1.5 to 2.5 mg/dL:
  - Maternal HTN and proteinuria in 50%
  - Decline or permanent loss of GFR in 30% of women
  - 10% incidence of ESKD soon after pregnancy
  - 60% risk of preterm delivery, 37% intrauterine growth retardation, and 7% fetal loss
- Cr > 2.5 mg/dL:
  - Progression to ESKD highly likely during or soon after pregnancy
  - High rate of fetal loss
  - Peritoneal dialysis (PD): Perform low-volume/frequent exchanges.
- For mothers requiring RRT:
  - Conception prior to HD initiation is associated with higher live birth rates, but similar birth weight and gestational age when compared to those conceived after HD initiation.
  - Preterm delivery may reach 80% among mothers receiving RRT.
  - The prevalence of small gestational age babies has been shown to be higher among mothers receiving PD compared with those receiving HD.

CKD Complications

Hypertension (HTN)

- Prevalence of HTN reaches ~80% to 90% in patients with CKD stage ≥ G3.
- Pathogenesis: sodium retention, increased peripheral resistance due to increased SNS and RAAS activities

Fluid overload

- Impaired pressure natriuresis
- Increased renal sodium reabsorption due to increased angiotensin II and aldosterone

Cardiovascular complications

Hyperlipidemia

- Statin therapy has been shown to have little or no effect on all-cause mortality or cardiovascular outcome in dialysis patients, unlike that observed in the general population.
- The difference in statin effect is thought to be due to nontraditional mechanisms of disease of CAD in dialysis patients.
- Initiation of statin therapy is not suggested in patients being started on dialysis. Continuation of existing statin therapy may be reasonable. Risks/benefits discussion should be done with patients.

Sudden cardiac deaths

- Account for up to 35% of all deaths in prevalent dialysis patients in the United States. This is 20 times higher than that observed in the general population.
- Potential contributing factors: low levels of long-chain n-3 fatty acids, low dialysate concentrations of potassium (<2 mmol/l) and calcium (<2.5 mmol/l), inadequate dialysis, higher uf volumes (>10 mL/h/kg body weight), long interdialytic window (higher risk on Sunday evening/Monday for patients receiving HD on Monday/Wednesday/Friday and Monday evening/Tuesday for patients receiving HD on Tuesday/Thursday/Saturday)
- Placement of an implantable cardioverter-defibrillator (ICD) for primary prevention is indicated in dialysis patients with left ventricular ejection fractions ≤35%.

Atrial fibrillation (AF)

- A stepwise increase in incident AF is observed among patients with higher CKD stages and increasing UACR. AF prevalence ranges from 16% to

21% in nondialysis CKD patients and 15% to 40% in those on dialysis.

- There is also a progressively increased risk of both ischemic stroke and hemorrhage among patients with AF and more advanced CKD.
- Rhythm control: Indications for rhythm control strategy in CKD patients mirror those in the general population.
- Rate control: The pharmacokinetics and dialyzability of the rate control agents should be considered.

Anticoagulation

- Observational data have suggested that anticoagulation threshold for CHA_2DS_2-VASC ≥2 is associated with benefit even in patients with CKD.
- Available data suggest that direct oral anticoagulants (DOACs) may be generally favored over warfarin (vitamin K antagonist).
  - Pivotal RCTs have established that DOACs are noninferior to warfarin among patients with CG estimated CrCl of 30 to 50 mL/min.
  - DOAC is associated with an approximately 50% reduction in intracranial hemorrhage risk and lower risk of vascular calcification and anticoagulant-associated nephropathy (i.e., warfarin-related nephropathy).
  - KDIGO recommendations are still pending.
    - There is insufficient high-quality evidence to recommend warfarin for the prevention of stroke in dialysis-dependent patients with AF. To reduce bleeding risk in this population, lower dose apixaban (2.5 mg twice daily [bid]) or rivaroxaban (15 mg daily) may be considered pending clinical safety data.
    - There is insufficient evidence to recommend single- or dual-antiplatelet therapy for prevention of stroke/thromboembolism among patients with AF and CKD stages G4 to G5D even when oral anticoagulation therapy is considered undesirable. In patients who recently received a coronary stent, the duration of concomitant antiplatelet therapy should be minimized and individualized based on clinical factors and type of stent used.
  - The US Food and Drug Administration (FDA) has approved reduced

doses of apixaban, edoxaban, and rivaroxaban in patients with eGFR 15 to 30 mL/min/1.73 m^2. Low-dose dabigatran 75 mg bid has also been approved for these patients.

- Anticoagulation is suggested to be "individualized" and discussed with patients based on risks and benefits. Other options including left atrial appendage occlusion or "no therapy" may be considered based on multidisciplinary team discussion.

Atrial flutter

- In patients with CKD and atrial flutter, radiofrequency ablation is considered first-line therapy due to its high success and low complication rates.

Coronary artery disease (CAD)

- Epidemiology:
  - Patients with CKD stages G3a to G4 have double and triple cardiovascular mortality risk, respectively, relative to patients without CKD.
  - Probability of developing CAD increases linearly with GFR below 60 to 75 mL/min/1.73 m^2.
- CAD risks:
  - Nontraditional risks (serum phosphate, albumin, C-reactive protein, dialysis vintage) may predict major cardiovascular events in HD patients.
  - Traditional risks (hyperlipidemia, BP, pulse pressure) may not predict outcomes.
- Clinical manifestations:
  - Atypical, "oligosymptomatic" presentation is common: chest, arm, shoulder, or neck pain is only reported in 44% among patients with acute MI (AMI) and CKD stages ≥G3a versus 72% among those with preserved kidney function. Anginal equivalents such as dyspnea and fatigue may be more common and must be recognized.
  - Patients with CKD may more commonly present with AMI rather than stable exertional angina.

    - Presentation is also more likely to be non–ST-elevation AMI (non-STEMI) rather than STEMI.
- CKD patients are less likely than non-CKD counterparts to receive cardiovascular intervention, cardiovascular diagnostic studies, and treatment including aspirin and β-blockers.
- Routine management of cardiovascular risks per KDIGO:
    - Level of care for ischemic heart disease should not be "prejudiced" by their CKD.
    - Adults at risk for atherosclerotic disease should be offered antiplatelet therapy if benefit outweighs bleeding risk.
    - In patients with GFR <60 ml/min/1.73 m^2, bnp/n-terminal-probnp and troponin levels should be interpreted with caution.
    - Invasive interventions: Coronary artery bypass grafting has been shown to be associated with a lower risk of death compared with percutaneous coronary intervention at 5-year follow-up for multivessel disease (USRDS data 1997 to 2009).
    - The use of drug-eluting stent improves revascularization of blood vessels compared with a bare-metal stent in patients with CKD stage 3.
    - Addition of spironolactone to ACEI or ARB therapy in patients receiving RRT: if safely tolerated (i.e., hyperkalemia), may reduce left ventricular hypertrophy and improve survival
    - Other interventions:
        - Fish oil (e.g., 4 g daily) has been suggested to lower risk for cardiovascular events.
        - Smoking cessation

Anemia/iron deficiency

- Hypoproliferative normochromic normocytic anemia, where anemia is defined as having Hb <13.0 g/dl in males and <12.0 g/dl in females
- Onset:
    - Typically occurs at CKD stage G3a for males and G3b for females
    - Patients with DM tend to have anemia at earlier CKD stage.
    - Patients with PKD tend to have anemia at later stage and less severe

anemia.
  - Patients with chronic tubulointerstitial disease tend to have earlier and more severe anemia.

Complications of anemia

- Fatigue, poor quality of life, difficulty with concentration, impaired judgment, sleep disturbance
- Left ventricular hypertrophy
- Sexual dysfunction
- Impaired immune response
- Platelet dysfunction
- Anemia is a “risk multiplier” for mortality in patients with CKD.

Pathogenesis of anemia in CKD

- Reduced renal erythropoietin (EPO) production due to loss of kidney mass. EPO is synthesized by peritubular interstitial fibroblasts and regulated as follows:
  - Under normoxic conditions, the hypoxia-inducible factor α (HIF-α) is hydroxylated by prolyl hydroxylase domain (PHD) enzymes, followed by ubiquitination by von Hippel–Lindau protein (pVHL) for subsequent degradation by proteasomes.
  - Under hypoxic conditions, HIF-α is not hydroxylated because of decreased PHD activity. The nonhydroxylated HIF-α translocates into the nucleus where it dimerizes with HIF-β, followed by binding of the HIF-α–HIF-β dimer to the hypoxia response element (HRE) at regulatory regions of target genes, thereby activating the transcription of hypoxia-related genes including EPO (Fig. 4.1).

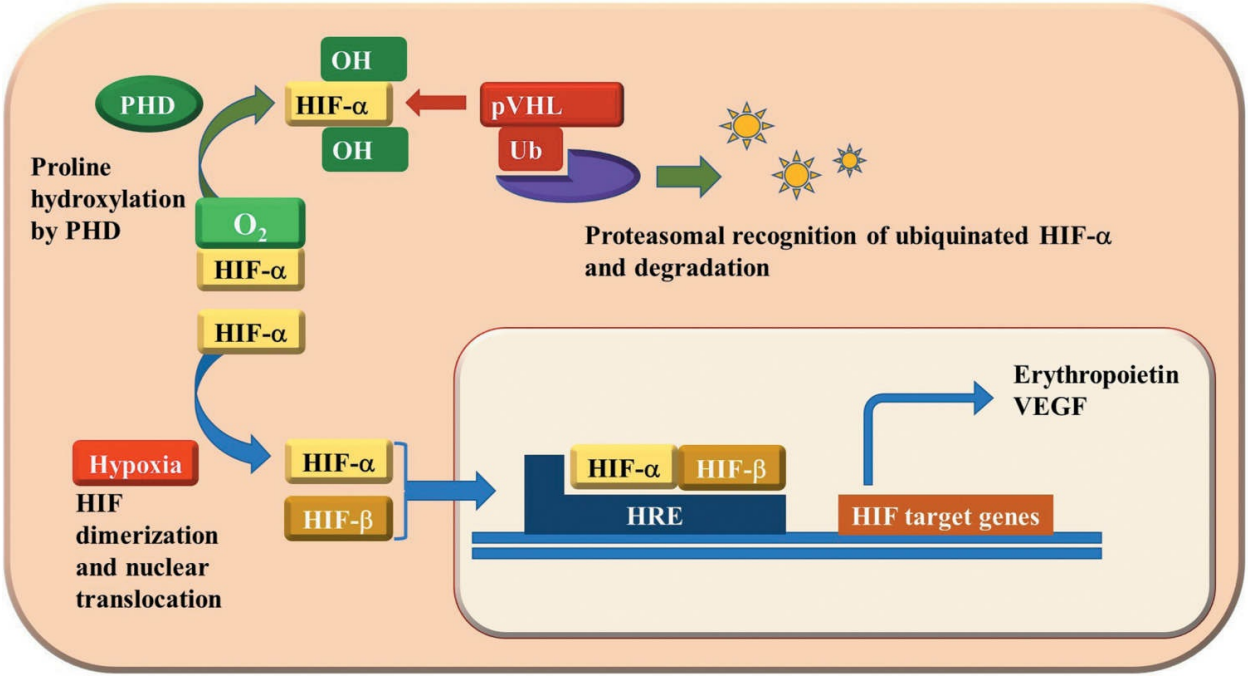

FIGURE 4.1 Regulation of HIF by PHD enzymes. HIF-α is continuously made in cells. In normoxic condition, PHD hydroxylates HIF-α at specific proline residues. The hydroxylated HIF-α is tagged for proteasomal degradation by pVHL, a process called ubiquitination. Under hypoxic condition, PHD leaves HIF-α unhydroxylated, allowing it to form dimers with HIF-β and translocate into the nuclei. Binding of the HIF-α–HIF-β dimers to the HRE activates the transcription of HIF target genes, including erythropoietin and VEGF, among others. Abbreviations: HIF, hypoxia-inducible factor; HRE, hypoxia response element; PHD, prolyl hydroxylase domain enzyme; pVHL, von Hippel–Lindau protein; Ub, ubiquitin; VEGF, vascular endothelial growth factor.

  - Anemia of CKD occurs in part because of:
    - insufficient HIF expression and function as well as
    - transformation of EPO-producing fibroblasts into EPO-nonproducing myofibroblasts
- Inflammatory state in CKD reduces EPO production and increases hepatic synthesis of hepcidin. Hepcidin reduces gastrointestinal (GI) absorption of iron and enhances iron sequestration in macrophages and hepatocytes. Of note, HIF is also known to suppress hepcidin.
  - Ferroportin is a transmembrane protein on macrophages and enterocytes that normally exports intracellular iron into circulation for erythropoiesis. Hepcidin binds to and internalizes ferroportin, thereby reducing iron export into circulation for effective erythropoiesis.
- Red blood cell (RBC) half-life is shortened in uremia.

- Severe secondary hyperparathyroidism (SHPT) can induce bone marrow fibrosis and results in ineffective erythropoiesis.

Management of anemia

KDIGO 2012 suggestions

- Monitor Hb at least yearly for patients with CKD stage G3, twice yearly for stage G4, every 3 months for stage 5.
- Evaluation of anemia: complete blood count with differential, absolute reticulocyte count, serum ferritin, serum transferrin saturation (TSAT), B_{12}, folate levels
- Iron deficiency:
  - For CKD stages G3 and G4: Ferritin < 100 ng/ml and tsat < 20% usually indicate absolute iron deficiency.
  - For dialysis patients: Ferritin < 200 ng/ml and tsat < 20% usually indicate absolute iron deficiency.
- EPO level is not generally checked because "normal" level may still be inadequate for patients with CKD when there may be some degree of bone marrow resistance to EPO.
- Exclude other common causes of anemia.

Iron therapy

- Iron supplement trial (1 to 3 months) in CKD patients with anemia if ferritin ≤500 µg/L and total iron saturation ≤30%

NOTE Risks associated with intravenous (IV) iron include increased oxidative stress, endothelial injury, vascular calcifications, plaque formation, and impaired leukocyte function, which may facilitate bacterial growth.

- The use of IV iron in patients with systemic infections is traditionally not recommended. *A systematic review and meta-analysis performed in 2018 by Hougen et al. revealed that "higher-dose IV iron did not seem to be associated with higher risk of mortality, infection, cardiovascular events, or hospitalizations in adult patients on dialysis." However, the study was "limited by small numbers of participants and events in included RCTs and statistical heterogeneity in observational studies."*

- Hold IV iron if ferritin >500 ng/mL. Note, however, that even when KDOQI iron parameters have been reached, anemia may still respond to iron therapy in some patients. This is referred to as “functional iron deficiency.”
- Monitor iron status (TSAT and ferritin) ≥3 months during erythropoiesis stimulating agent (ESA) therapy.

Use of erythropoiesis stimulating agent

- Avoid in patients with active malignancy particularly when cure is anticipated, history of stroke, or history of malignancy (increased thromboembolic risk and survival in some cancers). See ESA packaging inserts for specific malignancies.
- Initiate when Hb values trend downward and reach levels <9 to 10 g/dl after iron store has been repleted. monitor hb ≥1 month while on esa.
- Goal Hb 10 to 11 g/dL. Avoid ESA when Hb >10 g/dL.
- ESA is not recommended to maintain Hb >11.5 g/dL.
- Monitor Hb every 3 months when on stable ESA doses.
- Empirical use of adjuvant therapies including androgens; vitamins C, D, and E; folic acid; L-carnitine; and PTF is not suggested. Although carnitine is involved in RBC plasma membrane remodeling, hence improved RBC survival, routine carnitine replacement has *not* been shown to improve responsiveness to ESA.

Erythropoiesis stimulating agent hyporesponsiveness

- Initial ESA hyporesponsiveness is defined as having no increase in Hb levels from baseline after 1 month of appropriate ESA weight-based dosing.
- ESA dose escalation greater than doubling of initial weight-based dose should be avoided.
- Initial hyporesponsiveness despite appropriate weight-based dosing:
  - Evaluate for common deficiencies: iron, vitamin B_{12}/folate/carnitine
  - Other possible causes: inflammatory or infectious state, underdialysis, severe SHPT, aluminum toxicity, use of RAAS inhibitors, underlying bone marrow disorders, hemoglobinopathies, blood loss/hemolysis,

immunosuppressive medications

- Subsequent ESA hyporesponsiveness:
  - This is defined as having two increases in ESA doses up to 50% beyond initial stable maintenance dose for desired Hb.
  - Evaluation for subsequent hyporesponsiveness:
    - Routine evaluation similar to initial hyporesponsiveness above
    - Consider pure red cell aplasia, a very rare condition where ESA is inactivated by anti-ESA antibodies after >8 weeks use.
    - Suspect pure red cell aplasia if there is a sudden and rapid drop of Hb, normal white blood cell (WBC) and platelet count, and low reticulocyte count

Hypoxia-inducible factor stabilizers

- Agents in clinical trials include roxadustat, daprodustat, and vadadustat.
- Potential advantages:
  - Provide consistent, although not continuous and more physiologic doses of endogenous EPO
  - Increased availability of iron for erythropoiesis
  - Oral administration
- Potential concerns:
  - Tumor-producing effects
    - HIF signaling activates vascular endothelial growth factor (VEGF) transcription, thus potentially allowing angiogenesis to support rapidly growing tumors.
    - HIF also promotes tumor metastasis via stimulation of epithelial-to-mesenchymal transition, thereby potentially inducing tumor cell invasion.

Red blood cells (RBCs) transfusions

- Avoid if possible, particularly in kidney transplant candidates due to risk of allosensitization.
- Consider RBC transfusions if refractory or contraindicated to ESA.

CKD-Mineral Bone Disease

- CKD-mineral bone disease (CKD-MBD) refers to disorders of systemic mineral metabolism involving abnormalities in biochemical profile, bone turnover, mineralization and volume, and/or vascular and soft-tissue calcifications. Biochemical profile refers to serum calcium, phosphate, bone-specific alkaline phosphatase (AP), and parathyroid hormone (PTH). KDOQI recommendations on monitoring and management of CKD-MBD are summarized in Table 4.2. See **Chapter 3** for management of SHPT.

Table 4.2 Summary of KDIGO 2017 CKD-MBD recommendations

	CKD Stage	3	4	5/5D
	Ca, PO_4	q6–12m	q3–6m	q1–3m
Profile		• May increase monitoring frequency for trends and treatment frequency and side effects • **Therapeutic decisions should be based on trends of all available CKD-MBD assessments rather than on any single laboratory value** • *Individual* values of Ca and PO_4 should be evaluated together to guide clinical practice rather than the Ca × PO_4 *product*		
	iPTH	Based on baseline level and CKD progression	q6–12m	q3–6m for CKD 5D
	Bone-specific alkaline phosphatase		q12m or more frequently in the presence of elevated iPTH	
	25(OH)D	• Measurement is suggested with repeated testing per baseline values and therapeutic interventions • Vitamin D deficiency and insufficiency may be corrected as for the general population		

• Diagnosis	Bone	• In patients with evidence of CKD-MBD and/or risk factors for osteoporosis, BMD testing to assess fracture risk is suggested if results impact treatment decisions • Performing a bone biopsy is reasonable if result impacts treatment decision • Measurements of iPTH and AP can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover
	Vascular calcifications	• A lateral abdominal radiograph may be used to detect the presence of vascular calcification and an echocardiogram to detect valvular calcification in lieu of computed tomography-based imaging • Known vascular/valvular calcification can be considered as highest cardiovascular risk to guide management

• Treatment	Serum phosphate	• Treatments of CKD-MBD should be based on serial assessments of Ca, PO_4, and iPTH levels, considered together
		• Lower PO_4 levels toward normal range
		• Treatment decision should be based on progressively or persistently elevated PO_4 levels
		• Restrict dose of calcium-based phosphate binders in adults
		• Limit dietary phosphate intake in the treatment of hyperphosphatemia either alone or in combination with other treatments
		• **Avoid long-term use of aluminum-containing phosphate binders**
		• For patients receiving hemodialysis (CKD G5D):
		  • Use dialysate calcium concentration in the range of 1.25–1.50 mmol/L (2.5–3.0 mmol/L)
		  • Increase dialytic phosphate removal in patients with persistent hyperphosphatemia
		  • **Avoid dialysate aluminum contamination**

	iPTH	• Optimal iPTH level is not known
		• For elevated levels, evaluate for modifiable factors (hyperphosphatemia, hypocalcemia, high-phosphate intake, vitamin D deficiency)
		• Calcitriol and vitamin D analog should not be used routinely but reasonable to be used for patients with CKD G4–G5 and severe and progressive hyperparathyroidism
		• For patients receiving dialysis (CKD G5D):
		  • Maintain iPTH levels ~ two to nine times upper normal limit
		  • Calcimimetics may be used for PTH-lowering therapy and/or calcitriol or vitamin D analogs

	Use of bisphosphonates, osteoporosis medications	• In patients with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, consider the magnitude and reversibility of the biochemical abnormalities and progression of CKD in treatment choices. • Consider bone biopsy

Abbreviations: AP, alkaline phosphatase (bone specific); BMD, bone mass density; Ca, calcium; CKD, chronic kidney disease; iPTH, intact parathyroid hormone; KDIGO, Kidney Dialysis Initiatives on Global Outcomes; MBD, mineral bone disease; PO_4, phosphate; q, every.

CKD-related bone diseases (Table 4.3)

Table 4.3 CKD-MBD bone disease

Bone Disease	Turnover	Mineralization	Volume	Comments
Osteitis fibrosa cystica	High	Normal or defective	Variable	Seen with SHPT Most common bone disorder seen in HD patients Labs: normal to high Ca; high PO_4; high PTH
Adynamic bone disease	Low	Abnormal (no osteoid, no mineralization)	Normal	Associated with oversuppression of SHPT with VDRA and calcium-based phosphate binders Most common bone disorder seen in PD patients Risks: oversuppression of SHPT with VDRA and calcium-based phosphate binders, DM, advanced age, aluminum deposition Labs: high Ca; normal-to-low PO_4; normal-to-low PTH
Osteomalacia	Normal	Abnormal	Increased	Low bone formation and bone density May be seen with aluminum toxicity
Mixed uremic osteodystrophy	High	Abnormal	Low	Most common bone disorder in patients with CKD G3–G5
Osteoporosis	Increased bone breakdown relative to bone production	Abnormal	Low	Treatment of concurrent CKD-MBD takes precedence over osteoporosis in patients with CKD Obtain alkaline phosphatase in addition to DEXA scan to determine low, normal, vs. high bone turnover to guide treatment (see text)

Abbreviations: SHPT, secondary hyperparathyroidism; Ca, calcium; CKD, chronic kidney disease; DEXA, dual-energy X-ray absorptiometry; DM, diabetes mellitus; HD, hemodialysis; MBD, mineral bone disease; PD, peritoneal dialysis; PO_4, phosphate; PTH, parathyroid hormone; VDRA, active vitamin D–receptor agonist.

- Bone “TMV” terminology:
  - **T**urnover: low, normal, or high
  - **M**ineralization: normal or abnormal
  - **V**olume (reflects net bone formation and resorption rates and is related to bone porosity, strength, and fragility): low, normal, or high

Renal osteodystrophy refers to various bone histomorphologic abnormalities due to disturbances in bone turnover, mineralization, and volume as a consequence of CKD-MBD. All bone disorders are associated with increased fracture risks.

Osteitis fibrosa cystica

- High bone turnover disease: high rates of bone formation and resorption
- Condition seen with SHPT
- Most common bone disorder observed in patients receiving HD
- Bone histomorphology: increased osteoblastic and osteoclastic activity with a high fraction of trabecular surface covered by osteoid seams, osteoid–osteoblast interface, abnormal collagen deposition, marrow fibrosis
  - **T**urnover: high (increased osteoblastic and osteoclastic activity, may be evidenced by increased tetracycline uptake)
  - **M**ineralization: normal or defective
  - **V**olume: variable

Adynamic bone disease (ABD)

- Low rates of bone formation and resorption; may be evidenced by low tetracycline uptake
- Associated with oversuppression of SHPT with overzealous administration of active vitamin D and calcium in patients with relative PTH resistance
- Most common bone disorder observed in patients receiving PD
- Bone histomorphology:
  - **T**urnover: low (absence of active bone resorption and bone formation)
  - **M**ineralization: abnormal (no osteoid, no mineralization)
  - **V**olume: normal
- Risks for ABD:
  - Oversuppression of PTH
  - Advanced age
  - DM
  - Aluminum deposition (e.g., previously observed in patients receiving

aluminum-based phosphate binders)

- Clinical clues for ABD:
  - Relatively low serum intact PTH level
  - Hypercalcemia (serum calcium is not taken up by bone due to low bone formation)
  - Hypophosphatemia (due to low bone resorption)

Osteomalacia

- Low bone formation and low bone density, poor bone mineralization
- May be seen with aluminum toxicity
- Bone histomorphology:
  - **T**urnover: normal
  - **M**ineralization: abnormal
  - **V**olume: increased

Mixed uremic osteodystrophy: mixed findings of above conditions

- Most common bone disorder in patients with CKD stages 3 to 5
- Bone histomorphology:
  - **T**urnover: high
  - **M**ineralization: abnormal
  - **V**olume: low

Osteoporosis

- Increased bone breakdown relative to bone production
- Bone density (or mass) is at least 2.5 standard deviation less than peak bone mass
- Diagnosis: dual-energy X-ray absorptiometry (DEXA) scan every 1 to 2 years (see **Diagnostic Testing** below)
- Management of osteoporosis in patients with CKD:
  - Treatment of concurrent CKD-MBD has priority over treatment of osteoporosis.
    - If T-score ≤−2.5, assess bone turnover with bone-specific AP.
    - If AP is elevated, high bone turnover is likely; initiate antiresorptive agent (e.g., bisphosphonates, denosumab).

    - If AP is low, low bone turnover is likely; initiate anabolic agent (e.g., teriparatide, abaloparatide).
    - If AP is within the middle of normal range, perform bone biopsy to exclude low bone turnover disease prior to administration of bisphosphonates.
        - Severe hypocalcemia may occur with bisphosphonates in patients with vitamin D deficiency.
        - Safety issue: FDA warnings against the use of bisphosphonates in patients with GFR <30 ml/min/1.73 m^2.
        - KDIGO suggests *not* to prescribe bisphosphonate to patients with eGFR <30 ml/min/1.73 m^2 without a strong clinical rationale.
- Strict phosphorus/protein restriction improves renal osteodystrophy but thought to worsen osteoporosis. Low-protein intake is associated with lower bone mass density (BMD).
- Other therapeutic options:
    - Assess adequacy of protein intake
    - Correction of metabolic acidosis
    - Maintain muscle mass as it provides an increased load for stimulation of bone turnover
    - Nitric oxide supplementation (e.g., nitrates) may be considered. Canadian multicenter osteoporosis study showed significant positive association between nitrate use and higher BMD. Although similar study in CKD patients is lacking, consideration for use of nitrates is worthwhile as they also benefit endothelial dysfunction, a common problem in CKD patients.

Osteopenia

- Similar to osteoporosis but milder condition
- Bone density is 1 to 2.5 standard deviation less than peak bone mass.

Diagnostic testing

Imaging studies

- Dual-energy X-ray absorptiometry (DEXA):
    - Determines both mineral content and bone area

- Limitations: DEXA may overestimate BMD in CKD patients, likely due to vascular calcifications and/or hPTH-induced increased trabecular-to-cortical bone ratio. KDIGO suggests DEXA testing to assess fracture risk in patients with CKD stages G3a to G5D "if the results impact treatment decisions."
  - Quantitative computed tomography (CT):
    - Measures three-dimensional (3D) bone volume and can differentiate cortical and trabecular bone geometry and morphology
  - Micro magnetic resonance imaging (MRI): high-resolution MRI
  - Quantitative ultrasound: measures appendicular skeletal density (most often calcaneal bone); may be better than DEXA. Limited data in CKD

Bone biopsy

- Gold standard
- Bone biopsy is obtained from anterior iliac crest after tetracycline labeling at two different times separated by 11 to 14 days. Tetracycline binds to newly formed bone at unmineralized bone interface. Measuring the distance between the two lines allows for calculation of bone formation rate during that interval.
- Indications for bone biopsy:
  - Unexplained fractures
  - Persistent bone pain
  - Unexplained hypophosphatemia
  - Possible aluminum toxicity
  - Prior to therapy with bisphosphonates (CKD stage G3 with abnormalities of CKD-MBD and low BMD)

Extraosseous and vascular calcifications

- Basic arterial layers starting from outside the lumen: adventitia > media > intima
- Medial artery calcifications (MACs):
  - Concentric calcifications that can lead to arterial stiffening

- MAC is associated with better survival compared with those with intimal calcifications (seen with classic CAD risks), but worse survival compared to those with no calcification.

Immune dysfunction

Contributing factors

- Diabetes, malnutrition, peripheral vascular disease, skin breaks (e.g., dialysis access, diabetic foot ulcers)
- Impaired host–defense mechanisms, affecting all cell lines (neutrophils, monocytes, lymphocytes, dendritic cells, macrophages)

Clinical impact

- Increased infection risks:
  - Increased infection risks for *Staphylococcus* sp., *Pseudomonas* sp., other gram-negative bacteria, atypical bacteria including *Mycobacterium tuberculosis*, viruses (herpes simplex)
  - ESKD patients are estimated to have a 50-fold increased risk in developing active tuberculosis (TB) infection.
  - Interferon-release assays (e.g., QuantiFERON or T-SPOT.TB testing), which measure the response of sensitized T cells to mycobacterial antigens, correlate with past TB radiologic evidence better than traditional skin testing.

Increased malignancy risks

- Increased malignancy risk has been reported in patients receiving RRT involving kidney, bladder, cervix, multiple myeloma, thyroid, and other endocrine glands.
- No increased risks reported in the breast, prostate, stomach, intestine, lungs.
- Management: Malignancy screening guidelines for CKD are not well established. Screen at least per routine for age, gender, personal risk factors, family history, and pretransplant evaluation.

Acquired cystic kidney disease (ACKD) and renal cell carcinoma (RCC)

Definition: presence of >3 to 5 macroscopic cysts in individuals without a hereditary cause of cystic disease

- Prevalence:
  - May occur prior to dialysis
  - At dialysis initiation: 5% to 20%
  - By 10 years on dialysis: 80% to 100%
- Pathogenesis of ACKD is likely multifactorial and may be related to:
  - Loss of nephrons followed by tubular cell hypertrophy, hyperplasia, and epithelial cyst formation
  - Activation of proto-oncogenes and accumulation of mutagens in a uremic milieu
  - Genetic susceptibility
- Malignant transformation to RCC:
  - Cumulative incidence <1% up to 7% among ackd
  - Up to 40-fold increased risk of RCC in ACKD compared with the general population
  - Risk factors associated with RCC transformation: male gender (7:1 compared to females), African American, prolonged dialysis, severe ACKD with marked kidney enlargement
  - Management: surveillance imaging studies per symptoms and patient life expectancy:
    - Low life expectancy: no screening
    - Good life expectancy: yearly kidney ultrasound
  - Presence of hematuria, flank pain, unexplained fevers, erythrocytosis, worsening BP: immediate kidney ultrasound, consider CT urogram. See Chapter 6 for interpretations of cystic findings related to malignancy of the kidneys.
  - ACKD may regress to some degree with a successful kidney transplant.

Malnutrition

- Contributing factors:
  - Poor appetite, inappropriate protein restriction
  - Increased inflammatory state

- Poor GI absorption (e.g., gastroparesis, nausea, vomiting)
- Increased albumin loss with PD
- Inadequate dialysis dose

- Malnutrition adversely affects survival in ESKD.
- Global assessment of malnutrition:
  - Physical characteristics:
    - Body mass index (BMI):
      - Better survival with higher BMI (i.e., >25 kg/m^2) compared with counterpart with normal or low BMI
      - Survival advantage of higher BMI may more specifically pertain to patients > 65 years of age and not necessarily younger patients.
      - Cause of death is more commonly due to cardiovascular events in patients with higher BMI and noncardiovascular etiology in those with lower BMI.
    - Anthropometric measurements (e.g., skin-fold thickness, limb circumference)
  - Biomarkers for both nutritional and inflammatory status:
    - Serum albumin (accuracy may be reduced with dilutional hypervolemia, severe albuminuria). Lower albumin level is a strong predictor of mortality in dialysis patients.
    - Total iron-binding capacity is reduced in inflammatory states.
    - C-reactive protein level is increased in inflammatory states.
- Malnutrition–inflammation complex syndrome (i.e., protein-energy wasting syndrome):
  - Concurrent malnutrition and inflammation
  - Prevalence is up to 70% in dialysis patients.
  - May arise from poor dietary intake, coexisting illnesses, genetic susceptibility, dialysis procedures, infections
- Management:
  - Collaboration between a registered dietician nutritionist (RDN) and a physician or other provider (e.g., nurse practitioner or physician assistant) to provide medical nutrition therapy is recommended.

- Protein supplements (e.g., 14 to 20 g three times weekly) given to patients with serum albumin concentration <3.5 g/dl has been shown to improve hospitalization and survival rates.
- Nutritional recommendations per KDOQI (Table 4.1)

Neurologic complications

- Mood swings, agitation, delirium
- Impaired cognition, perception, concentration, loss of recent memory, visual hallucinations
- Hyperreflexia, tremors, asterixis
- Dysarthria, altered gait, clumsiness, convulsions

Depression

- Most common psychiatric disorder in chronic dialysis patients
- Most common psychiatric disorder requiring hospitalization in dialysis patients
- Correlates with a ≥30% increase in mortality
- Risk for increased cardiovascular disease and mortality
- Risks: younger age, patients with lower SCr and albumin
- Routine screening recommended at first dialysis, biannually, or more often as needed.
- Treatment: antidepressants and/or psychiatric referral. Most antidepressants are hepatically metabolized and do not require dose adjustment, with the exceptions of paroxetine and venlafaxine.

Sleep disorders

- Poor sleeping score is associated with increased relative risk of death ~1.3 (Dialysis Outcomes and Practice Patterns Study or DOPPS).
- Insomnia:
  - Most common sleep disorder in dialysis patients (prevalence up to 70%)
  - Insomnia is associated with restless leg syndrome, depression, and pain, and vice versa.
- Sleep apnea:
  - Prevalence up to 50% compared to <5% in general population

- Pathogenesis: fluid overload leading to upper airway congestion “rostral fluid shift” during sleep, uremia induced alteration in central ventilator control, presence of comorbid conditions
- Nocturnal episode of arterial oxygen desaturation is associated with higher cardiovascular events and worse survival in HD patients.
- Compared to conventional HD, daily nocturnal HD reduces the apnea–hypopnea index (episodes of apnea per hour of sleep).
- Treatment of sleep apnea improves survival.

Uremic neuropathy (UN)

- Uremic neuropathy (UN) is defined as a distal symmetric sensorimotor polyneuropathy that typically affects lower limbs but may also spread to upper limbs.
- Occurs in 60% to 100% of patients with CKD and ESKD
- Pathogenesis:
  - Thought to be due to accumulation of uremic toxins, “middle molecules,” in association with oxidative stress–related free radical activity, leading to motor, sensory, and autonomic nerve damage
  - Electrolyte disturbances, particularly dyskalemias, may also contribute.
- Clinical manifestations:
  - May be asymptomatic until GFR <15%
  - Both slowly and rapidly progressive disease may occur, the latter in association with acute illnesses such as sepsis
  - Symptoms: typically slowly progressive sensorimotor axonal neuropathy that advances proximally, starting from lower limbs with possible spread to upper limbs; paresthesia, numbness, hyperesthesia to noxious stimuli, thermal sensitivity impairment, restless leg syndrome, cramps, impaired deep tendon reflexes, weakness, imbalance, lower limb atrophy, optic neuritis (sudden vision deterioration, blurry vision)

NOTE In contrast to uremic neuropathy, a sensorimotor axonal neuropathy that starts from the lower limbs and advances proximally, diabetic neuropathy primarily manifests as a sensory deficit in a “stocking-and-glove” distribution.

- Risks: DM, advanced age, advanced CKD

- Diagnosis:
  - Nerve conduction study revealing severe reduction in nerve conduction velocity (may be severe and <50% to 60% of normal)
  - Light touch and vibratory perception changes may be more sensitive to evaluate for disease progression or recovery than nerve conduction velocity.
- Pathology: demyelination of large nerve fibers leading to axonal degeneration
- Management: optimize/intensify dialysis dose, transplantation to halt disease progression, symptomatic relief (see **Restless Leg Syndrome** below)

Restless leg syndrome

- Unpleasant sensation in lower extremities with compulsive need to move legs, worse in the evening, improves with walking
- Incidence reported to be up to 60%.
- Associated with higher risk for cardiovascular events *and* mortality
- Contributing factors:
  - Reduced dopaminergic modulation of intracortical excitability, with reduced supraspinal inhibition and resultant spinal cord excitability
  - Iron (Fe) deficiency: Fe is a cofactor for tyrosine hydroxylase, the rate-limiting step in the synthesis of dopamine.
  - Others: altered calcium/phosphate metabolism, hyperhomocysteinemia, anemia, sympathetic nervous system (SNS) activation, peripheral neuropathy
- Treatment options: provide adequate dialysis; Fe supplementation if deficient; dopamine-receptor agonists such as pramipexole or ropinirole, levodopa plus decarboxylase inhibitors (Sinemet); others: gabapentin or pregabalin (renal dose adjustment is required), opioids, benzodiazepines, aerobic exercise, avoidance of caffeine, alcohol, and nicotine at bedtime

Bleeding diathesis

Contributing factors

- Platelet dysfunction

- Uremic toxins (e.g., urea, guanidinosuccinic acid, phenolic acid, methylguanidine) may interfere with adenosine diphosphate (ADP)–induced platelet aggregation and thromboxane A_2 (thromboxane A_2 increases platelet aggregation).
- Anemia:
  - Dilutional effect of platelets with reduced RBC mass
  - RBCs bind NO. With anemia, increased free NO stimulates cyclic guanosine monophosphate (cGMP) production, with subsequent suppression of thromboxane A_2 and ADP production. RBCs also release thromboxane A_2 and ADP.
  - EPO deficiency: EPO increases platelet production.
- von Willebrand factor (vWF) abnormalities
- Vessel abnormalities, resulting in ineffective vasoconstriction

Corrective measures

Dialysis

- Rapid onset of action with dialysis removal of uremic toxins

ESA administration

- Requires ~7 days to increase platelet count and function.

DDAVP

- Rapid (within an hour) onset of action with endothelial release of factor VIII and vWF
- 0.3 µg/kg IV administered over 30 minutes
  - Therapeutic effect of DDAVP is ~24 hours and becomes refractory within 48 hours due to depletion of stored factors.
  - Use with great caution in patients with increased risks for cardiovascular diseases and heart failure due to potential rapid changes in BP and heart rate

Cryoprecipitate

- Administer 10 units IV
- Immediate onset of action, duration of action 4 to 12 hours
- Contains factors VIII and XIII, vWF, fibrinogen, and other clotting factors

Conjugated estrogen

- Onset of action 6 hours to 5 to 7 days, duration of action 2 to 3 weeks
- Mechanism of action: decrease L-arginine production (NO precursor), decrease antithrombin III and protein S levels, increase factor VII

Other CKD-Related Issues

- IV contrast media with imaging studies: see **Chapter 11**
- Phosphate-containing bowel preparation is not recommended in patients with GFR <60 ml/min/1.73 m^2 due to risk of acute phosphate nephropathy.
- Gadolinium:
  - KDIGO recommends against its use in those with GFR <15 ml/min/1.73 m^2.
  - For patients with GFR <30 ml/min/1.73 m^2 who require the use of an mri contrast agent, a macrocyclic chelate preparation should be offered.

KDIGO immunization recommendations for CKD patients

- Annual influenza vaccine if not contraindicated
- Polyvalent pneumococcal vaccine for all adult CKD patients, regardless of stage, if no contraindication. The vaccine is to be given in the following order:
  1. Pneumococcal 13-valent conjugate vaccine (PCV13)
  2. First dose of pneumococcal polysaccharide vaccine (PPSV23) 8 weeks after PCV13
  3. Second dose of PPSV23 5 years later
  4. Additionally, those who receive PPSV23 before age 65 should receive another dose at age 65 or later if 5 years or more have elapsed since the previous PPSV23 dose.
- Hepatitis B vaccine for all adults with eGFR <30 ml/min/1.73 m^2 and those with high risk of ckd progression. confirm response with serology. antibody titer above 10 confers immunity.
- Others per routine: tetanus, diphtheria, pertussis (Td/Tdap), varicella, human papillomavirus, zoster, measles, mumps, rubella (MMR)
- See **Chapter 9**. Live vaccines are contraindicated posttransplantation.

Stages 4 and 5 CKD

- Advanced uremic symptoms: see CKD complications and associated symptoms

Preparation for end-stage kidney disease

- KDOQI: It is reasonable to educate all patients with CKD G4/G4T with progressive decline in kidney function on all modalities of kidney replacement options, including kidney transplantation.
- RRT modality selection depends on goals of care, local resources, capacities of regional health care facilities, family/social support, patient's own cost of care, level of independence/dependence, preservation of residual kidney function, and underlying medical conditions.
- Dialysis access and preparation
  - PD access should be placed whenever possible at least 2 weeks prior to RRT. Urgent start PD may be an option if medically safe and performed properly.
  - HD vascular access:
    - KDOQI: Referral for surgical evaluation and creation of a new arteriovenous (AV) access should be done at eGFR 15 to 20 mL/min/1.73 m^2 or earlier in patients with unstable and/or eGFR decline of >10 mL/min/1.73 m^2/y.
    - Type of access depends on:
      - Remaining life expectancy (e.g., permacath may be reasonable if life expectancy is less than a year, whereas arteriovenous fistula [AVF] or arteriovenous graft [AVG] would be preferred in patients with longer life expectancy)
      - Quality of blood vessels
  - Postoperative AV access considerations:
    - Whole-arm exercise rather than finger exercise is recommended following AVF creation.
    - KDOQI does not suggest the use of heparin, clopidogrel monotherapy, glyceryl-trinitrate, cholecalciferol, or clopidogrel-prostacyclin for AVF maturation or improvement of

primary/secondary patency.

Initiation of maintenance dialysis

- Timing for initiation:
  - Still not established
  - KDOQI: “When patients reach stage 5 CKD (eGFR < 15 ml/min/1.73 m^2), nephrologists should evaluate the benefits, risks, and disadvantages of beginning kidney replacement therapy. particular clinical considerations and certain characteristic complications of kidney failure may prompt initiation of therapy before stage 5.”
    - “Particular considerations” for earlier initiation:
      - Recurring hyperkalemia despite corrections of all contributing factors
      - Volume overload, leading to pulmonary edema or refractory to diuretics
      - Uremic pericarditis, unexplained pericardial effusion
      - Nausea/vomiting
      - Severe metabolic acidosis, particularly if cannot tolerate oral alkalinization
      - Declining health
      - Malnutrition:
        - General indicators: decline in serum albumin, weight loss
        - Patients with <90% of standard body weight (sbw) are considered to be mildly to moderately malnourished, and those who are <70% of sbw are considered severely malnourished. it is recommended that a target body weight for maintenance dialysis patients is between 90% and 110% of sbw (nhanes iii).
  - IDEAL trial: There is no survival benefit between early versus late start (initiate HD at eGFR 10 to 15 mL/min/1.73 m^2 vs. 5.0 to 7.0 mL/min/1.73 m^2) if patient can tolerate late start (absence of uremic symptoms or complications associated with ESKD).
  - Patient’s preference for a trial of medical nondialytic management prior to dialysis initiation should be considered when patient is medically

stable and asymptomatic.

- For patients older than 60 years: In the absence of AKI/illnesses, delay in dialysis initiation until eGFR <6 ml/min/1.73 m^2 may be acceptable.
  - GFR decline may be relatively slow in this population.
  - 20% to 35% of older patients with CKD G4 to G5 die per year prior to reaching dialysis.
  - Older patients have a lower likelihood of survival in the 90 days following dialysis initiation.
- Consider use of risk equations for predicting time frame to needing RRT.
- Criteria for dialysis initiation for those with a failed transplant are similar to those with ESKD of native kidneys.

Planning for end-of-life care or withdrawal of RRT

- Estimate and discuss with patients regarding prognosis and quality of life both with and without RRT.
- Patients with deteriorating condition/comorbidities despite dialysis should be given consideration for end-of-life care.
- For patients with poor life expectancy, maintain a supportive care registry to ensure care needs are met and provide opportunity for advance care planning.
- Dialysis withdrawal should include end-of-life care planning by patient and all involved health care professionals. Assessment for competence and evaluation for depression should be performed.

End-Stage Kidney Disease

- 2020 KDIGO Consensus Conference suggests the term “kidney failure” instead of “end-stage kidney disease.” However, ESKD is still being used throughout this book because the authors feel that “kidney failure” does not reflect irreversibility of the kidney disease as does ESKD.

Epidemiology of ESKD

- The most common etiologies leading to ESKD in the United States are DM

and HTN.

- Dialysis initiation for a failed kidney transplant comprises ~5% of all incident dialysis patients in the United States over the past two decades.
- Regional differences are likely due to population differences: Network 16 (Pacific Northwest) has the lowest rate of ESKD, whereas Network 8 (Southeastern United States) has the highest rate of ESKD.

US Policies in the Care of ESKD

- In 2011, the US Centers for Medicare & Medicaid Services (CMS) launched the prospective payment system (PPS) for ESKD care, when the "bundled" payment system was created.
- In July 2019, the Center for Medicare and Medicaid Innovation's Advancing American Kidney Care aimed to improve CKD and ESKD outcomes.
- See **Appendix A** for details on above policies.

Factors Associated With Worse Survival in the Dialysis Patient

- Patient factors: Caucasians have decreased survival compared to African Americans, poor nutritional status (lower serum albumin, lower cholesterol levels, lower BMI), presence of inflammation or high inflammatory markers (higher C-reactive peptide levels), troponin leaks, lower predialysis serum potassium levels, poor control of MBD, depression, sleep apnea, restless leg syndrome, loss of residual kidney function. The presence of residual kidney function has been suggested to improve both cardiovascular events and mortality.
- Dialysis factors: (Highest death rates on) Sunday evening/Monday for Monday/Wednesday/Friday HD patients and Monday evening/Tuesdays for Tuesday/Thursday/Saturday dialysis patients (presumably due to cardiovascular complications/volume overload/electrolyte abnormalities), use of dialysate K^+ <2 mmol/l, lower dialysis duration, higher uf rate (i.e., >13 mL/kg/h), intradialytic myocardial stunning (measured as intradialytic regional wall motion abnormalities; higher risk of myocardial stunning with higher UF and intradialytic hypotensive episodes)

Principles of Dialysis

Solute clearance by dialysis occurs via diffusion or convection or both

- Diffusion is determined by concentration difference between blood and dialysate.
- Convection, also known as “solvent drag,” occurs with UF where smaller solutes are “dragged” by the movement of water across the dialysis membrane.

Forms of maintenance dialysis

- PD relies on both diffusion and convection across peritoneal membrane for solute clearance. Water clearance relies on the osmolality of the dialysate via osmosis.
- HD relies mostly on diffusion for solute clearance.

Dialysis membrane characteristics

Hemodialysis membrane

- Membrane used for dialysis is made of substituted cellulose, cellulosynthetics, or synthetics.
- Resistance for solute movement across membrane depends on membrane thickness and unstirred fluid layers next to the membrane.
- Type/size of solute removal depends on pore size of membrane.

Peritoneal membrane

- Membrane used is the peritoneal membrane.
- Resistance for solute movement from the circulation across the membrane into the abdominal cavity depends on stagnant capillary fluid film, capillary endothelium, endothelial basement membrane, interstitium, mesothelium, and stagnant peritoneal membrane fluid film.
- The natural peritoneal membrane has pores of various sizes that allow the bidirectional movement of solutes of different sizes, mostly removal. In general, these pores are classified into three-pore sizes, known as the “three-pore size model”:
  - Large pores, 20 to 40 nm, are responsible for solute removal by convection and protein loss.
  - Small pores, 4 to 6 nm, correspond to interendothelial clefts, allow for

diffusion of smaller molecules across the membrane, including urea, Cr, Na^+, K^+. Small pores also allow dextrose to move from the peritoneal fluid, across the membrane, and into the circulation.

- Ultrapores, <0.8 nm, correspond to aquaporins, which are responsible for h_2o removal without concurrent solute/sodium removal, a process known as "h_2o transport sieving" or "sodium sieving" since solutes/sodium are "left behind."

Optimization of dialysis membrane

Hemodialysis (HD)

- Membrane material: The frequency of complement activation occurs in the following order: cellulose > substituted cellulose, cellulosynthetics > synthetics. Membranes with high degree of complement activation induce more problems with anaphylactic shock or nonspecific allergic reactions to patients. Cellulose membranes are no longer used.
- Sterilization techniques: γ radiation, electron (E) beam (risk of thrombocytopenia), ethylene oxide (risk of anaphylactoid reactions)
- UF coefficient: K_{uf}: 3.3 to 83 mL/h/mm Hg
  - Higher K_{uf} provides greater dialysis efficiency and flux. The former is due to increased "solvent drag" from convection.
  - Use lower transmembrane pressure (TMP) for membranes with higher K_{uf} to achieve the same volume of UF.
  - Example: What should the TMP be to remove 500 mL/h for membranes with the following K_{uf}?
  - K_{uf} 50 mL/h/mm Hg: TMP = 500 mL/h ÷ 50 mL/h/mm Hg = 10 mm Hg
- Membranes with larger pore size provide "higher flux" dialysis.
- Mass transfer coefficient for urea: KoA urea (maximum theoretical clearance): 245 to $1{,}000^+$ mL/min (<500 "low efficiency," 500 to 700 "moderate efficiency," >700 "high efficiency")
- Surface area of dialysis membrane: 1 to 2.1 m^2. The larger the surface area, the greater the dialysis efficiency.

Peritoneal dialysis (PD)

- The peritoneal surface area may be increased by using a larger dialysate

volume for greater dialysis efficiency. The larger the volume, the larger the contact surface for dialysis. The maximum peritoneal dialysate volume tolerated is typically 2 to 3 L.

- Unlike HD membranes, the intrinsic characteristics of the peritoneal membrane cannot be "changed" to optimize dialysis efficiency:
- Intrinsic peritoneal membrane resistance
- Hydraulic conductance (density of small pores and ultrapores, distance of capillaries from mesothelium)
- Inflammatory versus sclerotic state (increased peritoneal vascularity with acute inflammation leads to higher solute transport into dialysate, but lower UF with prolonged dwell due to more rapid achievement of osmotic equilibrium between blood and dialysate)

Factors that determine dialysis efficiency

Hemodialysis: The greater the following factors, the greater the "dialysis efficiency"

- Membrane surface area
- KoA and K_{uf} of membrane
- Duration of dialysis
- Dialysate flow rate (Q_d)
- Blood flow rate (Q_b)
- Vascular access flow (Q_a)
- Concentration gradient difference of solute between dialysate and blood
- Access recirculation reduces dialysis efficiency.
- For central venous catheter (CVC), cardiopulmonary recirculation is higher in patients with lower cardiac output, thus lowers dialysis efficiency.

NOTE Dialysis efficiency is *not* dependent on dialyzer membrane type, but rather KoA, K_{uf}, and surface area of the membrane.

Peritoneal dialysis

- Peritoneal membrane characteristics:
- Patient mobility: Inefficient dialysis in immobilized patient is due to stagnant dialysate.
- Concentration gradient between blood and dialysate

- Dwell time and number of exchanges
- UF, which depends on:
  - Concentration of osmotically active agent in dialysate determines UF rate (e.g., glucose, icodextrin)
  - Hydrostatic pressure gradient (patient's BP)
  - Fluid absorption back into the circulation
  - Capillary vasodilatory versus vasoconstrictive state
  - Oncotic pressure gradient, which depends on:
    - Sieving property of solute: The higher the sieving coefficient (solute crosses membrane more easily), the greater convective transport for the solute.
    - Reflection coefficient of osmotic agent in dialysate (high value suggests agent does not cross the membrane easily, but "reflects" back into peritoneal fluid). Maintenance of osmotic gradient depends on the reflection coefficient for the osmotic agent (i.e., glucose: 0.03, polyglucose icodextrin ~1.0). The agent with a high reflection coefficient (icodextrin) is able to maintain the osmotic difference between blood and dialysate better, hence better osmotic force favoring UF into peritoneum.

NOTE Icodextrin solution may be considered in patients with DM (or high transporters) who do not achieve adequate UF with dextrose solutions.

Caution with the use of icodextrin (Table 4.4)

Table 4.4 Icodextrin

Icodextrin (Extraneal, Baxter)

Basic Characteristics

- Icodextrin is a product of enzymatic dissolution of corn starch that is subjected to fractionalization to create polymers 13–19 kDa, thought to be more biocompatible.
- Icodextrin solutions are iso-osmotic—No water movement occurs via aquaporins, thus no Na sieving effect. Ultrafiltration (UF) with icodextrin occurs via convection through small pores.

Advantages

- High reflection coefficient: Better UF than dextrose-containing dialysate
- →Glucose-induced lipid abnormalities
- Threefold higher "UF efficiency" compared with dextrose solution (i.e., lower carbohydrates

absorbed per UF volume achieved)

Potential Problems

- Icodextrin is not absorbed across the peritoneal membrane (due to size) but is picked up by lymphatics and returned to circulation where it is → degraded to **maltose** by serum amylase and → converted by maltase to glucose intracellularly. ***Glucose monitors that use glucose dehydrogenase with pyrroloquinoline quinone or the glucose-dye-oxidoreductase–based reagents are contraindicated as they can read maltose as glucose.***
- *Hypersensitivity to cornstarch → macular papular* ***skin rash*** *in 10% of patients*
- *Falsely low* ***amylase*** *as amylase is partially consumed with the degradation of icodextrin to maltose. Conditions such as pancreatitis may have falsely low amylase but true high lipase levels.*
- ***Contraindications:*** *preexisting lactic acidosis, hypersensitivity to cornstarch, glycogen storage disease, intolerance to maltose or isomaltose*

- The metabolites of icodextrin, maltose and polysaccharides, can lead to falsely high glucose–level readings with certain finger glucose check devices, thus *masking life-threatening hypoglycemia or potentially administering insulin for a normoglycemic individual with a falsely high glucose level resulting in hypoglycemia.*
- Icodextrin can lead to falsely low levels of amylase in patients with pancreatitis.
- Contraindicated in patients with known allergy to cornstarch or icodextrin, maltose or isomaltose intolerance, glycogen storage disease, and preexisting severe lactic acidosis
- Blistering and exfoliative skin eruptions have been reported with the use of icodextrin.

Sodium sieving

- Early dwell: Dialysate is diluted by UF from H_2O transport across AQ1 without concurrent Na^+ movement across peritoneal membrane. Hypernatremia is possible in this phase.
- Longer dwell: Concentration gradient (lower [Na^+] in dialysate compared to that of blood) favors Na^+ loss into dialysate via smaller peritoneal membrane pores.
- Na^+ loss with a 4-hour, 1.5% dextrose, 2 L exchange is minimal, but a 4-hour 4.25% dextrose, 2 L dwell can be up to 70 mEq.
- *Isotonic* icodextrin solution does not activate aquaporins as do *hypertonic* dextrose solutions. Water transport with icodextrin-containing dialysate

only occurs along with solute transport through interendothelial cell pores. There is no sodium sieving with icodextrin.

Hemodialysis

Adequacy and prescription

- Traditionally, adequacy refers to small-solute clearance (Kt/V and urea reduction ratio [URR] in HD and Kt/V and urea clearance in PD). The clinical significance of this concept is being questioned as evidence for the relationship between small-solute clearance and clinical outcomes is weak. Future direction may move toward "goal-directed dialysis care" rather than just small-solute clearance. In essence, in addition to measuring small-solute clearance, factors such as residual kidney function, volume status, biochemical measures, nutritional status, cardiovascular function, symptoms, and patient's experiences and goals will also be considered. Dialysis adequacy herein refers solely to small-solute clearance as traditionally defined.

Dialysis adequacy (See Appendix A for definitions of terms)

- KDOQI recommendations
  - HD, given three times per week:
    - For patients with residual kidney urea clearance K_r <2 ml/min/1.73 m^2:
      - Minimally adequate dose of HD:
        - Single-pool Kt/V (spKt/V) ≥1.2 per dialysis (not including K_r), or
        - URR ≥ 65%
      - Target dialysis dose:
        - spKt/V ≥ 1.4 (~ equilibrated Kt/V [eKt/V] ≥ 1.2) per dialysis (not including K_r), or
        - URR ≥ 70%
    - Current concerns with Kt/V:
      - Current Kt/V target dosing may not be adequate in women or small patients.

- spKt/V, where V is based on the volume of distribution of urea or total body volume, is not associated with improved survival, whereas higher Kt/V normalized for BSA is associated with survival benefit.

- For patients with residual kidney urea clearance K_r ≥2 mL/min/1.73 m^2:
  - Minimally adequate dose of HD: spKt/V may be reduced.
  - Target dialysis dose: ≥15% of minimum dose

Dialysis duration

- Optimal dialysis time and frequency are undefined. Performing HD ≥ 3.5 hours has been suggested. Frequent HD has been suggested for patients with nutritional problems or volume overload, but current data show no benefit in terms of improved nutritional status or anemia control. Additionally, for patients with residual kidney function with >100 mL/d urine output, frequent HD provides no benefit in terms of regression of left ventricular hypertrophy.
- DOPPS: Increasing dialysis treatment time was associated with a reduction in all-cause mortality, increased Hb and albumin and decreased WBC count and phosphate levels.
- Nocturnal HD:
  - Associated with lower interdialytic weight gain, better serum albumin levels, SBP, serum phosphorus, and WBC count compared with matched control from in-center HD patients
  - 25% reduction in risk for death after adjustment for age, BMI, and dialysis vintage
  - Potential problems: high dropout rate, higher vascular access complications compared to in-center HD

Ultrafiltration

- UF rate >13 mL/kg/h is associated with increased mortality. UF rate <10 ml/kg/h is suggested.

Dialyzers and dialysate

Dialyzers

- High-flux dialysis may confer improved cardiovascular mortality over low-flux in multicenter analyses but questioned at facility-level analysis.
- Reuse of dialyzers: No significant harm or benefit has been shown with dialyzer reuse compared with single-use dialyzers.

Dialysate electrolyte concentrations

Sodium

- Sodium modeling: Using dialysate [Na^+] greater than that of patient's plasma minimizes intradialytic hypotension and symptoms of disequilibrium at the expense of sodium gain, increased thirst, increased interdialytic weight gain (IDWG), and predialysis HTN. Sodium modeling has fallen out of favor due to these side effects.
- Using dialysate [Na^+] lower (e.g., 5%) than that of patient's plasma can improve UF to achieve dry weight (temporary measure only).
- DOPPS: Patients with serum [Na^+] <137 mmol/l appear to have survival benefits when higher dialysate [na^+] (>140 mmol/L) was used. Similar findings were not appreciated in patients with higher S[Na^+].

Potassium

- There is a theoretical concern that rapid change in plasma potassium (i.e., use of much lower dialysate [K+] compared to patient's plasma level) may induce arrhythmias.
    - This concern remains to be proven. Nonetheless, there are data to suggest increased risk of sudden cardiac death with the use of dialysate [K^+] <2 mmol/l for patients with s[k^+] <6.5 mmol/l.

Calcium

- Ideal dialysate calcium concentration is 2.5 to 2.75 mmol/L.
- Lower dialysate calcium concentration is associated with increased risk for cardiac arrest, intradialytic hypotension, and SHPT.
- Higher dialysate calcium concentration may lead to increased vascular and soft-tissue calcifications.

Bicarbonate

- HD patients with serum bicarbonate concentration <22 mmol/l have an

increased risk of all-cause and cardiovascular mortality compared to those with levels 24 to 25 mmol/l.

- Predialysis serum bicarbonate concentration >27 mmol/L is also associated with higher risk of death. Bottom line: Keep goal serum bicarbonate between 22 and 27 mmol/L.

HD Vascular Access

- Type of vascular access goal for chronic HD: AVF 60%, AVG 30%, temporary CVC < 10%

Acute temporary catheters or cuffed, tunneled catheter (permacath)

- Low-flow rates (300 mL/min for temporary catheters, 400 mL/min for permacath)
- KDOQI: When there are valid reasons for CVC use and duration of use is expected to be >3 months, without anticipated availability of AV access, CVC may be placed in the following veins in order of preference: internal jugular > external jugular > femoral > subclavian > lumbar.
- Access infections:
  - Higher rates for infections compared to AVG and AVF
  - Femoral lines are not at increased risk for infections unless patient has markedly elevated BMI.
- Clearance (URR):
  - Femoral = jugular catheters in terms of clearance if femoral catheters are >20 cm.
  - For blood flow >200 mL/min, URR is lower in femoral compared with jugular.
  - Bottom line:
    - Femoral access placement is an acceptable alternative to right jugular vein access placement in critically ill patients.
    - Femoral catheters should be longer than 20 cm to reach the inferior vena cava for better clearance.
    - Femoral catheters may have a higher rate of infection in patients with markedly elevated BMI.

- Catheter dysfunction:
  - Signs of access dysfunction or thrombosis: reduced HD blood flow or reduced Kt/V
  - Management: trial of a thrombolytic agent (e.g., tissue plasminogen activator [tPA] 2 mg/port for 30 to 60 minutes)
  - Central vein stenosis, particularly with subclavian catheters

Arteriovenous fistula (AVF)

- Preferred access due to lower risk of infectious and thrombotic complications
- High rate of primary failure (nonmaturation), but better long-term patency compared to grafts
- Preoperative vascular mapping increases fistula placement but fails to improve primary failure (nonmaturation). Optimal venous mapping findings:
  - Arterial diameter ≥ 2.0 mm, vein diameter ≥ 2.5 mm
  - Brachial artery flow > 80 mL/min
  - Absence of stenosis or thrombosis of draining vein up to shoulder and central vein
- Clinical risks for AVF nonmaturation: older age, females, peripheral vascular disease, prior peripherally inserted central catheter (PICC) line, forearm AVF compared to upper arm AVF
- Optimizing AVF maturation success: 6-week postoperative ultrasound—vein depth <5.0 mm, vein diameter >4.0 mm, length of fistula thrill/bruit >5.0 cm, access flow >500 mL/min
  - Consideration may be given for the use of adjuvant far-infrared therapy to improve primary patency based on individual circumstances, feasibility, and clinician's expertise. There is inadequate evidence to make recommendation on the use of simvastatin and ezetimibe to reduce AVF dysfunction or clopidogrel-prostacyclin to improve AVF primary failure.
- Early surgical repair:
  - Vein is too deep: repair by superficialization

- Low access flow:
  - Due to stenosis at anastomosis or draining vein: repair by angioplasty or surgical revision
  - Due to large accessory veins: repair by surgical ligation
- Risks for secondary AVF failure: intradialytic hypotension, frequent cannulation rate (i.e., daily HD)

Arteriovenous graft (AVG)

- May be considered in patients with suboptimal venous mapping parameters, failed AVF, or low expected patient survival
- Synthetic conduit (e.g., polytetrafluoroethylene) created between an artery and a vein
- AVG maturation typically requires 2 to 3 weeks. However, Vectra or Flexine grafts may be used in 12 hours.
- Risks for graft thrombosis: stenosis at anastomotic site, draining vein, or central veins
- AVG has higher infection risks compared to AVF. Infectious lesions that involve the underlying AVG require complete surgical resection.
- Pseudoaneurysms caused by repeated cannulations at the same site of the AVG may result in life-threatening bleeding and must be repaired surgically or with covered stent placement.
- Improving graft patency:
  - Anticoagulation for protection against graft thrombosis and survival:
    - Not helpful: warfarin, clopidogrel plus aspirin combination
    - Minimally helpful: dipyridamole + aspirin. Risks and benefits must be carefully weighed prior to the use of dipyridamole (200 mg) and aspirin (25 mg) bid to improve AVG primary unassisted patency.
  - Fish oil reduces risk of thrombosis, but not long-term graft event. Consideration may be given for the use of oral fish oil in patients with newly created AVG to reduce patient morbidity associated with AVG dysfunction. However, there is inadequate evidence to make recommendations on the use of fish oil to prolong AVG cumulative

patency or the use of simvastatin and ezetimibe for reducing dialysis AVG interventions and thrombosis.

Vascular access use and monitoring per KDOQI

- Rope-ladder cannulation is "recommended" over buttonhole technique for AVF and "suggested" for polytetrafluoroethylene grafts.
  - Rope-ladder technique refers to rotating cannulation sites for HD access.
  - Buttonhole technique refers to needling at the same site for HD access:
    - Presumed to be easier with lower pain scores with prolonged use due to the development of a skin "tract" or buttonhole
    - Increased rate of infections, presumably due to poor cleaning techniques and/or failure to remove scab prior to cannulation
- Regular physical examination to detect flow dysfunction is recommended. (Clinical clues for AV access stenosis: prolonged bleeding, unexpected fall in Kt/V, distal edema, abnormal bruits or reduced thrill)
- Routine AVG and AVF surveillance by measuring access blood flow, pressure monitoring, or imaging for stenosis is not suggested. (However, whenever a Doppler is obtained for suboptimal access function, findings of reduced blood flow, defined as <600 ml/min or fall by >25% from baseline, suggest significant stenosis.)

Water Treatment for HD

- On average, weekly HD requires ~500 L of H_2O (assuming an average dialysate flow of 800 mL/min, 3 to 4 h/dialysis treatment, three treatments per week).

Carbon filtration

- Carbon filtration removes chlorine and chloramine (added to municipal water) and organic contaminants. Chloramine can cause hemolysis.

NOTE Required steps in water purification for HD include **carbon filtration** and **reverse osmosis**.

  - Carbon filtration is done prior to reverse osmosis (see below) because chlorine and chloramine can damage the membrane used in reverse osmosis.

Softeners

- Exchanges calcium and magnesium ions for sodium ions
- “This is optional in regions with hard water to protect the reverse osmosis membrane.”
- This step may be added prior to reverse osmosis to protect the reverse osmosis membrane. Accumulation of calcium and magnesium can cause fouling of osmosis membrane.

Reverse osmosis

- A process whereby water is forced across a semipermeable membrane by a high-pressure system
- Reverse osmosis removes dissolved inorganic elements, including metal ions (i.e., zinc, fluoride, copper, aluminum, arsenic), salts, chemicals, organic elements, bacteria, viruses, and endotoxins.

Deionization

- Further removes residual ions by exchange resins made up of both cations and anions (e.g., hydrogen and hydroxyl ions, respectively) to exchange for negatively and positively charged ionic contaminants, respectively, following reverse osmosis
- Close monitoring of the product water-specific resistivity or conductivity is required to detect changes consistent with depletion of resins.

NOTE Depletion of resins can cause release of previously removed ions such as *fluoride and may result in acute toxicity and death*. Chronic fluoride exposure can contribute to osteodystrophy.

- Note that the deionizer provides a good milieu for bacterial proliferation. Extra step for bacterial control is needed.

UF/endotoxin filter

- Extra and optional step used to remove any residual bacteria and endotoxins:
  - Routine microbiologic testing must be performed for both bacterial count (<100 cfu/ml) and endotoxins (<0.5 eu/ml). corrective measures must be done at half of maximal allowable levels. water purification for

dialysis does not produce “sterile” water.

- Hospital bedside and home HD water purification:
  - Water treatment approach is similar as outpatient fixed-station systems.
  - Mobile units similarly require a carbon filtration, reverse osmosis system, and point-of-use UF, with or without a softener prior to carbon filtration.
  - Bacterial proliferation is a major concern for mobile units.
- Steps to minimize bacterial proliferation:
  - Use a direct water feed system instead of storage tank.
  - Use a point-of-use ultrafilter.
  - Use a backflow prevention device in case the mobile system is connected directly to the hospital potable water supply.

HD Complications

Hypertension (HTN)

- Predialysis SBP >160 mm Hg or <130 mm hg is thought to have worse survival (“u” curve).

NOTE Home BP and ambulatory BP measurement better diagnose HTN than dialysis unit measured values in the HD patient.

- Intradialytic BP variations: Either significant SBP increase or fall observed with HD is associated with higher mortality, regardless of absolute BP level.

Intradialytic HTN

Mechanisms

- Removal of dialyzable antihypertensive medications with HD
- Activation of renin–angiotensin system
- Activation of SNS
- Vascular endothelial damage
- Higher dialysate sodium compared with that of plasma with net sodium retention

- Cold dialysate (dialysate temperature <0.50c compared to patient's tympanic membrane temperature)

Advantages of using carvedilol in patients with intradialytic HTN

- Nondialyzability allows for stable intradialytic blood level.
- Shown to improve endothelial function, intradialytic HTN, as well as ambulatory interdialytic BP
- May improve survival from cardiovascular complications

Target BP

- Predialysis < 140/90 mm hg, postdialysis < 130/80 mm hg
- Ambulatory BP measurements: daytime < 135/80 mm hg, nighttime < 120/80 mm hg
- Treatment to target BP must be individualized.

Strategies to achieve BP goal in the HD patient

- Volume control:
  - Dietary sodium restriction < 2 g/d
  - Maximize UF as tolerated and/or increase dialysis duration as needed to achieve "dry weight."
  - Dry weight is not just a nonedematous weight, but the weight at which normotension is achieved without the use (or minimal use) of antihypertensive medications without signs and symptoms of hypotension.
  - To achieve dry weight as defined, gradually withdraw antihypertensive medications as safely tolerated along with sequential UF as tolerated.
  - Amount of UF (L) at each session may be roughly estimated as follows:
  - Interdialytic weight gain (IDWG) + 0.005 to 0.01 × total body weight per dialysis session until "dry weight" is reached. Example: IDWG = 2 kg, patient's total body weight is 70 kg. Attempt UF in the range of (2 + 0.005 × 70) to (2 + 0.01 × 70) = 2.35 to 2.7 L as tolerated. Avoid UF rate >13 mL/kg/h due to association with higher mortality.
  - Minimize dialysate [Na^+] to minimize thirst, hence IDWG and BP (e.g., consider using dialysate [Na^+] that is 0.95 × predialysis S[Na^+] if safely

tolerated and possible).

- More frequent dialysis:
  - Nocturnal or frequent (six times per week) dialysis reduces BP, the number of antihypertensive medications, and left ventricular mass.
  - However, frequent dialysis is associated with more access complications and patient burnout.
  - Addition of antihypertensive medications: use nondialyzable medications such as carvedilol, ARBs, or fosinopril.

NOTE Most ACEI are dialyzable. Atenolol and metoprolol are dialyzable. Other less dialyzable drugs: labetalol, amlodipine, clonidine, hydralazine, aldosterone blockers, α-blockers.

Intradialytic hypotension

- Defined as a symptomatic fall in SBP ≥20 mm Hg or MAP ≥10 mm Hg requiring intervention
- Associated with increased mortality, clotted vascular access, cardiovascular events
- Risks: age ≥65, low baseline BP, clinically significant pericardial effusion or poor cardiac function, ischemic heart disease, autonomic dysfunction (diabetes, prolonged uremia), malnutrition, severe anemia
- Contributing factors: excessive fluid and/or rapid solute removal, GI blood pooling if eating during dialysis, dialysate factors (use of acetate or low-calcium concentrations), dialyzer reaction, warm room temperature, air embolism
- Management:
  - Patient-related behavior: dietary sodium and water restriction to prevent high IDWG and the need for high UF, avoidance of eating prior to and during dialysis
  - Target body dry weight, body volume:
    - Higher IDWG is associated with increased mortality.
    - Measurements of body volume to optimize UF:
      - Point-of-care ultrasound to measure B line as a marker of lung water
      - Blood volume monitoring (BVM, also known as “crit-line”): A

method whereby blood volume changes are detected by changes in intravascular hematocrit (Hct). Theoretically, when the UF rate is at the same as the rate of interstitial fluid mobilizing into the intravascular volume, there is no change in Hct. When UF rate is higher than that of interstitial fluid moving into the intravascular space, Hct is expected to increase. The increase in Hct >5% suggests that maximally safe interstitial fluid removal has been reached, which should alarm the dialysis nurse to stop further UF or return fluid as needed to avoid impending hypotension. BVM is designed to reduce hypotension episodes during UF with HD, but it does not detect the excess volume in interstitial space and cannot determine dry weights in HD patients.

    - Bioimpedance: A method whereby current frequencies ranging from 5 to 1,000 kHz are passed through the skin. While low-frequency currents preferentially pass through the extracellular fluid space due to its inability to penetrate cell membranes, high-frequency current can penetrate the extracellular and intracellular space. Comparisons of these values to those of nonuremic patients can help quantify total body water volume, intracellular and extracellular volumes in dialysis patients.
- Adjust antihypertensive medications: hold antihypertensive medications prior to dialysis; avoid use of long-acting vasodilators.
- Dialysis procedure: reassess dry weight, avoid excessive and aggressive UF, consider increasing dialysis time for slower UF rate (<10 ml/kg/h), reduce dialysate temperature by 1°c below standard temperature or 0.5°c below patient's body temperature, avoid dialysate [ca^{2+}] < 2.25 mmol/l and [mg^{2+}] < 1.0 mmol/l.
- Avoid sodium modeling or hypertonic saline because sodium infusion results in increased thirst. A vicious cycle of increased volume intake, increased need for intradialytic volume removal, resultant hypotension, subsequent sodium infusion, increased thirst.
- Other:
    - Obtain 2D echocardiogram for evaluation of left ventricular function and pericardial effusion.

- Correct (underlying etiologies) anemia and hypoalbuminemia if applicable.
- Consider adding midodrine 5 to 10 mg 30 minutes prior the dialysis. Note that midodrine is dialyzable, so it should not last postdialysis. Also, be aware that midodrine can cause bradycardia and is contraindicated in patients with bradycardia or severe heart disease.

Infections

- Most commonly, access related

Headaches, nausea, vomiting: Conditions to consider

- Dialysis disequilibrium due to rapid solute removal and subsequent cerebral edema
  - Risks: patients with high BUN level who are aggressively dialyzed, younger age, preexisting neurologic disorders or intracranial pathology, first dialysis, hyponatremia, liver disease, use of low sodium dialysate
  - Other associated symptoms: blurred vision, altered mental status, muscle twitching, seizures, coma
  - Prevention is key:
    - Limit first HD session to 2.0 to 2.5 hours.
    - Limit blood flow to 200 to 250 mL/min.
    - Consider sodium modeling or high sodium dialysate to offset rapid extracellular osmolality change (each 1 mmol/L of Na offsets effect of 12 mg/dL of BUN).
    - Consider mannitol in patients with BUN levels >100 mg/dL (1 g/kg).
    - Consider continuous RRT in patients at high risk for dialysis disequilibrium syndrome (preexisting intracranial injury, mass, hemorrhage).
- Large volume removal, hypotension
- Acute fall in caffeine level during dialysis in those with habitual high-caffeine intake
- Other electrolyte changes: rapid change in serum sodium concentrations, hypoglycemia (particularly in patients with poorly controlled DM)
- Others: subdural hematoma, increased intraocular pressure with dialysis

(rare), psychological factors

- Unlikely contributing factors: dialyzer membrane composition, biocompatibility
- Fluoride contaminants from water system (headaches, nausea, chest pain, hypotension, neuromuscular symptoms, cardiac arrhythmias)

Chest pain

- Angina:
  - Underlying coronary artery disease
  - Management: aspirin, oxygen supplement, nitrates, morphine as indicated if safely tolerated, cardiac evaluation
  - If patient is on a β-blocker, make sure it is nondialyzable (carvedilol, labetalol).
  - Dialyzer first use syndrome (reaction to dialyzer membrane)

Hemolysis (dialysis induced)

- This is a potentially rapid fatal condition if not recognized immediately.
- Hemolysis differential diagnoses:
  - Problems with dialysate (e.g., overheating of dialysate, erroneous electrolyte mixing leading to hypotonic dialysate, faulty water treatments with residual contaminants such as metal ions [copper, nitrates], disinfectants [hyperchlorite or bleach, formalin], chloramine from municipal water)
  - Problems with blood flow: kinking of dialysis lines, problems with arterial cannulation or flow-limiting blood inflow (using high blood flow through a small gauge needle), blood-pump malocclusion
  - Problems unrelated to dialysis procedure: autoimmune hemolysis, thrombotic microangiopathy, sickle cell anemia
  - Clinical signs/symptoms suggestive of hemolysis:
    - Chest pain, dyspnea, abdominal/back pain, bradycardia if significant hyperkalemia, port-wine appearance of blood in venous line, pink plasma in centrifuged blood specimens
    - A simultaneous fall of >25 mm Hg in the arterial and venous pressures suggests a severe postpump kinked tubing.

- Management:
  - Stop HD, but do not return hemolyzed blood back to patient. Monitor patient for hyperkalemia.
  - Perform root cause analysis

Air embolism

- Rare with current use of air detectors. Air may also be introduced during placement or removal of CVCs.
- Preventive measures: Avoid extremely high dialysis blood flow; tighten arterial luer-lock well, prime dialyzer, and tubing system; maintain high blood level in venous air catcher.
- Symptoms:
  - Chest pain, dyspnea, syncope
  - Cerebral air embolism may cause blurry vision, altered mental status, seizures, or stroke.
- Management:
  - Stop HD, clamp venous return, provide 100% oxygen, attempt aspiration of air if catheter is still in place.
  - Traditionally, it is recommended that patient be placed in left Trendelenburg position to get air bubbles to float up away from brain and lungs for symptomatic relief and possibly withdrawal of air from the AV access. Benefit of this maneuver versus leaving patient in supine position is being questioned due to negative study in dogs. Supine positioning may facilitate bedside care.

Pulmonary embolism (thrombus migration from vascular access)

Arrhythmias

- Risks likely associated with underlying ischemic or structural heart disease, left ventricular hypertrophy, mitral valve calcifications
- Rapid change in potassium with dialysis is a concern, but is yet to be a proven risk.
- Low calcium dialysate is also a risk for arrhythmias

Dyspnea

- Prior to dialysis: volume overload, pneumonia, subacute bacterial infections
- Intradialysis or postdialysis: angina, allergic reaction to dialysis membrane, pericardial effusion, aspiration, pneumonia, bacteremia, reaction to any IV drugs given during dialysis (e.g., iron)

Allergic reactions

- Implicated etiologic agents: dialyzer components, sterilant, disinfectant, heparin, or other medications (e.g., IV iron, antibiotics) infused during dialysis

Type A allergic reaction: rare, anaphylactoid response

- Mediated by bradykinin and/or histamine, IgE
- Possible causes: use of ethylene oxide for dialyzer sterilization; IV iron; use of acrylonitrile 69 membranes in patients receiving ACEI (mediated by bradykinin)
- Onset within 5 to 20 minutes of starting dialysis
- Major symptoms: urticaria, bronchospasm, laryngeal edema, burning sensation at access site or systemically, angioedema, anaphylactic shock
- Minor symptoms: reproducible symptoms with dialysis, rhinorrhea or lacrimation, abdominal cramping, itching
- Management: stop dialysis and discard blood, supportive therapy with oxygen, antihistamines, epinephrine, and corticosteroid

Type B allergic reaction: mild reaction

- Complement mediated
- Previously thought to be due to membrane biocompatibility. Current data do not support this.
- Onset later than type A and occurs within 20 to 40 minutes of starting dialysis
- Symptoms dissipate with subsequent dialysis treatments.
- Preventive measures against allergic reactions:
  - Prime dialyzer with saline to wash out the sterilant.
  - Switch sterilization from ethylene oxide to steam (heat) or γ or β

radiation.
    - Use polyacrylonitrile membrane pretreated with polyethyleneimine markedly reduces bradykinin activation and can be used in patients on ACEI.

Other reactions

- Water-related reactions
    - Fevers/chills: consider bacterial or endotoxin contamination, possibly via back filtration at zero net UF pressure.
- Thrombocytopenia: likely due to heparin-induced thrombocytopenia with or without thrombosis (HITT), particularly if seen 4 to 10 days following heparin administration. This condition is due to the production of antibodies that bind to complexes of heparin and platelet factor 4, leading to platelet activation and promotion of a prothrombotic state.
    - Symptoms may include HTN, transient global amnesia, profuse diarrhea.
    - Thrombocytopenia may occur with E-beam sterilization.

Vascular access issues

Access recirculation

- The uptake of freshly dialyzed blood back into the dialyzer occurs when the dialyzer blood flow is greater than that of access blood flow
- Causes of access recirculation:
    - Downstream stenosis or thrombosis
    - Arterial stenosis
    - Close needle placement or reversal of lines
- Screening options if clinically indicated:
    - Doppler ultrasound
    - Transonic access blood flow: flow <600 ml/min or reduced by ≥25% from baseline flow suggests increased risk for access recirculation.
    - Ultrasound dilution: reverse lines and saline dilution
    - Static venous pressure
    - Obtain peripheral, arterial, and venous urea concentrations to assess the

percentage of recirculation:

$$\% \text{ recirculation} = ([P - A]/[P - V]) \times 100$$

where P, A, and V refer to urea concentrations in the **P**eripheral blood, pre-dialyzer **A**rterial line, and post-dialyzer **V**enous circuit, respectively. A value >10% warrants investigation for recirculation. A value greater than 25% suggests significant access recirculation.

Vascular access hemorrhage

- May occur with rupture of a pseudoaneurysm or aneurysm (pseudo/aneurysm)
- A pseudoaneurysm is composed of a hematoma and fibrous tissue that may expand with recurrent injury at the same vascular access site.
- An aneurysm may form at the outflow vein/graft of an AV access, resulting in progressive dilatation from the high blood flow and vascular damage.
- KDOQI:
  - "It is reasonable to obtain" surgical evaluation when clinical findings suggest pseudoaneurysm/aneurysm to be at risk of complications (e.g., evidence of skin breakdown, shiny thinning of overlying skin).
  - "It is reasonable to obtain emergent surgical assessment and treatment" for overlying erosions/hemorrhage of pseudoaneurysm/aneurysm.
  - "It is reasonable to use Duplex ultrasound to corroborate" physical findings consistent with pseudo/aneurysm.
- If rupture occurs, apply direct pressure over area with finger.
- Rope-ladder technique in cannulation is thought to minimize the risk of pseudo/aneurysm formation compared with buttonhole technique.

High-flow AV access

- Increased flow rates through an AV access can lead to high output heart failure, pulmonary HTN, central venous stenosis, venous HTN, aneurysmal degeneration of the AVF, and hand ischemia.
- AV-arterial flow rate (Q_a) >1.0 to 1.5 L/min or Q_a >20% of cardiac output indicates high flow.

- Management:
  - KDOQI: Evaluation with 2D echocardiogram for changes in cardiac function and Q_a/CO depending on patient's circumstances and local resources.
  - If significant, consider "flow-reducing therapies" or "banding" of AV access.

AVG seroma

- AVG seromas are fluid collections that form in the early postoperative period around prosthetic AVGs, typically near the anastomotic site.
- Causes: transudation of fluid through the graft material or disruption of surrounding lymphatic system
- Management: typically resolves with observation; if persistent, consider AVG replacement with a different material tunneled through a different anatomic course.

Peritoneal Dialysis

Indications

- Patients who prefer PD or refuse HD
- Patients who cannot tolerate HD due to poor cardiovascular function or who have no vascular access (e.g., severe congestive heart disease, extensive vascular disease)
- Patients who prefer home dialysis modality and cannot perform home HD
- No HD availability

Absolute contraindications for PD

- Loss of peritoneal function, UF failure
- Intra-abdominal adhesions blocking dialysate flow
- Surgically uncorrectable abdominal hernia
- Abdominal wall stoma
- Diaphragmatic fluid leak
- Inability to perform exchanges in absence of suitable assistant
- Poor hygiene, inability to safely perform PD for any reasons (e.g., severe

physical or mental disabilities)
- Active abdominal inflammatory diseases (e.g., diverticulitis, ischemic bowel disease, intra-abdominal abscess)
- Homelessness

Relative contraindications for PD

- Recent abdominal aortic graft
- Large kidneys due to PKD
- Hernias
- Ostomy
- Abdominal adhesions
- Ventriculoperitoneal shunt
- Intolerance of intra-abdominal fluid in patients with morbid obesity
- Severe malnutrition
- Uncontrolled skin infection
- Bowel disease
- *Staphylococcus aureus* carrier

Dialysis adequacy for PD

- For patients with residual kidney function (defined as urine volume >100 mL/d):
  - Minimal "delivered" dose of total small-solute clearance should be a total (PD and kidney) $Kt/V_{urea} \geq 1.7$/week.
    - Total (PD plus residual kidney function) Kt/V_{urea} should be measured within the first month following dialysis initiation and no less than every 4 months thereafter.
    - Whenever residual kidney function is added to PD Kt/V_{urea} to achieve goal, a repeat 24-hour urine collection for K_r must be done at least every 2 months.
  - For patients without residual kidney function (defined as urine volume ≤100 mL/d):
    - Minimal "delivered" dose of total small-solute clearance should be a PD $Kt/V_{urea} \geq 1.7$/week. This is measured within the first month

following PD initiation and at least every 4 months thereafter.

NOTE Kt/V_{urea} as a measure for dialysis adequacy in PD is being questioned:

- PD does not have good small-solute clearance (e.g., urea clearance), which explains why PD patients have higher BUN and Cr than HD patients. However, PD clears many other clinically significant uremic toxins that are not captured with Kt/V_{urea}.
- Lack of data to show that Kt/V_{urea} predicts outcome in PD.
- Optimal molecule (middle molecule) to assess Kt/V in PD is not defined.
- Current expert opinions suggest a comprehensive evaluation for PD adequacy based on multiple markers rather than just focusing on Kt/V_{urea} (Kt/V_{urea} is only a marker for small molecule clearance). Other markers to consider include preservation of residual kidney function, mineral metabolism (phosphorus) control, β2-microglobulins, and p-cresol.

- Maintenance of residual renal function:
  - Even preservation of 1 mL/min reduces annual mortality by 15% to 25%.
  - Use of RAAS inhibitors can also slow deterioration of residual kidney function.
  - Avoid contrast dye, nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, nephrotoxic agents.
  - Use of diuretics for volume control has not been shown to accelerate progression of residual kidney function loss.

Prescription for PD

- Empirical prescription (see Table 4.5)

Table 4.5 Empirical prescription for chronic peritoneal dialysis

Empirical Therapy:

- **Automated PD:** 10 L/d to be exchanged as 4 × 2 L/night and 2 L day dwell or 5 × 2 L/night
- **Continuous ambulatory PD:** 8 L/d to be exchanged as 4 × 2 L

Special considerations

- If good residual function → reduce dwell volume
- If higher UF is needed → increase glucose concentration to 2.5% or 4.25%; if absolutely necessary, consider doing one exchange using icodextrin dialysate

Empirical therapy × 1 mo

Determine Kt/V in 1 mo

PET in 4–8 wk after PD initiation to determine transporter type

Adjust PD dose as needed to achieve target total Kt/V urea of 1.7 (the United States)

Dose adjustment per Kt/V and PET

- **Low Kt/V:** increase dwell volume (up to 2.5–3.0 L) or add one extra exchange if possible
- **PET** may be used as needed to address inadequate clearance or UF concerns.
- **HIGH (RAPID) transporters:** use shorter dwell time, more exchanges; consider one extra exchange using icodextrin
- **LOW transporters:** use higher volume and longer dwell times

Abbreviations: PD, peritoneal dialysis; PET, peritoneal equilibrium testing; UF, ultrafiltration.

- PD prescription modification may be done to achieve dialysis adequacy based on peritoneal equilibrium testing (PET):
  - PET assesses membrane solute transport characteristics of individual patients by measuring both membrane diffusive and ultrafiltrative capacity. PET is determined by the molecular weight of the solute of interest, membrane permeability, and effective surface area.
  - PET protocol (see **Appendix A**)
  - Interpretation of PET (Table 4.6):

Table 4.6 Interpretation of peritoneal equilibrium testing

D/P Creatinine	D/D_0 Glucose	Transporter Type	Comments
0.34–0.50	>0.49	Low	Slow transporters may be inadequately dialyzed due to low solute removal. Possible PD prescription modifications to increase Kt/V_{urea}: Increase volume and dwell time HD switch if all else fails
>0.50–0.65	>0.38–0.49	Low average	Adjust per lifestyle May need longer day dwell if APD
>0.65–0.81	>0.26–0.38	High average	Adjust per lifestyle May need shorter day dwell if APD
>0.81	0.12–0.26	High (rapid)	High transporters may be predisposed to malnutrition from increased amino acid losses in the dialysate and decreased fluid removal due to the rapid dissipation of the glucose concentration difference between plasma and dialysate. Possible PD prescription modifications to increase Kt/V_{urea}: More frequent exchanges, shorter dwell May need icodextrin-containing dialysate to improve ultrafiltration HD switch if all else fails

Note: D/P creatinine and D/D_0 glucose ratios as measured after 4-hour dwell of 2 L of 4.25% dextrose.
Abbreviations: APD, automated peritoneal dialysis; D, dialysate concentration at 4 hours; D_0, dialysate concentration at start of test, which is essentially the dextrose concentration in 4.25% dextrose solution; HD, hemodialysis; Kt/V_{urea}, measure of urea clearance; P, plasma concentration at 4 hours; PD,

peritoneal dialysis; UF, ultrafiltration.

- Patients may be categorized as high, high average, low average, or low transporters based on the ratio of dialysate to plasma (D/P) Cr at 4 hours following a 2-L 4.25% dextrose dwell. Similarly, patients may also be categorized as high, high average, low average, or low transporters based on the ratio of dialysate glucose at 4 hours and dialysate glucose at start of PET testing (D/D_0).
- A difference in one category between D/D_0 glucose and D/P Cr is acceptable.
- A difference in two categories is *not* acceptable.

- Causes for discrepancy:
  - Serum glucose > 235 mg/dL
  - Data collection or entry error
  - In the case of unexplained discrepancy, rely on D/P Cr.
- High transporters have more rapid absorption of glucose and dissipation of the osmotic gradient, which results in low UF with long dwells.
  - Prescription considerations: More frequent, shorter duration dwells would optimize solute clearance and UF.
  - Volume control for high transporters:
    - Strict dietary salt and water restriction
    - Use high-dose diuretics if there is residual kidney function
  - Replace one or two 1.5% exchanges with a more hypertonic dialysate (2.5% or even 4.25% dextrose); consider one exchange with icodextrin daily.
  - Consider switching from continuous ambulatory peritoneal dialysis (CAPD) to nighttime-automated PD with or without mid-day exchange depending on residual kidney function.
  - Switch to HD if inadequate solute removal and UF despite all considerations above.
- Low transporters diffuse solute more slowly across the peritoneal membrane and require longer dwells to reach significant equilibrium. UF will be sustained as glucose osmotic gradient is maintained for a longer period of time. However, solute clearance will be slow.

- Prescription considerations: Higher volume and longer dwells would optimize solute clearance.

- Average transporters:
  - Adjust PD prescription to best suit lifestyle.
  - Average transporters using automated PD and a long-day dwell may have problem with net fluid reabsorption with the long-day dwell, in which case the day dwell may be shortened or performed with icodextrin.

PD dialysate: see Table 4.7

Table 4.7 Content of commonly used dialysate for peritoneal dialysis

Content	Dextrose		Icodextrin
Dextrose	1.5%, 2.5%, or 4.25%	**Icodextrin**	7.5 g
Sodium (mmol/L)	132		132
Chloride (mmol/L)	96–102		96
Calcium (mmol/L)	3.5, 2.5		3.5
Magnesium (mmol/L)	0.5–1.5		0.5
L-Lactate (mmol/L)	35, 40		40
Osmolality (mOsm/kg)	346–485		282–286
pH	5.2		5–6

- Higher UF requirement may be done by using solutions with higher dextrose content or icodextrin.

PD catheters

- Placement of PD catheter should be done at least 2 weeks prior to PD initiation unless urgent start is necessary.
- Antibiotic prophylaxis is recommended for the following:
  - Initial catheter insertion: The preoperative use of prophylactic antibiotic (e.g., 1 g IV vancomycin) has been shown to reduce postoperative peritonitis compared to cefazolin and control.
  - Prior to invasive procedure (e.g., dental, colonoscopy, hysteroscopy, cholecystectomy)

NOTE Patient should report to colonoscopy without PD fluid (or ≤200 mL) in the peritoneal cavity

because dextrose provides an ideal culture medium.

- PD access issues:
  - May be done surgically via laparoscopic approach or with interventional radiology under fluoroscopic guidance
  - Surgically placed catheter should have folding of omentum to avoid catheter tip migration and malfunction.
  - A surgically inserted catheter with a straight intraperitoneal (IP) segment has been shown to improve catheter survival, not the number of cuffs or configuration of subcutaneous segment.

Special PD issues

- Both lower (<3.5 mmol/l) and higher (>5.5 mmol/L) serum potassium concentration ranges are associated with higher risk for all-cause mortality.
- Unplanned PD (acute PD initiation) does not appear to increase infectious complications compared with planned PD.
- Mortality data regarding the use of PD versus HD for AKI are conflicting. Nonetheless, it must be noted that PD may be the only available option in developing countries.
- Risks for early switch to HD (i.e., by 6 months on PD):
  - HD initiation prior to PD
  - Development of peritonitis within 6 months on PD
  - PD following a failed kidney transplant
  - Poor PD expertise by dialysis staff
- PD BP and volume control:
  - BP in PD tends to improve in the first 2 years but subsequently worsens.
  - Similar to HD, BP control in PD may be achieved with salt restriction and optimal fluid removal via UF. Diuretic should be added if there is residual renal function.
  - Inadequate UF is a predictor of worse survival.
  - Excessive salt restriction and UF, however, are associated with reduced urine volume, possibly loss of residual kidney function, and ultimately reduced survival. CANUSA study revealed reduction of relative

mortality risk to 0.64 for every 250 mL of daily urine output and 0.88 for every 5 L/wk of residual renal GFR.

- RAAS inhibitors should be considered first-line antihypertensive therapy:
  - Has been shown to preserve residual kidney function
  - Has been shown to preserve peritoneal membrane function, evidenced by slower conversion to rapid transporters. Protective effect is presumed to be via antifibrotic properties of RAAS inhibition.
  - Known to be cardioprotective

PD complications

Exit-site infections

- Typical organisms: *Staphylococcus epidermidis* or *S. aureus* > gram-negative organisms (e.g., *Pseudomonas aeruginosa*)
- *Seasonal variations in causative pathogens: S. epidermidis* and gram-negative species in warmer seasons; *Corynebacterium* and fungal species in cold seasons
- Prophylaxis: use daily topical mupirocin or gentamicin cream. Polysporin cream may be associated with increased fungal infections.
- Check nasal culture for *S. aureus* carriers and use mupirocin ointment for 7 days monthly for prophylaxis to reduce exit-site infection.

Tunnel infections

- May be diagnosed with ultrasound (or CT) for evidence of fluid collection along the catheter tunnel

Peritonitis

- May contribute up to 15% of deaths in PD

Risks

- Exit-site or tunnel infection
- Dialysate contamination
- Leaking from catheter exit site with fluid flowing back into the catheter tract

- Summer greater than colder months (presumably due to increased sweating, moisture in summer months)
- Low dialysate [Ca^{2+}] < 1.75 mmol/l
- Hypokalemia: thought to reduce intestinal motility and bacterial overgrowth
- Risks for fungal infections: immunosuppressive state, DM, malnutrition, recurrent use of multiple antibiotics

Prophylactic measures

- Patient education for proper PD techniques
- Routine use of topical exit-site antibiotic creams (mupirocin or gentamicin)
- "Flush before fill" should be performed for manual PD exchanges to minimize infections.
- Correction of electrolyte abnormalities, particularly hypokalemia, hypocalcemia, constipation

Diagnosis

- Must meet at least two out of three criteria: (1) clinical signs consistent with peritonitis such as abdominal pain and/or cloudy effluent; (2) PD cell count with >100 WBCs/μL or with >50% polymorphonuclear leukocytes (PMNs) in differential count (>50% PMN is likely a better indicator for peritonitis than having >100 WBC/μL). False negatives may be seen if cell count is obtained early in the course of peritonitis or during short dwell (collect fluid after at least 2-hour dwell time); (3) identification of infective organism(s) from the dialysis effluent via Gram stain or culture
- Most common organism: gram-positive cocci (e.g., *S. epidermidis*), culture negative, gram-negative organisms, polymicrobials, much less commonly, fungi (*Candida* is most common), and, rarely, TB
- Of interest, streptococcal peritonitis is associated with severe abdominal pain.
- If gram-negative organisms (e.g., *Escherichia coli* or *Enterobacter*) or polymicrobials, consider bowel perforation or diverticulitis. Diarrhea and constipation are frequent causes for gram-negative organism peritonitis.

Management of peritonitis

- Antibiotic administration:
  - IP route is generally preferred over IV route.
  - Empirical therapy per International Society for PD (ISPD): vancomycin or first-generation cephalosporins *plus* third-generation cephalosporin or gentamicin (choice may be based on local organism susceptibility)
  - Duration of treatment is generally 2 weeks for *S. epidermidis* and *streptococcal peritonitis* and 3 weeks for *S. aureus* and *Corynebacterium peritonitis, and at least 3 weeks for non-pseudomonal gram-negative peritonitis*. A short course of oral rifampicin to eradicate carrier state and adherent or intracellular organisms should also be considered for *S. aureus* peritonitis.
  - Enterococcal peritonitis: IP vancomycin for 3 weeks with IP aminoglycoside added for severe cases
  - Pseudomonal peritonitis: two antibiotics (e.g., IP gentamicin or oral ciprofloxacin with IP ceftazidime or cefepime) for 3 weeks
  - Polymicrobial peritonitis: double empirical coverage as above plus metronidazole for at least 3 weeks; evaluate for abdominal pathology/bowel perforation and promptly obtain surgical evaluation
  - The fear for gentamicin-induced loss of residual kidney function (with use up to three courses) is likely unwarranted based on data from ANZDATA registry. However, IP aminoglycoside for over 3 weeks should be avoided due to high ototoxicity risk.
- Antifungal administration:
  - IP antifungal agent has no preferential role over systemic therapy.
  - *Aspergillus* and non-albicans *Candida* species: consider echinocandins (e.g., caspofungin)
  - Filamentous fungi: consider second-generation azoles (e.g., posaconazole, voriconazole)
- Definitions of relapsing, recurrent, repeat, and refractory peritonitis:
  - Relapsing: same organism within 4 weeks of treatment completion. Likely due to biofilm. Retreat and try tPA, for example, Alteplase instillation (1 to 6 hours) to remove biofilm. Catheter replacement would be indicated if peritonitis persists or relapses after tPA cleared the

infection.

- Recurrent: different organisms within 4 weeks of treatment completion
- Repeat: same organism after 4 weeks of treatment completion
- Refractory: persistent infection after 5 days of appropriate antibiotics
- For culture negative peritonitis not responding to empirical antibiotic or monocytic/eosinophilic peritonitis:
  - Resend PD fluid for special culture techniques
  - Consider other causes: fungi, virus, mycobacterium, allergic response to peritoneal dialysate (e.g., icodextrin) or drugs (look for systemic signs/symptoms of allergic reactions), underlying malignancies, lymphoproliferative diseases, CO_2 infusion with laparoscopic procedures

UF failure

Evaluate for common causes of apparent UF "failure"

- Rule out volume overload from other etiologies: loss of residual kidney function, CHF, dietary noncompliance, PD noncompliance
- PD-related causes: mechanical problems with PD procedure (migration, kinking of catheter), constipation affecting dialysate flow, fibrin plug (fibrin may be seen in drainage bags), dialysate leaks to other body cavities, peritoneal membrane failure. In the case of fibrin plugs, irrigate tubing system and add heparin to dialysate bags.
- Poorly controlled diabetes, for example, blood glucose >250 mg/dL, dissipates the osmotic gradient necessary for optimal UF.
- Increased lymphatic reabsorption associated with increased intra-abdominal pressure
  - Sitting position is worse than standing and lying positions.
  - Severe constipation
  - Intra-abdominal pathology
- Peritoneal membrane failure:
  - Definition of peritoneal membrane failure:
    - Inability to maintain euvolemia despite use of >3 hypertonic dialysate solutions per day, or

        - Failure to ultrafilter >400 mL with a 4.25% solution over 4 hours (Rule of 4s)
        - Peritoneal equilibration testing reveals high D/P of Cr (i.e., >0.8).
    - Causes of peritoneal membrane failure:
        - Early: acute inflammation
        - Late: alterations in peritoneal membrane (e.g., thickening, fibrosis thickening or fibrosis of peritoneal membrane, high transporters, encapsulating peritoneal sclerosis)

Peritoneal fibrosis

- Suggested fibrosis-inducing factors: TGF-β, atrial natriuretic peptide, aldosterone

Encapsulating peritoneal sclerosis (EPS)

- Severe form of peritoneal sclerosis, manifested as abdominal pain, thickened bowel walls, bowel obstruction, with possible associated weight loss
- Risk factors: severe peritonitis, discontinuation of PD, genetic predisposition, PD vintage, younger age, high glucose load, and chronic exposure to glucose degradation products
- Clinical manifestations:
    - Symptoms: abdominal pain, bowel obstruction, UF failure, malnutrition, weight loss, bloody dialysate
    - CT findings of thickening of peritoneal membrane or encapsulation of bowel loops, bowel tethering, peritoneal calcifications
- Diagnosis: The diagnosis of EPS requires the presence of both clinical and radiologic features of intestinal obstruction and encapsulation.
- Management:
    - Early dietetic referral
    - Medical therapy:
        - No clear evidence to support recommendation for use
        - Reported therapies that may be considered at the discretion of the treating clinician: tamoxifen (inhibitor of TGF-β production), immunosuppressive therapy (e.g., prednisone, azathioprine,

mycophenolate mofetil)
    - Experimental interventions: *N*-acetylcysteine, eplerenone, glutamine supplementation, and the vasoactive glycosaminoglycan sulodexide
  - Surgical intervention by experienced EPS surgical team
  - Peritoneal rest, transfer to HD (per patient wishes, life expectancy, quality of life), consider total parenteral nutrition

Other potential PD complications

Dialysate leaks (subcutaneous or other body cavities)

- Early leaks (usually external leak):
  - Poor tissue healing due to early use of PD following catheter insertion
  - Faulty catheter implantation, trauma
  - Diagnosis: Check glucose concentration with Chemstrip to confirm pericatheter leaks. This should reflect the glucose concentration from the dialysate.
  - Management: Provide prophylactic antibiotic to prevent peritonitis and hold PD for 1 to 3 weeks.
  - Late leaks: hernias, straining, infections
    - Obtain T2-weighted MRI (dialysate can be detected without the use of gadolinium), CT with addition of contrast to dialysate, or nuclear study with addition of tracer to dialysate.

NOTE CT and nuclear study only detect current leaks, whereas MRI can detect existing leaks.

    - Perform physical examination to assess for obvious fluid collections.
    - If icodextrin dialysate is used, addition of povidone-iodine to the aspirated fluid will turn bluish black. This is due to the reaction between iodine and icodextrin starch.

Infusion pain

- Underlying etiologies:
  - Usually transient and observed in new patients
  - Persistent infusion pain:
    - Low dialysate pH

        - Hypertonic glucose solutions
        - Aged dialysis solution
        - Overdistention of abdomen with high dialysate volume
        - Extremes in dialysate temperature
        - Catheter related:
            - Straight tip catheters have higher incidence of mechanical inflow pain compared with coiled catheters.
            - Catheter malposition with tip against abdominal wall or tube restriction by attached tissues can produce both inflow and outflow pain.
    - Diagnosis: Consider all above—clinical judgment.
    - Interventions:
        - Use bicarbonate/lactate-buffered dialysis solutions (pH 7.0 to 7.4).
        - Consider adding 1% to 2% lidocaine solution to dialysate (5 mL/L).
        - Other considerations: Use slow infusion rate, lower volume, adjust dialysate temperature; consider imaging study (CT).

Drain pain

- Underlying etiologies:
    - End-of-drain pain: Typically occurs at end of drain as catheter touches sensitive parietal peritoneum; pain is typically experienced in genital or anorectal region and more commonly occurs with use of cycler.
    - Low catheter implant: Catheters implanted too low on abdominal wall can wedge tubing into deep pelvis, resulting in drain pain.
    - Constipation: crowding of bowels around catheter
- Diagnosis: clinical judgment—rule out conditions above
- Interventions:
    - Avoid complete drain
    - Consider tidal PD (fill following incomplete drain)
    - Treat constipation if applicable
    - Consider repositioning of catheter

Outflow failure

- Etiologies:
  - Constipation and urinary retention: Compression on catheter may block catheter side holes or displace catheter tip into a position of poor drainage.
    - Urinary retention: Drain bladder as needed.
    - Constipation: Administer oral emollient, stool softeners. Note that stimulants such as bisacodyl and saline enemas *are reserved for refractory cases* due to possible chemical and mechanical irritation of colonic mucosa and potential transmural migration of bacteria and development of peritonitis.
- Tubing kink: typically results in two-way obstruction; Diagnosis: abdominal X-ray; Treatment: catheter revision or replacement
- Fibrin strands and plugs: Diagnosis: fibrin strands and plugs may be seen in effluent; Treatment: add heparin 500 units/L of dialysate
- Obstructed catheter:
  - Attempt dislodging intraluminal debris by brisk irrigation of catheter with saline; if this fails, consider trial of tPA instillation.
  - If tPA still fails, consult interventional radiology or general surgery for catheter manipulation.

Shoulder pain (other than anginal causes)

- May be caused by unintentional air infusion during dialysate solution instillation
- Management: Infuse full exchange volume, then drain dialysate with patient in knee-chest position.

Respiratory distress

- May be due to excessively high volume of dialysate in the peritoneal cavity

Dialysate color changes

- Bloody dialysate: menstruation, ruptured ovarian cysts, ruptured capillary, bowel ischemia/infarction, intra-abdominal malignancy, trauma, early EPS, mycobacterium. Performing an exchange with room temperature PD fluid

may clear bloody dialysate. Add heparin to dialysate to avoid clotting of catheter if benign cause.

- Green dialysate: Consider biliary source.
- Milky white dialysate: hyperlipidemia (triglycerides or chylomicrons), disruption of lymphatics

Consider PD catheter removal

Indications for PD removal

- Refractory tunnel infection or severe exit-site infection
- Refractory peritonitis (treatment failure despite appropriate antibiotics >5 days)
- Catheter-related sepsis
- Fungal peritonitis
- Abdominal perforation
- Presence of biofilm in patients with relapsing peritonitis that failed tPA administration to clear the biofilm

Considerations for PD removal

- Repeat peritonitis
- Mycobacterial peritonitis
- Peritonitis caused by multiple enteric organisms
- Catheter reinsertion:
  - Systemic antibiotics should be continued for at least 2 weeks prior to reinsertion.
  - Reinsertion may be done at least 2 weeks after catheter removal and complete resolution of peritoneal symptoms.

Special Topics in CKD

Dermatology

Nonspecific manifestations

- Pallor (40%): likely due to anemia
- Hyperpigmentation (20%): thought to be due to increased concentrations of melanocyte-stimulating hormone. Treatment: sunscreen

- Half-and-half nails (i.e., Lindsay nails) (20%): Proximal half of nail is white, distal half of nail is normal or brown in color. Thought to be due to increased tissue concentration of melanocyte-stimulating hormone. Benign, no treatment.
- Xerosis, dry scaly skin (50% to 85%): thought to be due to dehydration of stratum corneum and reduced sebum and sweat production. Treatment: routine skin emollient application, avoid excessive washing.
- Uremic pruritus:
  - Likely multifactorial, suggested contributing factors: hypervitaminosis A; SHPT; high levels of calcium, phosphorus, and magnesium; iron deficiency anemia; xerosis; increased inflammatory cytokines; abnormal neurologic signaling; imbalance of endogenous CNS opioid peptides; downregulation of κ-opioid receptors
    - Treatment options: Correction of electrolyte abnormalities, skin emollient application; consider small doses of gabapentin (100 mg daily), pregabalin (25 mg daily), or the κ-receptor agonist nalfurafine (5 µg daily).

Acquired perforating dermatosis (up to 10%)

- Unclear etiology, mostly affect African Americans, strongly associated with CKD and DM, characterized by transepidermal absence of dermal structures (i.e., collagen, keratin, elastic fibers)
- Clinically manifested as localized pruritus, presence of firm, dome-shaped papules or nodules with central keratotic plugs on extensor surfaces of extremities and trunk. New lesions with trauma/scratching may form (Koebnerization).
- Treatment options:
  - Topicals: steroid creams (clobetasol or β-methasone) and/or a keratolytic agent (salicylic acid, urea, or ammonium lactate); retinoid; cantharidin
  - Oral therapies: antihistamines, low-dose allopurinol, acitretin, doxycycline, or minocycline
  - Others: cryotherapy, phototherapy

Bullous diseases

- Porphyria cutanea tarda (PCT) is due to uroporphyrinogen decarboxylase (URO-D) deficiency and is exaggerated by alcohol abuse, hepatitis C, HIV, and iron supplementation. HD patients may develop PCT due to decreased URO-D activity and poor clearance of plasma porphyrins. PD patients are less susceptible to PCT due to better porphyrin clearance. Management: avoidance of triggers (e.g., alcohol, hepatotoxic medications, sun exposure, iron overload) and use of high-flux dialyzers for effective porphyrin removal.
- Pseudoporphyria is clinically and histologically similar to PCT, but without serum and urine porphyrin abnormalities. Management: avoidance of triggers (e.g., diuretics, antibiotics, antifungals) and sun exposure. Consider *N*-acetylcysteine.

Calcific uremic arteriolopathy (calciphylaxis)

- Condition characterized by systemic medial calcification of arterioles, ischemic necrosis of skin and subcutaneous tissues
- Associated with high morbidity and mortality (up to 45% to 80% mortality within 1 year)

Patient-related risk factors

- Skin trauma may be key factor (i.e., repeated insulin injections in patients with DM).
- Others: female gender, obesity (associated with truncal lesions rather than distal lesions), dialysis vintage, hypoalbuminemia, underlying autoimmune disease, DM

Medication-related risk factors

- Steroids, warfarin, subcutaneous insulin, vitamin D analogs, calcium-based phosphate binders, iron therapy

Potential therapy

- Avoid: warfarin, vitamin D analogs, calcium-based phosphate binders
- Supportive care: wound care, control of SHPT and hyperphosphatemia, use lower calcium dialysate (only if safely tolerated due to hypotension

associated with lower calcium dialysate), debridement only when absolutely necessary due to increased risk of infections, consider bisphosphonate therapy and cinacalcet if clinically appropriate

- IV sodium thiosulfate 25 g thrice weekly can be administered during the last 30 minutes of each HD session. Efficacy is variable, and duration of therapy is undefined.
- Optimize dialysis dose; consider intensive dialysis.

Nephrogenic systemic fibrosis (NSF)

- Scleroderma-like disorder seen in patients with severely impaired kidney function (i.e., GFR < 15 to 30 ml/min/1.73 m^2) who receive gadolinium-based contrast agents (mostly reported with omniscan).
- Clinical manifestations: painful, symmetric erythema and edema that become firm papules/plaques and nodules resembling burn scars. Internal organ fibrosis may occur.
- Pathogenesis: increased production and migration of circulating fibrocytes to susceptible tissues with ongoing inflammation or injury
- Increased risks: PD compared to HD, elevated serum phosphate levels, exposure to high-dose or repeated exposures
- Triggering factors: underlying ischemic or thrombotic vascular injury, infection, high-dose EPO therapy

Management of NSF

- **Key:** Avoidance of linear and ionic gadolinium in patients with GFR <30 ml/min or aki.
- Perform HD if gadolinium exposure had already occurred AND patient has ESKD (*only if* ESKD). Recommend three daily dialysis treatments. Note, however, that even with immediate postexposure dialysis, patient may not be protected from developing NSF due to first-pass effect. Initiating HD in non-ESKD patient for the sole purpose of gadolinium removal is not recommended.
- Beneficial medical therapies reported: corticosteroids, sirolimus, pentoxifylline, methotrexate, high-dose IV Ig, imatinib mesylate, sodium thiosulfate

- Other reported beneficial interventions: successful renal transplant, ultraviolet A phototherapy, plasmapheresis

Dialysis a2-microglobulin amyloidosis

- β2-Microglobulin is a major constituent of amyloid fibrils that can deposit in synovial membranes and osteoarticular sites, leading to destructive osteoarthropathies or major solid organs such as the heart and GI tract.
- Incidence >95% with >15 years of HD vintage in the past, but likely lower at present due to greater removal of β2-microglobulin with high-flux dialysis.
- Increased risk: long-term HD or CAPD
- Clinical manifestations: carpal tunnel syndrome, flexor tenosynovitis, subchondral bone cysts/erosions, fractures, heart failure, pulmonary HTN, GI bleed
- Pathogenesis: poor clearance without residual kidney function, inflammatory state, prolonged uremic exposure, advanced glycation end products of β2-microglobulin
- Management: supportive, physical and/or occupational therapy, surgical repair

Medical Director Responsibilities and Conditions of Coverage

Responsibilities

- Responsible for the delivery of patient care and outcomes
- Responsible for ensuring that all individuals who treat patients at the facility, including attending physicians and nonphysician providers, adhere to all policies relative to:
  - Patient admissions
  - Infection control
  - Safety
- Responsible for ensuring that the interdisciplinary team adheres to discharge and transfer policies and procedures
- Accountable to the governing body for the quality of medical care provided to patients

- Responsible for Quality Assessment and Performance Improvement (QAPI) program
- Ultimately responsible for all staff education, training, and performance
- Responsible for developing, periodically reviewing, and approving a "Patient Care Policies and Procedures Manual"
- Responsible for emergency preparedness:
  - Plans for emergency preparedness that include fire, equipment or power failure, interruption of water supply, natural disasters
  - Training and orientation in emergency preparedness to the staff that are assessed at least annually
  - Decide on specific emergency drugs to be available and describe these drugs in the facilities
- The medical director should devote sufficient time to ensure that safe and effective care is delivered to all patients. This requires the medical director be actively involved in the oversight of the facility, which includes:
  - Attending care plan meetings (if he/she has patients in the facility)
  - QAPI committee meetings
  - Guiding development of performance improvement/action plans
  - Assuring that staff are sufficiently trained to perform their assigned roles
  - As a guide, each facility's financial cost report, filed with the CMS, considers the medical director role as 0.25 full-time employment.

Self-referral and Stark law

- Started in 1989, barring medical directors to self-refer patients to own unit where there is a "financial relationship." It was later recognized that Stark law would prevent medical directors from practicing patient care.
- Later amendments exempted medical directors to refer patients to own dialysis units.

Qualifications of the medical director

- Board certified in internal medicine or pediatrics by a nationally recognized professional board
- Completion of a board-approved nephrology training program

- 12 months experience in caring for dialysis patients, including time spent in nephrology training

Conditions of coverage for end-stage renal disease

- Facilities refer to conditions that dialysis facilities must meet to be certified under the Medicare program. The established rules are focused on:
- The patient and the results of care provided to the patient
- Performance expectations for facilities
- Patient participation in their plan of care and treatment
- Preservation of strong process measures when necessary to promote meaningful patient safety, well-being, and continuous quality improvement
- The final rule, https://www.cms.gov/Regulations-and-Guidance/Legislation/CFCsAndCoPs/Downloads/ESRDfinalrule0415.pdf (accessed December 15, 2019), reflects the advances in dialysis technology and standard care practices since the requirements were last revised in their entirety in 1976.

Access the eBook for self-assessment questions.

CHAPTER 5

Hypertension

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DEFINITIONS/GENERAL CONCEPTS

Epidemiology

- Worldwide trends in blood pressure (BP) from 1975 to 2015 based on pooled analysis of 1,479 population-based measurement studies with 19.1 million participants:
  - Global age-standardized prevalence of hypertension (HTN), defined as systolic blood pressure (SBP) >140/90 mm Hg, was 24% in men and 20% in women in 2015.
  - The number of people with HTN has increased by 90% during the four decades studied, presumably due to population growth and aging.
  - Prevalence of HTN decreased in high-income, increased in low-income countries in South Asia and Sub-Saharan Africa, and remains persistently high in Central and Eastern Europe.

HTN in the United States (Centers for Disease control and Prevention 2020)

- Over 100 million have HTN, defined as SBP ≥130 mm Hg or diastolic blood pressure (DBP) ≥80 mm Hg, or are taking antihypertensive medications.
- Half of adults with BP ≥140/90 mm Hg who should be taking

antihypertensives are not prescribed or taking the medication.
  - Only about one in four adults have their HTN under control.
  - HTN costs the United States approximately $131 billion annually, averaged from 2003 to 2014.
  - Geographic prevalence: HTN is most prevalent in the southeast and eastern urban regions of the United States.
  - HTN by gender: 47% of men and 43% of women have HTN.
  - HTN by race: 54% in non-Hispanic black adults, 46% in non-Hispanic white adults, 39% in non-Hispanic Asian adults, and 36% in Hispanic adults
  - Among those recommended to take antihypertensive medications, BP control is seen in 32% of non-Hispanic white adults, 25% in non-Hispanic black adults, 19% in non-Hispanic Asian adults, and 25% in Hispanic adults.

BP Measurements

- Standardized office or home BP measuring techniques: (1) no conversation; (2) no exercise, nicotine, or caffeine at least 30 minutes prior; (3) empty bladder; (4) place correct cuff size on bare arm; (5) support arm at heart level; (6) keep legs uncrossed; (7) support back and feet
- For automated oscillometric BP (AOBP) office measurements: after 5-minute rest, average two to five measurements at intervals of 1 to 2 minutes
- Variability in BP measurements:
  - Casual office BP (defined as not following standardized techniques outlined above) is generally 5 to 10 mm Hg higher than standardized office or home BP, AOBP, and awake ambulatory BP.
  - Standardized office BP may be lower than awake ambulatory BP.
- Out-of-office BP may provide better prediction of kidney disease progression and cardiovascular (CV) events than in-office BP measurements among patients with chronic kidney disease (CKD).
- Between-arm BP measurement differences:

- Between-arm BP differences of 4 to 5 mm Hg occur in healthy individuals.
- Values >10 mm Hg should be considered for vascular assessment.
- Values >15 mm Hg is a predictor of prevalent vascular disease and death.
- BP treatment should be based on higher BP arm.

Indications for Ambulatory BP Measurements

- Suspected white coat hypertension (WCH) or masked HTN
- Apparent drug resistance (BP not at goal while seemingly being on maximal and optimal drug combination, WCH, noncompliance, proper BP measuring techniques, etc., have not been ruled out.)
- Hypotensive symptoms
- Autonomic dysfunction
- Episodic HTN
- Evaluation of nocturnal BP dipper or riser as prognostic factor for target organ damage
- Evaluation of BP changes in patients with paroxysmal nocturnal dyspnea and nocturnal angina
- Carotid sinus syncope
- Pacemaker syndromes
- Safety of withdrawing antihypertensive medications
- Assess 24-hour BP control on once-daily medication
- Borderline HTN with target organ damage
- Evaluation of antihypertensive drug therapy in clinical trials

BP Categories

- BP categorization below is based on the average of two or more properly measured readings obtained on at least two separate visits after initial screen.
- Adults >18 years of age:
  - Normal: SBP < 120 mm hg *and* DBP < 80 mm hg
  - *Elevated BP:

        - SBP 120 to 129 mm Hg *and* DBP < 80 mm hg
        - *Pre-HTN category is no longer used.
    - Stage 1: 130 to 139 mm Hg *or* DBP 80 to 89 mm Hg
    - Stage 2: SBP ≥ 140 mm Hg *or* DBP ≥ 90 mm Hg
    - HTN based on ambulatory BP monitoring:
        - 24-hour average > 130/80 mm Hg
        - Daytime (awake) average > 135/85 mm Hg
        - Nighttime (asleep) average > 120/70 mm Hg
- Categorization of HTN in pregnancy is defined in **Pregnancy and HTN** section.

BP Goals

- 2017 Hypertension Clinical Practice Guidelines of the American College of Cardiology/American Heart Association (ACC/AHA):
    - The 2017 Hypertension Clinical Practice Guidelines relies on average BP readings.
    - BP should be categorized as normal, elevated, or stage 1 or 2 HTN.
    - Out-of-office BP measurements are recommended to confirm the diagnosis of HTN and titrate BP-lowering medication.
    - Goal BP for everyone is <130/80 mm hg, *except*:
        - Older adults ≥65 years old with HTN and a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit are reasonable for decisions regarding intensity of BP-lowering and choice of antihypertensive drugs.

Management

General management regardless of BP level

- Promote optimal lifestyle habits
- Nonpharmacologic therapy (see **Routine Management of HTN** section)

Addition of pharmacologic therapy is recommended for

- HTN stage 2 (average SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg) *or*

- HTN stage 1 (average SBP 130 to 139 mm Hg or DBP 80 to 89 mm Hg) if:
  - Known atherosclerotic cardiovascular disease (ASCVD) or 10-year risk ≥10%
  - Diabetes mellitus (DM) type 2, or
  - CKD

Special considerations

- For patients with asymptomatic mild or moderate aortic stenosis with normal left ventricular systolic function: BP target of 130–139/70–89 mm Hg is reasonable. A post hoc analysis of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial revealed the lowest all-cause mortality rate for patients in the BP range of 120–139/70–79 mm Hg. All-cause mortality was significantly associated with average SBP < 120 mm hg and average dbp ≥ 90 mm hg.
- For patients >65 years old, be cautious not to lower DBP <65 mm hg because this has been suggested to be associated with increased stroke risk.

Types of HTN

White coat hypertension (WCH)

- Definition: having home or daytime ambulatory SBP < 130/80 mm hg but office bp > 130/80 mm Hg after 3 months of diet and lifestyle modification
- Prevalence among patients with CKD has been estimated to range from 2% to 41%.
- Clinical significance of WCH:
  - Some studies revealed increased left ventricular mass index compared to individuals with normal BP.
  - Affected individuals may have impaired diastolic function and higher levels of catecholamines, renin/aldosterone, low-density lipoproteins.
  - Conversion to sustained HTN occurs in 1% to 5% annually.
- Start antihypertensive if office BP is persistently elevated with evidence of target organ damage.

Masked HTN

- Definition: BP measured in the office is lower than that measured in the

out-of-office setting (opposite of WCH).

- Prevalence in the general population is estimated at 10% to 20% and higher at 20% to 50%$^{+}$ in patients with CKD.
- A systemic review of published literature from 2000 to 2018 reported similar risks of fatal and nonfatal cardiac and CV events among patients with masked HTN compared with those with sustained HTN (hazard ratio [HR] ~2.1 vs. 2.3).
- Initiate antihypertensive therapy if elevated 24-hour ambulatory BP and evidence of target organ damage.

Sustained HTN

- HTN in both in-office and out-of-office settings

Pseudo-HTN

- Cuff BP is higher when compared with intra-arterial pressure because of excessive atheromatosis and/or medial hypertrophy in arterial tree.
- May be diagnosed by Osler maneuver:
  - Inflate BP cuff above SBP (detected by loss of pulse with auscultation). Osler maneuver is positive when either brachial or radial artery remains palpable despite loss of pulse by auscultation.
  - Pseudo-HTN is defined as cuff-measured DBP >10 to 15 mm Hg compared with that of intra-arterial measurement.
  - Management of BP should be based on intra-arterial value.

Isolated systolic hypertension (ISH)

- Occurs with stiffening of large arteries leading to reduced vessel capacitance and acceleration of pulse wave velocity, hence widening of pulse pressure
- Increase in SBP continues throughout life, in contrast to DBP, which increases and peaks by age of 50 and then decreases later in life.
- After 50 years, SBP is more important than DBP.

Isolated diastolic hypertension (IDH)

- IDH is defined as having DBP ≥ 80 mm Hg with SBP <130 mm hg (per 2017 acc/aha)

- More common among young men, individuals with sedentary lifestyle, overweight/obesity
- IDH is more common than combined systolic and diastolic HTN (SDH) and ISH in individuals <40 years of age. idh is rare in individuals >60 years old.

Clinical significance of IDH is unclear

- Rate of progression or conversion to SDH noted to be 55% in 6.7 years in Framingham Heart Study.
- Finland study involving 3,267 healthy men aged 32 to 45 years with untreated IDH had no increase in all-cause mortality.
- Cross-sectional analyses of the National Health and Nutrition Examination Survey (NHANES 2013 to 2016) and longitudinal analyses of the Atherosclerosis Risk in Communities Study revealed no significant association between IDH and increased risk for CV outcomes.

Management of IDH

- Focus on salt restriction and weight loss, the latter if overweight or obese
- Pharmacologic antihypertensive therapy if end-organ damage, that is, proteinuria or left ventricular HTN on electrocardiogram (ECG), or hypothyroidism. Hypothyroidism is associated with BP rise that is more pronounced with DBP than SBP.
- If no specific indication for any antihypertensive class, IDH patients tend to respond well with just one agent, typically better with angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB) than dihydropyridine calcium channel blocker (CCB).

Drug-resistant HTN

- BP is not at goal despite optimal doses (optimal dose, defined as >50% of maximal dose recommended for treatment of HTN) of three different appropriate antihypertensive drug classes, ideally one class being a diuretic.
- Alternatively, BP is at goal with optimal doses of four appropriate antihypertensive drug classes, ideally once class being a diuretic.

Refractory HTN

- BP not controlled despite being on ≥5 drugs including a diuretic.

Apparent (drug)-resistant HTN

- Patients with *apparent* "drug-resistant HTN" are those who meet criteria above but have *not* been ruled out for proper BP techniques, WCH, noncompliance, improper BP medication regimens.

Pseudoresistant HTN

- Patients who initially meet criteria for "drug-resistant HTN" but later proven to fail meeting the same criteria following proper BP measuring techniques, ambulatory BP measurements, and/or compliance with proper BP medication regimens

Apparent resistant HTN may be seen in 15% of the population treated for HTN in the United States. However, ~50% of whom have pseudoresistant HTN. True resistant HTN is approximated at 5% of treated hypertensives.

Other Definitions

Hypertensive urgency

- Severe HTN, typically, SBP > 180 mm Hg or DBP >110 mm Hg, in patients with or without symptoms such as severe headaches, dyspnea, or anxiety, but *without* ongoing end-organ damage

Hypertensive emergency

- Severe HTN, typically, SBP > 180 mm Hg or DBP >110 mm Hg, in symptomatic patients (e.g., severe headaches, chest pain, neurologic deficits) *with* ongoing end-organ damage

Dippers and risers

- Definitions:
  - Dippers are individuals who experience a physiologic nocturnal fall in BP of >10% compared with daytime BP.
  - Risers experience a physiologic nocturnal increase in BP of >10% compared with daytime BP.
- It has been suggested that nondippers or risers, particularly in association

with elevated absolute nighttime BP, may predict end-organ damage and adverse CV events.

- The proportion of dippers decreases with increasing CKD stage.
- The proportion of risers increases with increasing CKD stage.

END-ORGAN DAMAGE OF HTN

Kidney Injury

Acute hypertensive nephropathy associated with hypertensive emergencies

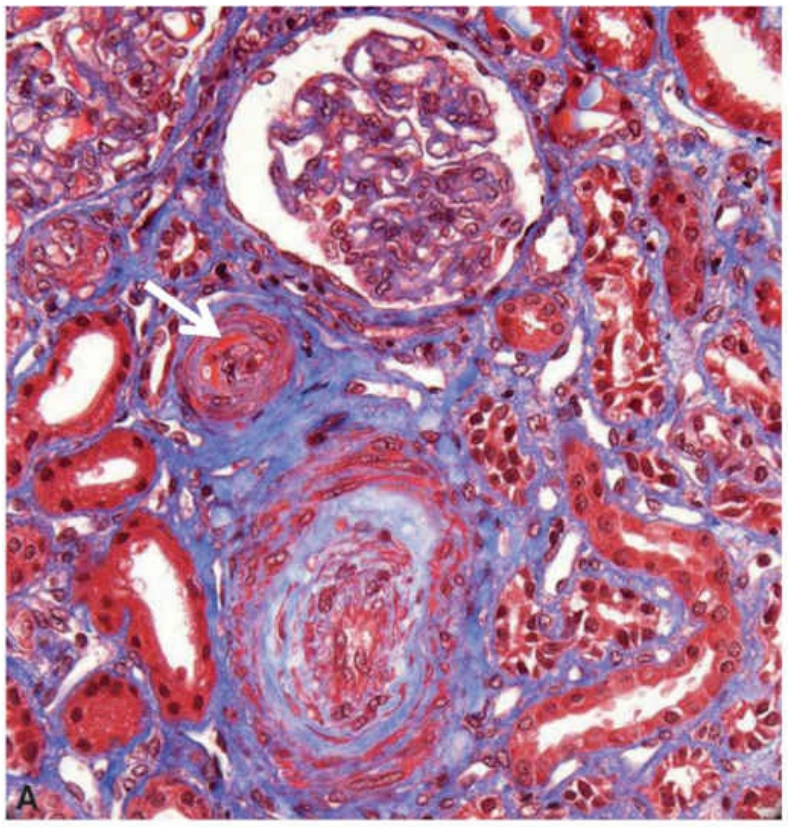
Clinical manifestations

- Hematuria, acute kidney injury (AKI)

Pathogenesis

- Direct endothelial damage, ischemic injury, microangiopathic hemolytic anemia causing obstruction of interlobular arteries

Histopathology (Fig. 5.1)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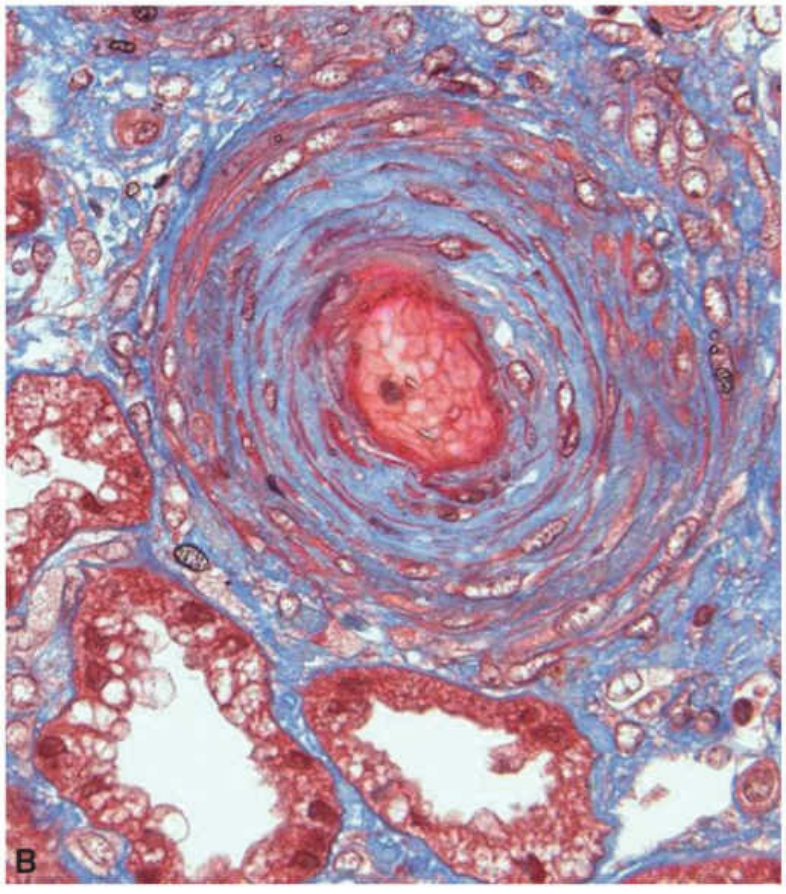

B

FIGURE 5.1 Accelerated/malignant hypertension/hypertensive renal emergency. **A.** Small artery and arteriole show mucoid intimal thickening, endothelial cell swelling, and severe luminal narrowing. Note fibrin (*arrow*) in the arteriolar intima and glomerular ischemic capillary wall corrugation (Masson's trichrome ×250). **B.** Small artery with "onion-skin" pattern thickening of the muscularis and luminal thrombosis (Masson's trichrome ×400).

- Fibrinoid necrosis of small arterioles (pink, amorphous fibrinoid materials within vessel wall due to necrosis) and "onion skinning" of small renal arteries. "Onion skinning" is used to describe hyperplastic arteriosclerosis with thickened concentric smooth muscle cell layer with thickened, duplicated basement membrane and narrowed lumen. In malignant HTN, these hyperplastic changes may be accompanied by fibrinoid necrosis of the arterial intima and media.

Chronic hypertensive nephropathy

Clinical manifestations

- Slowly progressive kidney injury with relatively bland urine, mild albuminuria
- End-stage kidney disease (ESKD) due solely to HTN is uncommon due to the relative preservation of glomerular injury until advanced stage, except for genetically susceptible subpopulation such as African Americans or those who suffer from frequent hypertensive emergency episodes and associated acute hypertensive nephrosclerosis. The relative glomerular sparing is consistent with the minimal albuminuria associated with chronic hypertensive nephropathy.

Histopathology

- Slowly progressive thickening and sclerosis of renal resistance vessels with relative sparing of glomerular capillaries. Ischemic glomerular loss occurs slowly over decades.

Cardiovascular

Acute cardiac complications associated with hypertensive emergencies

- Acute coronary syndrome, acute myocardial infarction (MI)
- Acute left ventricular dysfunction, acute heart failure (HF)
- Acute aortic dissection (see **Hypertensive Emergencies** section)

Chronic cardiac complications

- Left ventricular hypertrophy (LVH) that increases the risk of MI, HF, ventricular arrhythmias, sudden cardiac death
- Diastolic dysfunction
- HTN is a major risk factor for premature cardiovascular disease (CVD).
- In older patients, SBP and pulse pressure are better determinants of CVD risk than DBP. (Recall that DBP decreases after age 50.)

Cerebrovascular

Acute

- Ischemic stroke, intracerebral or subarachnoid hemorrhage

Chronic

- Ischemic stroke, vascular dementia
- Lacunar infarctions, microhemorrhages, and focal or diffuse white matter lesions may be seen in early hypertensive microangiopathic complications.

Evaluation of HTN

Routine evaluation in patients with HTN

- Recommended tests: lipid profile, kidney function, urinalysis, fasting blood glucose, hemoglobin A1C, complete blood count, ECG, thyroid-stimulating hormone
- Optional tests: echocardiogram, uric acid, urine albumin-to-creatinine ratio

Clinical clues that should prompt evaluation for secondary HTN

Age related

- Onset at age <30 years in nonobese, non-black patients with a negative family history of htn and no other risk factors for htn
- Onset of diastolic HTN in patients ≥ 65 years old

Acute changes in BP

- Abrupt-onset HTN
- Exacerbation of previously controlled HTN

HTN severity

- Drug-induced, drug-resistant, or refractory HTN

- Malignant or accelerated HTN (e.g., hypertensive urgency or emergency)
- Target organ damage is out of proportion to the degree of HTN.

Presence of signs/symptoms related to specific hypertensive conditions

- Unprovoked (absence of diuretic use) or severe hypokalemia (mineralocorticoid excess)

Evaluation of Suspected Secondary HTN

- Check for proper BP measurement techniques
- Check for volume overload
- Presence of obesity
- Review drug induced and related causes:
  - Inadequate doses
  - Inappropriate antihypertensive medication combinations (e.g., using several vasodilators in a patient with increased heart rate without a β-blocker [BB], using multiple sympatholytic drugs without any vasodilator, or using multiple drugs with reflex salt-retention but without a diuretic)
  - Prescribed drugs:
    - Nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors
    - Oral contraceptives
    - Adrenal steroids
    - Glucocorticoids
    - Cyclosporine (CSA) and tacrolimus
    - Antidepressants (monoamine oxidase [MAO] inhibitors)
    - Erythropoiesis-stimulating agents (reduced nitric oxide [NO] synthesis, increased entholin-1)
    - Vascular endothelial growth factor (VEGF) inhibitors, such as sunitinib (downregulate NO expression)
  - Selected over-the-counter dietary supplements and medicines:
    - Sympathomimetics (decongestants, anorectics)
    - Ephedra, ma huang, bitter orange
    - Licorice (including some chewing tobacco)

- Common drinks/recreational drugs:
  - Caffeine (small and transient increase in BP)
  - Excess alcohol intake
  - Cocaine, amphetamines, methamphetamines, other illicit drugs
- Medication nonadherence

- Identify secondary causes of HTN (**Fig. 5.2**). Important causes of secondary HTN are discussed in **Secondary Causes of Hypertension** section later in this chapter.

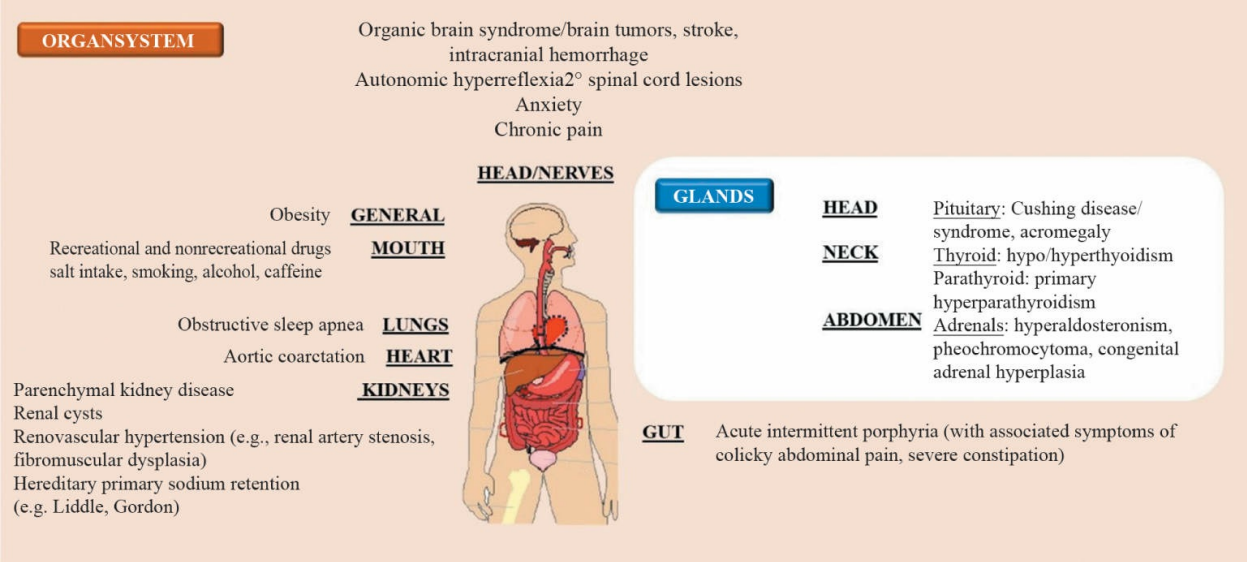


FIGURE 5.2 Secondary causes of hypertension by organ system and endocrine glands.

Routine Management of HTN (ACC/AHA 2019)

Best proven nonpharmacologic interventions for prevention and treatment of HTN

- Weight reduction:
  - Target ideal body weight or aim for a weight loss of at least 1 kg
  - SBP may reduce by 1 mm Hg/kg weight loss.
- Adopt DASH-like eating plan:
  - Encourage diet rich in fruits, vegetables, whole grains, low-fat dairy products with reduced saturated and total fat
  - SBP may reduce by 8 to 14 mm Hg.
- Sodium restriction:
  - <1,500 mg/d; aim for ≥1,000 mg/d reduction in most adults

    - SBP may reduce by 2 to 8 mm Hg.
- Increase potassium intake:
    - 3,500 to 5,000 mg/d unless patient has problems with hyperkalemia
    - SBP may reduce by 4 to 5 mm Hg.
- Physical activity:
    - Regular aerobic, dynamic resistance, or isometric resistance activity, for example, 30-minute brisk walk daily, most days of week, or 150-min/wk
    - SBP may reduce by 4 to 9 mm Hg.
- Moderation of alcohol consumption:
    - <2 drinks daily in most men, <1 drink daily in women and lightweight persons
    - SBP may reduce by 2 to 4 mm Hg.
- For overall CV risk reduction, stop smoking.

Initiate pharmacologic therapy

- See indications outlined in **BP Goals** section.

Follow-up

- Patients with elevated BP or stage 1 HTN not on drug therapy should have their BP reassessed every 3 to 6 months.
- Patients initiated on antihypertensive medications should be monitored monthly until BP is controlled and stable.

Pharmacologic Therapy for HTN

Initiating pharmacologic therapy

- Initial drug selection depends on underlying conditions, “compelling indications” (e.g., ACEI/ARB for systolic HF, post-MI, α-blockers for benign prostate hypertrophy, BBs for essential tremors, hyperthyroidism, migraine, atrial fibrillation/flutter with rapid ventricular rates, angina, mineralocorticoid receptor antagonist for hyperaldosteronism, thiazide diuretics for Gordon syndrome or osteoporosis, amiloride for Liddle syndrome).
    - Mainstay therapy for adults with or at risk for CVD includes BBs and/or ACEI or ARB, with subsequent addition of CCB and/or thiazide or

thiazide-like diuretics as needed. Loop diuretics should be reserved for severe HF or severe CKD. Mineralocorticoid-receptor antagonists (MRAs), such as spironolactone or eplerenone, may be considered in ischemic HF or resistant HTN.

- If there is no "compelling indication" for drug selection, first-line antihypertensive drugs include thiazide diuretics, CCBs, ACEIs, or ARBs. (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT] did not show any difference in coronary heart disease or nonfatal MI and stroke between CCB, ACEI, or thiazide diuretics.)
- For drug-naïve patients with SBP > 20/10 mm Hg above goal, two-drug therapy should be initiated.

Notes regarding thiazide diuretics

- Clinically available thiazide and thiazide-like diuretics include hydrochlorothiazide (HCTZ), chlorthalidone (CTDN), and indapamide (INDAP).
- The longer duration of diuretic and antihypertensive action of CTDN and INDAP compared with HCTZ may confer better nighttime BP control: HCTZ (<24 hours), ctdn (24 to 72 hours), indap (24 hours^{+} and 32 hours^{+} for immediate-release and sustained-release forms, respectively).
- Clinical data:
  - 2015 meta-analysis involving 14 randomized controlled trials (RCTs) comparing HCTZ versus CTDN and INDAP:
    - CTDN and INDAP reduced SBP by −3.6 and −5.1 mm Hg more than HCTZ, respectively.
    - No differences in metabolic adverse effects were detected.
  - 2.5-mg INDAP reduced stroke by 29% and all CV events by 23% in the Post Stroke Antihypertensive Treatment Study. Perindopril–INDAP combination also reduced CV events in two other placebo-controlled trials.
  - In an observational cohort study, CTDN was associated with lower LVH compared to HCTZ. In another observational cohort analysis (n = 12,866), the percentage risk reduction in CV events from CTDN versus

HCTZ was 21%. In network meta-analyses of randomized trials (*n* = 50,946), CTDN conferred a 25% risk reduction in congestive heart failure (CHF) and CV events compared with HCTZ.

- *Bottom line:* CTDN and INDAP reduce SBP more than HCTZ and confer ~21% risk reduction in CHF and CV events compared with HCTZ.
- Protection against fracture: The use of thiazide and thiazide-like diuretics has been shown to confer long-term protection against fracture compared to the use of other antihypertensive agents.
- Use of thiazide diuretics in CKD: CTDN has been shown to remain effective in reducing SBP by 19 to 20 mm Hg even in patients with advanced CKD G4. Continuation of thiazide diuretics rather than switching to loop diuretics may be appropriate in a stable patient if volume overload is not a concern. Loop diuretic switch is reasonable in the case of resistant HTN and/or volume overload.

The use of low-dose MRA (e.g., aldosterone)

- Confers additional benefits in CV outcomes in patients with New York Heart Association (NYHA) classes III and IV HF or decreased left ventricular ejection fraction after an MI.
- Recommended to be used concurrently with thiazide diuretics to offset hypokalemia
- May lower BP regardless of serum aldosterone levels
- BP-lowering effect has been shown to be more pronounced in patients with suppressed plasma renin activity (PRA).
- May reduce BP even in hemodialysis patients
- Recommended to be added in resistant HTN: spironolactone 25 to 50 mg daily. *Anglo-Scandinavian Cardiac Outcomes Trial revealed that the addition of spironolactone at median dose of 25 mg daily in addition to 2.9 other antihypertensive medications lead to a fall in BP of 21.9/9.5 mm Hg at 1.3-year follow-up. Optimum Treatment of Drug-Resistant Hypertension Study revealed the addition of spironolactone at 25 to 50 mg every day (qd) over a 12-week treatment period reduced SBP by 8.7 mm Hg on average compared to placebo.*

- Adverse effects: hyperkalemia, metabolic acidosis

Specific drug contraindications

- ACEI in angioedema (angioedema has also been reported with ARB), BBs with poorly controlled bronchospasm, reserpine in depression, methyldopa in liver disease, ACEI/ARB/or renin inhibitors in pregnancy or pregnancy planning, BBs and nondihydropyridine CCBs in second- or third-degree heart blocks

Special Considerations in Pharmacologic Therapy of HTN

Use of ACEI or ARB should be considered for the following

- Nondiabetics with HTN and albuminuria ≥30 mg/d
- Patients with HTN and CKD (including African Americans)

Direct renin inhibitor (DRI) combination with ACEI and ARB

Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) Trial

- Combination therapy consisting of losartan and aliskiren was minimally beneficial compared to lone losartan therapy in patients with DM type 2 with urine albumin-to-creatinine ratio >300 mg/g.
- Combination therapy was associated with higher rate of hyperkalemia (4.7% vs. 17%).

Aliskiren in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) trial

- Combination therapy with aliskiren and either an ACEI or ARB in patients with diabetic kidney disease reduced proteinuria and SBP by 1 to 2 mm Hg compared with placebo group receiving either ACEI or ARB alone.
- 25% greater stroke rate and more frequent hyperkalemia were observed with combination therapy.

Weight and antihypertensive therapy

- The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic HTN (ACCOMPLISH) trial suggests the preferential addition of a CCB over a diuretic to an ACEI in normal weight patients in terms of CV outcome (i.e., [CCB + ACEI] is better than [diuretic + ACEI] in normal weight patients). In obese high-risk hypertensive patients, the choice of adding either a diuretic or CCB to an

ACEI is less important.

- The difference in outcome was thought to be due to the difference in pathogenesis of HTN in normal versus obese patients. Lean individuals may have more prominent renin and sympathetic nervous system (SNS) activities with their HTN and are thus more sensitive to diuretics, which could further stimulate renin–angiotensin–aldosterone system (RAAS).

Antihypertensive therapy based on PRA: "renin profiling"

- PRA > 0.65 ng/mL/h (typically seen in younger Caucasians) may have HTN associated with vasoconstriction and respond well to ACEI, ARB, or BBs.
- PRA < 0.65 ng/ml/h (typically seen in african americans, afro-caribbeans, and older caucasians) may indicate volume expansion–related htn and may respond well to diuretics and ccb.
- A 2016 pilot study comparing the effectiveness of adding aldosterone antagonist (AA) versus administering renin-guided therapy (RGT) outlined above to patients with resistant HTN revealed fewer additional medications required for RGT versus AA to achieve the same antihypertensive effect.

Considerations for BP management in African Americans

- Use of two-drug combination therapy is recommended in most African Americans.
- For those *without* HF or CKD who do not meet criteria for two-drug therapy, a thiazide-type diuretic or CCB should be initially treated.
- For those with HF or CKD, renin–angiotensin system inhibition should be prescribed.

Considerations for BP management in the elderly

- Cognitive function:
  - Available data do not show cognitive decline in elderly patients who achieve target BP with the use of antihypertensive therapy (Hispanic Community Health Study/Study of Latinos). However, women with uncontrolled BP despite being treated with antihypertensive medications may have an associated cognitive decline (Women's Health Initiative Memory Study).

    - Intensive vs. Standard Ambulatory Blood Pressure Lowering to Lessen Functional Decline in the Elderly (INFINITY) trial: Among elderly patients with HTN, intensive lowering of ambulatory SBP reduced the development of subcortical white matter disease and nonfatal CV events but did not improve mobility or cognitive function.
- Caution with frail, institutionalized elderly: BP lowering to < 130/80 mm hg with the use of two or more antihypertensive agents in *older nursing home residents* is associated with increased mortality rates (Treatment with Multiple Blood Pressure Medications, Achieved Blood Pressure, and Mortality in Older Nursing Home Residents Study)

Other drug considerations in HTN

Sodium–glucose cotransporter 2 (SGLT2)

- SGLT2 are expressed in S1 and S2 segments of proximal renal tubule where 90% of glucose reabsorption occurs
- Inhibition of SGLT2 leads to glucosuria, hence glucose control in diabetics, and weight loss due to glucose-derived calories.
- Inhibition of SGLT2 also leads to mild BP reduction, presumably via (osmotic) diuretic effect.

Valsartan/sacubitril as an antihypertensive agent

- Although the combination drug has been shown to confer greater antihypertensive effect compared to ARB alone in elderly patients in a 2019 meta-analysis, safety and efficacy data for its use as an antihypertensive agent in RCTs are lacking. Recommendation for its use as an antihypertensive agent has not been made at the time of this writing.

Summary of Systolic Blood Pressure Intervention Trial (SPRINT)

Multicenter RCT of intensive versus standard BP control

- 9,361 persons with SBP ≥ 130 mm Hg with CVD risks but *without* DM were enrolled and randomized to SBP control <120 mm hg (intensive) or <140 mm hg (control)
- Inclusion: age ≥ 50 years with SBP ≥ 130 mm Hg and ≥1 of the following: history of CVD, CKD G3, intermediate to high risk for CVD other than stroke, or age ≥75 years

- Primary composite outcome was MI, other acute coronary syndromes, HF, or death from CV causes.

Results

Overall

- At 3.26 mean follow-up years, nondiabetic adults, age ≥50 years at increased CVD risk or with CKD with intense BP control had a 25% reduction in primary combined CV outcome and 27% reduction in mortality.
- Adverse effects:
  - Hypotensive and syncopal episodes and electrolyte disturbances, but not injurious falls, were more common in the intensive group.
  - Among individuals without CKD at enrollment, estimated glomerular filtration rate (eGFR) decline ≥30% to an eGFR of <60 ml/min/1.73 m^2 occurred more frequently in the intensive group (1.21%/year vs. 0.35%/year in the intensive vs. control group).

Women

- Benefit of intensive BP treatment appeared to be less for women compared with men.

Individuals with CKD at enrollment

- Intensive group had a lower all-cause mortality (HR 0.72), but not individual components of CVD outcome.

Individuals age ê 75 years

- Relative HR of primary CVD outcome and all-cause mortality were lower with marginal significance in the intensive group.
  - There was no difference in kidney outcome, defined as ≥50% decline in eGFR from baseline or reaching ESKD. Degree of albuminuria, but not incident albuminuria, was lower in the intensive group.
  - Adverse events: There were increased risks for AKI (HR 1.46) and dyskalemias in the intensive group.
- Individuals age ≥ 75 years old at enrollment:
  - Rates of all-cause mortality (HR 0.67) as well as fatal and nonfatal

major CV events were lower in the intensive group.
    - Kidney outcome defined above was higher in the intensive group but statistical significance was not reached due to low event numbers.
    - No difference in serious adverse events
- Note that BP measurement in Systolic Blood Pressure Intervention Trial (SPRINT) trial was based on automated office BP measurements, which are lower than office BP measurements performed by providers.

primary (essential) hypertension

Pathogenesis of primary HTN

- Increased sympathetic activity and responsiveness
- Increased angiotensin II (AII) activity and mineralocorticoid excess

Risks of primary HTN

- Genetics: twofold risk if both parents have HTN
- Reduced nephron mass due to immature birth, intrauterine developmental abnormality (e.g., maternal drug use, malnutrition), and postnatal disturbances (e.g., malnutrition, infections)
- Black ethnicity (more common and severe compared to non-blacks)
- Lifestyle associated: high salt intake, excess alcohol consumption, physical inactivity, vitamin D deficiency. Fructose intake, thus far, not proven to increase HTN risk.
- Metabolic: dyslipidemia, independent of obesity

Diagnosis of primary HTN

- Rule out WCH
- Rule out ingestions of medications/substances that can cause HTN (i.e., caffeine, tobacco smoking, amphetamines, cocaine, sympathomimetics, etc.)
- Rule out secondary causes as per risks, signs/symptoms. See **Secondary Causes of HTN** section.
- Routine testing:
    - Full history and physical examination

- Laboratory studies: See **Evaluation of HTN** section.
- In stage 1 HTN, consider microalbuminuria evaluation, ECG, and echocardiogram for determination of antihypertensive therapy initiation.

Management of primary HTN

See **Routine Management of HTN** section.

secondary hypertension

Indications for evaluation of secondary HTN

Difficult-to-treat HTN

- Not controlled on an appropriate combination of three antihypertensive agents of different classes, one of which is a diuretic or
- Controlled on an appropriate combination of four antihypertensive agents of different classes, one of which is a diuretic.

Refractory HTN

- Failure to achieve goal BP despite being treated by a HTN specialist over at least three visits over a 6-month period or longer
- Refractory HTN patients tend to have higher heart rate (81 vs. 70) compared to those who are controlled, despite being on more BB. Sympathetic dysregulation is thought to play a role.

Causes of secondary HTN

See Table 5.1.

Table 5.1 Evaluation of secondary hypertension by organ system

Conditions	Examples/Clinical Clues	Screening Tests
Conditions associated with secondary hypertension by organ system		
Oral	Prescribed medications, over-the-counter drugs, recreational drugs, high sodium intake	24-h urine creatinine and sodium if high salt intake is suspected in salt-sensitive individual, urine drug screen
Brain	Brain trauma, psychological disorders, pain, anxiety, autonomic dysreflexia (spinal cord injury above thoracic level 6)	Brain CT or MRI as indicated by suspected underlying pathology

Heart	Coarctation of aorta: midback thoracic, chest, or abdominal continuous murmur; rib notching on chest radiograph	BP measurements higher in upper than lower extremities; echocardiogram
Lungs	Obstructive sleep apnea: obese, loud snoring, daytime somnolence affecting daily activities	Sleep study
Kidneys	Parenchymal kidney disease: any glomerular, tubulointerstitial disease, obstructive condition, or cystic diseases	Urinalysis, urine protein-to-creatinine ratio Consider kidney ultrasound
	Congenital syndromes with renal sodium retention (Liddle syndrome, FHH [Gordon syndrome]).	Suppressed or low normal PRA and aldosterone level
	AME (syndrome): positive family history, licorice ingestion	Urine free cortisol-to-cortisone ratio >5 may be consistent with AME; ratio >1 may be consistent with licorice ingestion
	Mineralocorticoid receptor gain-of-function mutation (Geller syndrome): HTN may get worse with pregnancy; mineralocorticoid receptor antagonist (spironolactone) may worsen HTN	
	Glucocorticoid remediable aldosteronism	Suppressed PRA and high serum aldosterone, increased 18-hydroxy-cortisol, ACTH, and 18-oxo-cortisol levels
	Older individuals with high CVD risks, consider atherosclerotic disease Young females: fibromuscular dysplasia Others: history of trauma, aortic aneurysm, vascular thrombosis/emboli, malignancy, flash pulmonary edema	MRA or CTA Renal ultrasound with arterial duplex Doppler if eGFR < 30 mL/min/1.73 m^2
Gastrointestines (GI)	Acute intermittent porphyria with autonomic dysfunction and GI symptoms: Intermittent severe colicky abdominal pain, constipation, dystonic bladder with urinary retention, dark urine, tachycardia, sweating, neuropsychiatric disorders	Urinary porphobilinogen spot test
Conditions associated with secondary hypertension by endocrine glands		
Pituitary	Acromegaly: skull, hands, feet enlargement, excessive sweating, carpal tunnel syndrome, headaches, other endocrine disorders	Growth hormone, insulin-like growth factor-1
	Cushing disease (or syndrome): rapid weight gain, central obesity, “buffalo hump,” proximal weakness, glucose intolerance/hyperglycemia, hirsutism	24-h urine free cortisol excretion, late night/bedtime salivary cortisol levels, and 1 mg overnight dexamethasone suppression test to establish

		hypercortisolism
Thyroid	Hypothyroidism: relative hypothermia, bradycardia, may have low BP Hypothyroidism features: tachycardia, may have high BP	Thyroid-stimulating hormone; add free thyroxin if concerns for hyperthyroidism or central hyperthyroidism
Parathyroid	Hypercalcemia, hypophosphatemia	Serum calcium, phosphorus, parathyroid hormone level
Adrenals	Primary aldosteronism: hypokalemia with arrhythmias, particularly with atrial fibrillation or concurrent metabolic alkalosis	Plasma renin activity and aldosterone level
	Pheochromocytoma: paroxysmal HTN or crisis, BP lability, headaches, palpitations, pallor, sweating, adrenal incidentaloma, positive family history	Plasma-fractionated metanephrines (see text)
	Congenital adrenal hyperplasia: virilization, incomplete masculinization in males; primary amenorrhea in females	Plasma renin activity and aldosterone level; consider deoxycorticosterone, androgens, estrogen, corticosterone levels (consult endocrinology if high suspicion)

Note: Indications for evaluation of secondary hypertension include: (1) blood pressure not controlled while on three different antihypertensive agents of different classes, including a diuretic or (2) blood pressure controlled on four different antihypertensive agents of different classes, including a diuretic.

Abbreviations: ACTH, adrenocorticotropic hormone; AME, apparent mineralocorticoid excess; BP, blood pressure; CT, computed tomography; CTA, computed tomography angiogram; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HTN, hypertension; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; Neuro, neurologic system; PRA, plasma renin activity.

FHH, familial hyperkalemic hypertension

Obesity

- Proposed contributing factors: hyperleptinemia, hyperinsulinemia, endothelial dysfunction, SNS activation, kidney injury, fructose ingestion, hyperaldosteronism driven by circulating oxidized fatty acids (linoleic acid) or uric acid, concurrent obstructive sleep apnea (OSA)
  - Fructose gets phosphorylated rapidly intracellularly leading to → local adenosine triphosphate depletion and uric acid generation → uric acid–induced endothelial dysfunction, SNS activation.

Obstructive sleep apnea (OSA)

- OSA occurs in 30% of patients with HTN and up to 70% to 90% of

patients with resistant HTN.

- The association between OSA and HTN is dependent on OSA severity and presence of obesity. Association is not significant in individuals with body mass index (BMI) <25 kg/m^2 (nhanes data).
- Signs and symptoms to consider OSA in hypertensive patients: snoring, gasping/choking, daytime somnolence particularly with associated functional impairment (e.g., “sleeping on the job”)
- Use of continuous positive airway pressure (CPAP) ventilation “is an efficacious treatment for improving OSA. However, studies of the effects of CPAP on BP have demonstrated only small effects on BP (e.g., 2 to 3 mm Hg reductions), with results dependent on patient compliance with CPAP use (e.g., use >4 hours during sleep), severity of OSA, and presence of daytime sleepiness in study participants” (ACC/AHA 2017 Hypertension guidelines). More studies are needed.
  - BBs are thought to be most effective antihypertensive agent due to sympathetic overactivity.
  - Data on renal denervation suggest BP improvement but remain scant. Concerns regarding the renal denervation procedure include promotion of renal artery atherogenesis and interference with denervated kidney to tolerate insults, such as volume depletion, infection, trauma, or drug exposure.
- Bariatric surgery versus lifestyle modifications/medical therapy:
  - Greater weight loss with bariatric surgery confers greater BP reduction and lower antihypertensive drug requirement.
  - BP reduction correlates with the degree of weight loss, not type of bariatric surgery.
  - HTN relapse risk is increased among individuals with lower degree of weight loss compared to those with greater weight loss.

Neurogenic HTN

- Cerebral blood flow = Cerebral perfusion pressure/cerebrovascular resistance, where
- Cerebral perfusion pressure = Mean arterial pressure (MAP) − Intracranial pressure (ICP) and should be >60 mm Hg.

HTN after stroke

- Contributing factors: Cushing reflex, catecholamine and cortisol release, lesion involving brainstem or hypothalamus, nonspecific response, acute stress
- BP management per AHA/American Stroke Association:
  - For acute ischemic stroke patients receiving thrombolytic therapy:
    - Before thrombolytics: lower BP if SBP > 185 mm Hg or DBP > 110 mm Hg
    - After thrombolytics: lower BP if SBP > 180 mm Hg or DBP > 105 mm Hg for the first 24 hours
  - For acute ischemic stroke patients *not* receiving thrombolytic therapy:
    - Antihypertensive medications should be withheld unless SBP > 220 mm Hg or DBP > 120 mm Hg.
  - If BP lowering is indicated as outlined above, lower BP cautiously by about 15% during the first 24 hours after the onset of stroke.
  - Patients with acute ischemic stroke and BP < 180/105 mm hg in the first 72 hours do not seem to benefit from introduction or reintroduction of antihypertensive drugs. antihypertensive therapy after 72 hours should be considered for those who remain hypertensive and stable.
  - For acute intracerebral hemorrhage:
  - If SBP >180 mm Hg or MAP > 130 mm Hg *plus* evidence of or suspicion for elevated ICP, consider monitoring ICP and reducing BP to keep cerebral perfusion pressure at 61 to 80 mm Hg.
  - If SBP >180 mm Hg or MAP > 130 mm Hg *and* no evidence of or suspicion of elevated ICP, consider modest reduction of BP (e.g., MAP of 110 mm Hg or target BP of 160/90 mm Hg).
  - Most common agents used: intravenous (IV) labetalol and nicardipine

HTN after carotid endarterectomy (CEA) and endovascular procedures (e.g., angioplasty, stenting)

- Contributing factors: carotid baroreceptor impairment after surgical manipulation, elevated catecholamine levels, activation of trigeminovascular axon reflex
- Carotid hyperperfusion syndrome following CEA:

- Occurs during first week after surgery
- Cerebral hyperperfusion is defined as a postoperative increase in cerebral blood flow of >100% compared with preoperative flow, an increase that may only be ~20% compared with the "normal" contralateral side.
- Ipsilateral: pulsatile headaches, seizures, intracranial hemorrhage, cerebral edema
- Contralateral: neurologic symptoms
- Management:
  - Continuous intraoperative and postoperative BP monitoring
  - Strict BP control with SBP <120 mm hg
  - Preferred agents: IV labetalol or clonidine
  - Avoid vasodilators, such as nitroglycerin, sodium nitroprusside

Autonomic dysreflexia

- Defined as SBP >20% *from baseline* with associated change in heart rate (bradycardia to tachycardia) and at least one of the following: headache, facial flushing, blurry vision, stuffy nose, sweating, piloerection. Flush sweaty skin above lesion levels is due to brainstem parasympathetic activation.
- Occurs in up to 70% of patients with spinal injury at or above the sixth thoracic spinal nerve level.
- Pathophysiology:
  - Immediately following spinal injury, there is a loss of supraspinal sympathetic control.
  - Weeks to months following injury, there is extrajunctional sprouting of α-receptors, denervation hypersensitivity, impaired presynaptic uptake of norepinephrine, derangement of spinal glutaminergic interneurons.
  - Presence of any noxious stimulus below neurologic level of the lesion thereafter triggers a spinal reflex arc that results in increased sympathetic tone and HTN.
  - Noxious stimuli may include urinary tract infection, bladder over distention, and fecal impaction. Others include medical procedures,

surgeries, labor and delivery, and although rare, drugs such as sympathomimetics, sildenafil citrate used for sperm retrieval, and combination of duloxetine and amitriptyline.

- Management:
  - Preventive measures: good bowel, bladder, and skin care
  - Treatment:
    - Position patient upright to precipitate orthostatic BP.
    - Remove noxious stimuli (e.g., tight clothing, devices, fecal disimpaction, bladder catheterization as applicable)
    - Medications: select fast-acting, short-lived agents for persistent SBP elevation >150 mm Hg. Investigate for other noxious stimuli, hospitalization if no resolution.

Parenchymal Kidney Disease

Parenchymal kidney disease is the most common cause of secondary HTN

Simple kidney cysts and HTN

- Association thought to be due to cyst compression on adjacent renal parenchyma, resulting in focal ischemia and activation of RAAS.
- Association with HTN is strengthened with increased number of cysts ≥2 and increased cystic size >1.4 to 2.0 cm.
- Management:
  - Cyst decompression may reduce BP in anecdotal reports.
  - Use of renin–angiotensin blockers may be beneficial.

Proteinuria and HTN

- Proteinuria with loss of plasminogen in urine leads to the formation of plasmin by tubular urokinase-like plasminogen activator. Plasmin directly stimulates the distal tubular sodium epithelial channel (ENaC) via the proteolytic cleavage of ENaC extracellular α- and γ-subunits. The activated ENaC enhances sodium reabsorption.
- Based on the aforementioned mechanism, amiloride and triamterene may be considered in the management of edema and salt sensitivity in patients with proteinuria and HTN. Confirmatory clinical data are needed prior to routine use, given increased risks of hyperkalemia and AKI with both

agents.

Renovascular HTN

Clinical manifestations common to both unilateral and bilateral diseases

- New-onset HTN:
  - HTN occurs in the presence of a critical stenosis greater than 70% to 80%.
  - Less than 60% stenosis typically does not lead to measurable reduction in either pressure or flow. Activation of vasopressors to restore renal artery perfusion is thus not necessary, and HTN does not occur.
- Abdominal systolic–diastolic bruits (sensitivity 39% to 63%, specificity 90% to 99%)
- Paroxysmal symptoms due to SNS activation
- Loss of nocturnal BP dipping
- Accelerated end-organ damage, including LVH, microvascular disease, renal fibrosis

Diagnostic studies

- Recommendations per American College of Radiology (ACR) 2017:
  - For patients with high index of suspicion of renovascular HTN and normal kidney, contrast-enhanced computed tomography angiography (CTA) and magnetic resonance angiography (MRA) are preferred modalities.
  - For patients with high suspicion of renovascular HTN with eGFR < 30 ml/min/1.73 m^2, ultrasound with duplex is the preferred modality. unenhanced mra may be used as an alternative modality to avoid the risk of nephrogenic systemic fibrosis.
  - Captopril renal scintigraphy may be performed in selected cases, but is not routinely considered imaging study of choice.
- Specific notes about imaging studies in diagnosis renovascular HTN:
  - MRA versus CTA:
    - Both modalities are more accurate in diagnosing proximal than distal lesions.
    - In general, CTA depicts branch renal arteries better than MRA.

- ACEI (captopril) renal scintigraphy:
  - May be an appropriate modality in selected cases
  - Provides information on renal blood flow (uptake/appearance of isotope phase) and filtration (excretory phase). Delayed excretory phase following captopril administration suggests a significant role of AII in maintaining GFR.
  - Disadvantages: Sensitivity and specificity of captopril renal scintigraphy are reduced in patients with bilateral renal artery stenosis (RAS), impaired kidney function, and urinary obstruction.
  - Advantages:
    - High negative predictive value: a negative test essentially rules out clinically significant RAS.
    - Provides relative function of each kidney prior to invasive intervention
- Renal arterial Doppler (ultrasonography):
  - Most effective for detection of lesions in proximal main renal artery (thus likely not great study for fibromuscular dysplasia [FMD] where lesions are typically more distal)
  - Advantages: inexpensive, readily available
  - Disadvantages: does not provide functional information
- Arteriography:
  - Considered reference standard
  - Requirement for high contrast dose injection into the inferior vena cava or right atrium renders this modality “usually not appropriate” as a screening imaging study for renovascular HTN per ACR.

Pathogenesis of unilateral stenosis and clinical implications

- The reduced renal perfusion pressure in the stenosed kidney leads to activation of RAAS. Activated RAAS (increased AII and aldosterone) increases systemic BP to restore renal perfusion pressure and sodium retention.
- The normal contralateral kidney undergoes pressure natriuresis to restore sodium and volume balance, thereby counteracting the stenosed kidney’s

attempt to improve its own perfusion. The continued RAAS activation by the stenosed kidney leads to AII-dependent HTN and aldosterone-induced renal K^+ and H^+ secretion, hence hypokalemia and metabolic alkalosis.

- HTN seen with unilateral stenosis is, therefore, driven by activated RAAS (increased AII and aldosterone) and associated hypokalemia and metabolic alkalosis.
- Clinical implication for unilateral RAS:
  - RAAS inhibition is expected to be effective in reducing BP.
  - RAAS inhibition also enhances lateralization with nuclear testing by reducing GFR in the stenotic kidney (Captopril renal scan).
- Conditions equivalent to unilateral stenosis:
  - Unilateral FMD, atherosclerotic disease, renal artery aneurysm/dissection, renal artery trauma or occlusion by embolus or thrombus, arteriovenous fistula, vasospasm
  - Arteriovenous fistula
  - Aortic dissection affecting renal ostium; aortic stent occluding origin of renal artery
  - "Page" kidney (perinephric compression, i.e., large capsular hematoma, perinephric fibrosis)
  - Extrinsic compression (e.g., tumor) on a renal artery

Pathogenesis of bilateral RAS and clinical implications

- Both kidneys are exposed to reduced pressures from the bilateral stenosis.
- There is no "normal nonstenotic kidney."
- Initial activation of SNS and RAAS leads to sodium and water retention. Because there is no "normal kidney" to excrete the sodium and volume retained, volume overload eventually develops, which leads to inhibition of RAAS.
- Unlike bilateral RAS, HTN in bilateral RAS is dependent on volume, not RAAS.
- Clinical implications:
  - Patients can be highly salt sensitive and easily develop "flash pulmonary edema"; example: pulmonary edema may occur following a weekend of

high salt diet.

  - Diuretics may, therefore, be more effective as primary agent in lowering BP than RAAS inhibition in patients with bilateral RAS. However, RAAS inhibitors may be effective after euvolemia has been achieved (i.e., RAAS activation recurs after the negative feedback from volume expansion has been removed).
  - Because RAAS is inhibited by volume expansion, patients with bilateral renal stenosis or equivalent typically do not develop hypokalemia and metabolic alkalosis. In fact, the opposite, hyperkalemia and metabolic acidosis, may be present.
- Clinical conditions equivalent to bilateral RAS:
  - Bilateral arterial stenosis, anomalies or stenosis/anomaly of solitary kidney
  - Significant coarctation of aorta or any flow-limiting lesions (e.g., atheroembolic disease, aneurysms, extrinsic mass compression) of suprarenal abdominal aorta
  - Renal artery vasculitis

Fibromuscular dysplasia (FMD)

Background

- FMD is a nonatherosclerotic arteriopathy affecting large- and medium-sized arteries, typically mid- to distal vessel beyond the first 2 cm from aorta (**Fig. 5.3**)

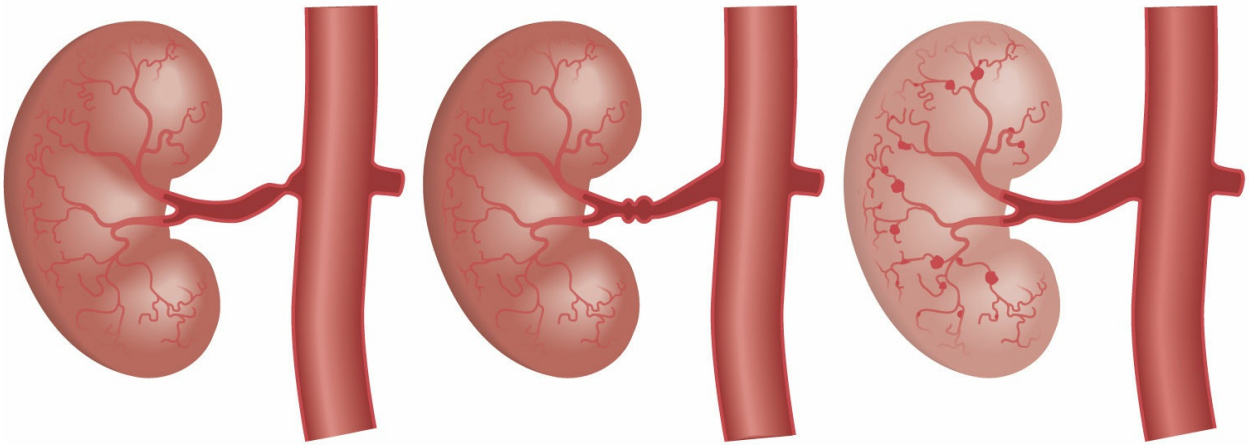


FIGURE 5.3 Renal artery stenosis, fibromuscular dysplasia, polyarteritis nodosa. Renal artery typically occurs within 2 cm from the aorta. Fibromuscular dysplasia typically occurs at the distal half to third of

the renal artery. Polyarteritis nodosa occurs within the kidneys.

- Lesions are characterized by disruptions of vascular wall components with abnormal collagen deposition in bands with or without disruption of elastic membrane.
- FMD may present with aneurysms, occlusion, dissection, arteriovenous fistulas, or thrombosis.
- FMD types:
  - Medial (85% to 100%) > intimal (<10%) > adventitial (<1%)
  - Medial and perimedial fibroplasia classically have “string-of-beads” appearance. Medial *hyperplasia* may only present as smooth stenosis of artery.
  - Intimal and adventitial fibroplasia present as smooth stenotic segments or diffuse attenuation of vessel lumen.

Epidemiology

- Prevalence of clinically significant renovascular FMD is 4/1,000, cerebrovascular involvement 1/1,000 (may present with carotid flow abnormalities, stroke); may be seen in up to 3% to 6% in normotensive individual.
- Familial presentation in 10% of cases, which is thought to be autosomal dominant

Clinical manifestations

- Commonly seen in young (15 to 50 years old) females with early-onset HTN
- Associated conditions: Marfan and Ehlers–Danlos syndromes, tuberous sclerosis, cystic medial necrosis, coarctation of aorta, Alport syndrome, renal agenesis or dysgenesis, α1-antitrypsin deficiency, medullary sponge kidney, pheochromocytoma (PHEO), infantile myofibromatosis, ergotamine preparation, methysergide, cigarette smoking, collagen III glomerulopathy, atherosclerotic renovascular disease

Natural history

- Progression of disease slows down with age.

- Rarely causes ischemic kidney failure, but associated thrombosis or dissection of affected renal vessel may lead to renal infarction

Management of FMD with HTN

- Invasive intervention may include percutaneous transluminal renal angioplasty (PTRA) or surgical revascularization.
- Percutaneous transluminal renal angioplasty (PTRA):
  - Higher chance of BP lowering following PTRA in younger patients or those with lower pre-PTRA BP, shorter duration of HTN, and positive captopril test.
  - If restenosis occurs, repeat PTRA may be performed as needed.
- Surgical revascularization:
  - If aneurysmal dilations >1.5 cm in diameter
  - Covered stent grafts may also be used in renal artery aneurysms.

Atherosclerotic renal artery stenosis

- Atherosclerotic plaque formed from the first 1 to 2 cm of renal artery or from aorta extending into renal ostium (more proximal involvement compared with FMD)

Epidemiology

- Seen in 10% to 40% of patients undergoing coronary angiography
- Similar prevalence in African Americans and Caucasians in one study cohort involving 870 patients >65 years old
- Autopsy series: prevalence of 4% to 20%; 25% to 30% in those >60 years old, 40% to 60% in those >75 years old
- Estimated to contribute to kidney function decline in 15% to 22% of patients with ESKD

Clinical diagnostic clues for atherosclerotic RAS

- Asymmetric kidney sizes
- AKI following use of ACEI or ARB due to acute reduction in intraglomerular filtration pressure: This is due to the loss of AII-dependent efferent vasoconstriction to maintain intraglomerular filtration pressure.
- AKI following acute systemic BP reduction with any other hypertensive

agents: This is due to the loss of the minimal renal artery pressure required to maintain glomerular filtration.

- Flash pulmonary edema, more common in bilateral stenosis
- Consider renal artery stenosis in patients with known or at increased risks for atherosclerotic disease and unexplained kidney function decline.

Management of atherosclerotic RAS

- Medical therapy:
  - Diuretics if volume overloaded
  - RAAS inhibition as safely tolerated (serum creatinine increases <20% to 30% from baseline is acceptable.)
  - Use of other agents as needed to control BP
  - Daily aspirin
  - Statin as tolerated, particularly if hyperlipidemia and/or CKD and >50 years old
  - Smoking cessation if applicable
- Invasive therapy:
  - There is no evidence of renal or CV benefits with invasive therapy if kidney function is stable and BP is medically controlled.
  - CV Outcomes of Renal Atherosclerotic Lesions (CORAL) trial: comparative trial for renal artery stenting versus best medical therapy involving 947 patients with uncontrolled HTN and *atherosclerotic* RAS, BP >155 mm Hg while on >2 antihypertensive drugs
    - Average SBP was 2.3 mm Hg lower in the stent group throughout the trial (median follow-up 3.6 years).
    - No difference in incidence of CV or renal death, MI, hospitalization for CHF, stroke, progressive CKD, or need for renal replacement therapy
  - Meta-analysis of five RCTs involving 1,159 patients comparing percutaneous renal artery revascularization (with or without stenting) versus medical therapy on future occurrence of nonfatal MI: Renal revascularization did not affect risk of nonfatal MI.
  - However, invasive therapy may be considered in younger viable (low

comorbidities) patients with:
  - Rapidly progressive disease (i.e., AKI with RAAS inhibition or achievement of BP control)
  - Failure to achieve BP despite being on appropriate medical therapy
  - Unexplained acute "flash pulmonary edema"
- Renal artery stenting versus surgical revascularization: Surgical revascularization is reserved for patients with technically challenging vascular lesions or associated aortic disease.
- Contraindications to invasive therapy: advanced kidney disease (e.g., SCr > 3 to 4 mg/dL, kidney length < 8 to 8.5 cm for an average height patient), poor surgical candidate, or low life expectancy.

NOTE

- Atherosclerotic RAS typically affects the proximal 1 to 2 cm of the renal artery from aorta, FMD involves the distal half to third of the renal artery, and polyarteritis nodosa involves multiple aneurysmal dilatations *within* the kidneys (**Fig. 5.3**).

Most patients with renovascular HTN do not develop AKI with ACEI/ARB because

- In unilateral RAS, the normal contralateral kidney may still have adequate function to mask any reduced filtration pressure in the affected kidney by ACEI/ARB.
- In bilateral RAS, AII is suppressed due to sodium retention. Hence, ACEI/ARB do not directly reduce glomerular filtration pressure.
- Those with AKI with ACEI/ARB tend to have other additional source(s) contributing to reduced renal perfusion, for example, volume depletion, poor cardiac function.

Endocrinologic Disorders

Endocrine causes of HTN: from pituitary (acromegaly, Cushing disease) → thyroid (hypothyroid, hyperthyroid) → parathyroid (hyperparathyroid) → adrenal glands (pheochromocytoma, multiple endocrine neoplasia type 2 (MEN-2), adrenal hyperplasia, adenoma, or carcinoma, congenital hyperplasia)

Acromegaly

- Pituitary tumor producing excessive circulating growth hormone (GH).

Note: other GH-producing tumors: pancreatic, hypothalamic, breast, bronchial malignancies.

- More commonly seen in women and older patients
- Clinical manifestations: skull, hands, feet enlargement, excessive sweating, carpal tunnel syndrome, sexual dysfunction, DM, thyromegaly, thyrotoxicosis, headaches, visual field defects
- Pathogenesis of HTN:
  - Sodium retention with inappropriately normal to only minimally low renin and aldosterone levels and normal atrial natriuretic peptide
  - Others: GH-induced vascular hypertrophy with decreased vascular compliance, increased SNS, circulating Na^+-K^+-ATPase, associated hyperthyroidism
- Diagnosis:
  - Elevated plasma GH, especially in response to an oral glucose tolerance test
  - Others: plasma insulin–like growth factor I, lateral skull X-ray (thickened skull vault, enlarged frontal sinuses), magnetic resonance imaging (MRI) of the pituitary fossa
- Management:
  - Transsphenoidal adenomectomy is the treatment of choice if possible.
  - Tumor radiation
  - Dopaminergic agents: bromocriptine and cabergoline, octreotide
  - HTN: diuretics as primary agent, addition of others as needed

Cushing disease and syndrome

- Cushing disease refers to pituitary adenoma producing excess adrenocorticotropic hormone [ACTH]; Cushing syndrome refers to excess ACTH produced by sources other than pituitary, e.g., adrenal tumors, bronchogenic carcinoma.
- Excess cortisol state is associated with HTN, DM, coagulopathy, CVD, infections, and fractures.

Pathogenesis of HTN

- Increased cardiac output and peripheral vascular resistance

- Concurrent production of mineralocorticoids
- Cortisol inhibition of NO
- Increased sensitivity to catecholamines, AII, and β-adrenergic stimulation
- Blunted response to atrial natriuretic peptide

Diagnosis

- Endocrine Society (ES) recommends using at least two of three different screening tests: 24-hour urine free cortisol excretion, late-night/bedtime salivary cortisol levels, and the 1-mg overnight dexamethasone suppression test (DST) or, alternatively, the 2-mg 2-day DST.
- Once hypercortisolism has been established, proceed to further testing to determine source, that is, ACTH dependent (pituitary, ectopic) or ACTH independent (primary adrenal).
  - Measure ACTH
  - If ACTH level is low or undetectable, obtain CT or MRI of the adrenals.
  - If normal or high ACTH levels, obtain pituitary MRI, inferior petrosal sinus sampling, corticotropin-releasing hormone, and/or 8-mg DST.
- Simultaneous bilateral inferior petrosal sinus sampling for ACTH measurements

Management

- Cushing disease:
  - Resection of pituitary adenoma
  - Medical therapy: Agents that target proopiomelanocortin transcription factors may be used to reduce ACTH production. These agents include somatostatin analog (pasireotide), dopamine analog (cabergoline), or retinoic acid (more data needed).
- Cushing syndrome:
  - Unilateral adrenalectomy if adrenal adenoma
  - Medical therapy: steroidogenesis inhibitors (metyrapone, ketoconazole, [possibly also fluconazole], mitotane), glucocorticoid-receptor antagonist (mifepristone), chemotherapy for adrenal carcinoma
- HTN: Consider potassium-sparing diuretics, specifically MRA.

Hypothyroidism

- Underlying mechanisms are thought to be due to reduced cardiac contractility and output and increased sodium retention.
- Hemodynamic alterations:
  - Bradycardia
  - Mild HTN with a narrow pulse pressure due to reduced cardiac contractility and output.
  - Elevated DBP is seen in ~30% of patients with overt hypothyroidism.

Hyperthyroidism

- HTN is thought to be due to increased cardiac output, heart rate, and myocardium contractility; volume expansion; and increased renin–angiotensin system activity (but not SNS).
- HTN may be associated with normal or high pulse pressure.

Hyperparathyroidism

- HTN is thought to be due to increased peripheral vascular resistance, presumably due to hypercalcemia.
- Parathyroidectomy has been reported to improve BP and reduce the number of antihypertensive medications in a 2012 literature review involving 88 patients.
- Data from the Atherosclerosis Risk in Communities seem to be conflicting:
  - Parathyroid hormone (PTH) levels were not independently associated with the risk of HTN.
  - However, elevated PTH may be associated with HTN in blacks.

Pheochromocytoma (PHEO)

- 90% arise from adrenals, 10% extra-adrenal (paraganglioma, PGL)
- Most are benign; 10% metastasize to regional lymph nodes
- Common hormones produced: norepinephrine, epinephrine, dopamine
- Malignant disease or large tumor mass may have very high dopamine levels.

Sporadic disease

- Often focal, unilateral involvement

- Up to 14% have somatic mutations

Familial disease (24% to 27% of adults with PHEO or PGL)

- Typically multifocal, bilateral, extra-adrenal disease, younger patients <50 years old, may be associated with germline mutations, mostly autosomal dominant.
- *RET* gene: Multiple endocrine neoplasia type 2 (MEN-2):
  - MEN-2a: Medullary thyroid carcinoma, hyperparathyroidism, cutaneous lichen amyloid; MEN-2b: medullary thyroid carcinoma, multiple neuromas, marfanoid habitus
  - Mostly epinephrine secretion
  - Paroxysmal symptoms
- von Hippel–Lindau gene: von Hippel–Lindau syndrome
  - Syndrome with retinal and central nervous system hemangioblastomas, renal cell carcinoma, pancreatic, endolymphatic sac, epididymal tumors
  - Predominant noradrenergic secretory pattern
  - Can present primarily with asymptomatic HTN due to downregulation of α-adrenoceptors
- Neurofibromatosis type 1 gene:
  - Neurofibromatosis type 1 (i.e., von Recklinghausen disease): neurofibromas, café-au-lait spots
  - Mostly epinephrine secretion
  - Paroxysmal symptoms
- Genes encoding the B- and D-subunits of mitochondrial succinate dehydrogenase (SDHB, SDHB): familial PGLs (head and neck) and PHEOs; no secretory activity; no symptoms related to catecholamines, but space-occupying effect
- Hypoxia-inducible factor 2α (HIF-2α), somatic mutation: multiple duodenal somatostatinomas, polycythemia

Common clinical manifestations of PHEOs

- Classic: paroxysmal HTN, headaches, diaphoresis, palpitations, anxiety, chest/abdominal pain, nausea/vomiting, dyspnea, pallor
- Severe HTN with trauma, delivery, surgical stress

- Catecholamine-associated cardiomyopathy (Takotsubo syndrome). Patients with PHEO-associated Takotsubo syndrome tend to present at a younger age with greater basal and global Takotsubo syndrome pattern and higher relapse rates compared to those who have acute Takotsubo syndrome.

Physical exam

- Two-thirds of patients present with labile HTN, one-third with persistent HTN; reciprocal changes in BP and heart rate may occur with predominantly norepinephrine secreting tumors; postural hypotension; low-grade fevers, tachycardia, skin may be cool, mottled appearing.

Biochemical diagnosis

- Plasma fractionated metanephrines (metanephrines and normetanephrines) greater than four- to fivefold of upper limit of normal suggests the presence of PHEO is highly probable (sensitivity of 97% and specificity of 93%). Plasma fractionated catecholamines (epinephrine, norepinephrine, and dopamine) testing is less sensitive, but levels >2 times upper limit of normal range are diagnostic.
- Acute illnesses and medications may increase levels of metanephrines and catecholamines (tricyclic antidepressants, antipsychotic agents, serotonin reuptake or norepinephrine reuptake inhibitors, and levodopa).
- If screening plasma fractionated metanephrines is highly positive (i.e., >4 to 5 times upper normal limit), localize tumor with either contrast-enhanced CT or T2-weighted MRI of entire retroperitoneum.
- If levels are in intermediate range (e.g., greater than upper normal range but not quite four to five times above upper normal limit), repeat testing, obtain both plasma and urinary fractionated metanephrines. Consider clonidine suppression test if repeat testing is equivocal. Administer 0.3 mg clonidine. Positive test: failure to reduce plasma catecholamines to >50% from baseline.

Imaging studies

- MRI or CT: abdomen/pelvis if no family history; neck to pelvis if family history or suspicion for genetic disease
- Functional testing may be used to evaluate for metastatic disease for the

identification of multiple chromaffin tumors.

- Functional testing may include: ^{123}iodine-labeled metaiodobenzylguanidine (MIBG) scan or positron emission tomography (PET)-CT scan with ^{68}Ga-labeled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-octreotate (DOTATATE) or ^{18} F-labeled L-dihydroxyphenylalanine (L-DOPA)

Management

- BP control:
  - α-Adrenergic blockers:
    - Initiate at least 7 days prior to surgery
    - First-line therapy: nonselective α-blocker phenoxybenzamine (start at 10 mg orally [po] twice daily [bid], titrate up to 30 mg three times daily [tid]) or
    - Selective α-blocker (doxazosin 1 mg qd, titrate up to 10 mg bid)
    - Note that phenoxybenzamine (PBZ) is an irreversible noncompetitive inhibitor of α-1- and α-2-receptors, whereas doxazosin (DOX) is a competitive inhibitor of α-1-receptor. Large surges of catecholamine release during surgical manipulation of the PHEO may overwhelm the competitive inhibitory effect of DOX. A randomized, multicenter, open-label clinical trial comparing the effect of PBZ and DOX on intraoperative hemodynamic instability (Phenoxybenzamine vs. Doxazosin in Pheochromocytoma Patients [PRESCRIPT]) involving 134 patients with nonmetastatic PHEO or sympathetic PGL revealed that treatment with PBZ or DOX starting 2 to 3 weeks before surgery resulted in 1) no difference in the duration of BP outside the target range during PPGL resection 2) PBZ was more effective in preventing intraoperative hemodynamic instability. However, whether this translated to better clinical outcome could not be established.
    - Liberalize sodium and fluid intake while on α-blockers.
  - Add BBs to control tachycardia or arrhythmias after BP has been controlled with α-adrenergic inhibition.

- Surgical removal:
  - Preoperative preparation: BP control as above
  - Intraoperative BP management options: phentolamine, sodium nitroprusside, and magnesium sulfate
  - Postoperative management: monitor for hypoglycemia and hypotension
  - Long-term management:
    - BP control if persistent HTN
    - If malignant PHEO, use both α- and β-adrenergic blockers as needed for symptoms, radiation therapy for bone metastatic disease, and chemotherapy (cyclophosphamide, vincristine, and dacarbazine).

Follow-up

- Biochemical profile (plasma or urine metanephrines) annually and imaging study every 1 to 2 years depending on risks. High-risk patients including young patients and those with genetic mutation, large tumor, and/or PGLs should be offered lifelong follow-up. For interested readers, review the European Society of Endocrinology Clinical Practice Guideline for long-term follow-up of patients operated on for a PHEO or PGL.

Adrenal incidentaloma/hyperplasia/adenoma/carcinoma

- Prevalence of primary aldosteronism (PA) is increased with increasing HTN severity.

Clinical manifestations

- Classic triad of HTN, hypokalemia, metabolic alkalosis may be present. Note, however, that hypokalemia is prevalent in only approximately 50% of patients with aldosterone-producing adenomas and 25% in bilateral adrenal hyperplasia. This is the rationale for PA screening in patients with severe HTN, regardless of serum potassium level.
- Hypokalemia and increased plasma aldosterone level may occur over time in patients with evolving PA. New-onset or worsening of existing hypokalemia should prompt reevaluation for PA.
- Increased risk of cardiac and cerebrovascular events and target organ damage involving kidneys and heart may be observed in patients with PA relative to those with essential HTN. The increased risk is thought to be

related to the elevated aldosterone level per se and independent of BP control.

Screening for PA

- Per the ES Clinical Practice Guidelines, screening for PA is recommended for patients with HTN and any one of the following:
  - Three sustained BP measurements >150/100 mm Hg obtained on different days
  - Difficult-to-treat HTN (defined in **Indications for Evaluation of Secondary HTN** section)
  - Spontaneous or diuretic-induced hypokalemia
  - Adrenal incidentaloma
  - Sleep apnea
  - Family history of early-onset HTN or cerebrovascular accident at a young age (<40 years old)
  - All first-degree relatives of patients with PA
- Screening for PA with plasma aldosterone level-to-PRA ratio (*ARR) (Table 5.2):
  - Liberalize sodium intake (minimum 5 g NaCl per day which is equivalent to 2 g Na/d) and replace potassium prior to ARR determination to reduce the chance of faulty results. Blood samples should be drawn at least 2 hours after getting out of bed in the morning.
  - Avoid the use of medications that can affect ARR *only if clinically safe*.
    - Withdraw 4 weeks prior to testing: diuretics, MRA
    - Withdraw 2 weeks prior to testing: BB, clonidine, methyldopa, NSAIDs, ACEI, ARB, direct renin inhibitors (DRIs), dihydropyridine CCB
    - Acceptable drugs to use during testing period: nondihydropyridine long-acting CCB (verapamil, diltiazem), hydralazine, α1-adrenergic receptor blockers (e.g., prazosin, doxazosin, terazosin)
    - If drug withdrawal along with substitution with “acceptable drugs” listed is not safe, interpret obtained ARR accordingly. See Funder et al. (2016).

- ARR cutoff level: In a 2005 publication by Tiu et al., an ARR cutoff of 23.6 ng/dL per ng/(mL·h) was shown to provide a sensitivity of 97% and specificity of 94%. A cutoff of 66.7 yields a sensitivity of 65% and specificity of 100%. "An ARR > 25 is suggestive of hyperaldosteronism if the aldosterone concentration is greater than 15 ng/dL" (ARUP Laboratories, 2019).

*In cases where plasma renin *concentration* instead of plasma renin *activity* is measured, an aldosterone-to-renin concentration (ARC) ratio is used. Cutoff level for ARC has been suggested to range between 26.35 and 59.66 ([ng/L]/[ng/L]). Note that with the use of DRIs, PRA is decreased, but the actual renin concentration is increased. The use of ARR in patients receiving DRI would thus yield falsely positive, whereas ARC would yield falsely negative results.

Confirmatory testing

- Confirmatory testing following positive ARR is mandatory for a definitive diagnosis of PA, *except* in the setting of undetectable PRA and aldosterone level >20 ng/dL, and spontaneous or diuretic-induced hypokalemia.
- See **Table 5.2** for confirmatory testing options.

Table 5.2 Evaluation of primary aldosteronism based on the Endocrine Society Clinical Practice Guideline

	Comments
Criteria for screening	• Sustained BP > 150/100 mm Hg on three separate BP measured on different days • BP not controlled on three antihypertensive drugs, including a diuretic • Controlled BP on four antihypertensive drugs, including a diuretic • HTN and any one of the following: spontaneous or diuretic induced hypokalemia, adrenal incidentaloma, sleep apnea, family history of early onset HTN or CVA at age <40 y old, first-degree relatives of patients with PA

Screening tests	• PAC (ng/dL) to PRA (ng/mL/h) ratio, referred to as aldosterone-to-renin ratio (ARR)[a]:
	  • In the setting of undetectable PRA and PAC >20 ng/dL and spontaneous- or diuretic-induced hypokalemia, no confirmatory testing is needed. → Proceed to adrenal CT or MRI.
	  • ARR >20 ng/dL/ng/mL/h. → Proceed to confirmatory testing.

Confirmatory	• Oral salt loading: Increase sodium intake to >200 mmol/d × 3 d and potassium

testing options (perform one or more)	supplement to maintain serum K level in normal range.[b] • Positive test: 24-h urine aldosterone measured on the morning of day 3 to morning of day 4 is >12–14 µg. Urine sodium should also be >200 mmol to assure compliance with sodium load. • Intravenous salt loading done at 8:00 to 9:00 am: infuse 2 L normal saline over 4 h (recumbent 1 h prior and during infusion or sitting for 30 min prior and during infusion).[b] • Positive test (recumbent)[c]: PAC > 5–10 ng/dL (<5 ng/dl in normal subjects) • Positive test (sitting)[c]: PAC > 6 ng/dL • Fludrocortisone-suppression test: Administer fludrocortisone acetate 0.1 mg po q6h with high-salt diet (3 mmol/kg/d) × 4 d and potassium supplement to maintain serum K level in normal range.[b] • Positive test[c]: Day 4, 10 am, in sitting position, PAC >6 ng/dL and PRA <1.0 ng/ml/h • Captopril challenge: Administer captopril 25–50 mg orally sitting or standing for ≥1 h.[d] • Positive test: After 1–2 h, PAC decreases ≤30% or ARR > 200 pg/mL/ng/ml/h.
Adrenal CT or MRI	• Assess for unilateral vs. bilateral disease
Adrenal vein sampling	• May be done if surgery is being considered to confirm affected side • Lateralization index > 8 confirms affected side and is associated with improved BP following surgical removal (see text for determination of lateralization index). • AVS is not necessary in young patients with unilateral adenoma by imaging study and marked PA.
Genetic testing	• Consider in patients with PA onsets at a young age (e.g., <20 y old), family history of PA, or strokes at a young age (e.g., < 40 y old)

[a]There is a lack of uniformity in diagnostic protocols and assay methods for measuring ARR ratios. Clinicians must review institutional units for measured PAC and PRA because these will affect the ratio cutoff values. Additionally, some centers may use plasma renin concentration rather than plasma renin activity, which also gives rise to different ratio cutoff values.

[b]Test should not be done in patients with heart failure, severe uncontrolled hypertension, severely reduced kidney function, cardiac arrhythmias, or severe hypokalemia. Clinical judgment is required.

[c]Plasma cortisol concentration following testing should be lower than the basal value at 7 am to exclude a confounding ACTH effect.

[d]Diagnostic sensitivity may not be optimal.

Abbreviations: ARR, aldosterone-to-renin ratio; AVS, adrenal vein sampling; BP, blood pressure; CT, computed tomography; CVA, cerebrovascular accident; HTN, hypertension; MRI, magnetic resonance imaging; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity.

For interested readers, refer to Funder JW, Carey RM, Mantero F, et al. *J Clin Endocrinol Metab*. 2016;101(5):1889–1916, for a full discussion of the evaluation of primary aldosteronism.

Imaging studies

- CT/MRI with adrenal cuts should be done following confirmatory testing.
- Adrenal carcinoma is more likely with increasing size; 2% of masses up to 4 cm, 6% of masses from 4 to 6 cm, 25% of masses >6 cm are malignant.

Adrenal venous sampling (AVS) for lateralization of hyperfunctioning gland

- *Confirm successful canalization of adrenal vein:* Cortisol levels at both the adrenal vein and inferior vena cava (IVC) are measured. An adrenal vein to IVC cortisol ratio, known as selectivity index (SI), of > 3 suggests successful adrenal vein catheterization. To improve sensitivity and specificity, consider adding a continuous infusion of cosyntropin at 50 mcg/h started 30 minutes prior to AVS. If cosyntropin is added, a ratio of > 5 is used as the cutoff.
- *Obtain aldosterone levels from both adrenal veins:* Since the aldosterone level may be diluted when it is collected further away from the adrenal gland, an aldosterone to cortisol ratio (A:C ratio) is used to correct for this effect. An A:C ratio is calculated for each side.
- *Calculate a lateralization index.* A lateralization index (LI) is defined as A:C ratio of suspected PA side divided by the A:C ratio of the contralateral side. An LI > 4 is suggestive of unilateral disease. An LI < 3 is suggestive of bilateral disease. an li > 8 has been shown to be significantly associated with BP improvement following adrenalectomy.
- NOTE: Prior to calculating LI, the SI from each side should be greater than 3:1 (if no cosyntropin is infused) or at least 5:1 (if cosyntropin is infused) for accurate interpretation.
- ES recommends AVS in good surgical candidates to confirm the correct side of the hyperfunctioning gland prior to removal.
- Young patients <35 years of age with spontaneous hypokalemia, marked aldosterone excess, and a unilateral adenoma on ct imaging do not need avs for lateralization.

Genetic mutations of PA

- Familial hyperaldosteronism type I (FH-I) (i.e., glucocorticoid-remediable aldosteronism [GRA] also known as dexamethasone-suppressible

hyperaldosteronism):

- FH results from the formation of a chimeric gene during uneven crossover during meiosis. The chimeric gene is made up of the 5′ end of CYP11B1 (encoding 11β-hydroxylase) and the 3′ end of CYP11B2 (encoding aldosterone synthase). The gene is expressed throughout the zona fasciculata as the promoter region is from CYP11B1 which is under the control of ACTH. Normally, aldosterone is only secreted transiently in response to ACTH because wild-type CYP11B2 is negatively regulated by elevated glucocorticoid levels, 5′ to its coding sequence. The chimeric gene lacks this negative regulation, thereby allowing sustained aldosterone secretion in response to ACTH.
- FH-I (GRA) may be treated with the lowest dose of dexamethasone.

- FH-II and in some patients with sporadic childhood-onset PA:
  - Germline heterozygous gain-of-function mutation in the voltage-gated chloride channel ClC-2. The associated increased chloride conductance at resting potentials results in increased expression of aldosterone synthase and aldosterone secretion.
- Familial hyperaldosteronism type III (FH-III):
  - Somatic mutation in the gene encoding the potassium channel KCNJ5 in one-third of adenomas (mutation in affected tissues only): Potassium selectivity of the channel is lost, thus allowing sodium influx through the channel and subsequent chronic cell depolarization. This leads to calcium influx thereby activation of aldosterone synthase and cell proliferation.
- Familial hyperaldosteronism type IV (FH-IV):
  - Somatic mutation in gene encoding the voltage-gated calcium channel CACNA1D can lead to increased calcium influx and subsequent activation of aldosterone synthase and cell proliferation.

Management

- Unilateral PA: adrenalectomy if surgical candidate
- Nonsurgical unilateral PA or bilateral PA:
  - MRA (e.g., spironolactone or eplerenone)
  - Selective aldosterone synthase activity blockers (RO6836191) are being

investigated clinically as these agents do not increase aldosterone levels and may confer better long-term end-organ protection compared with MRA. The latter increases plasma aldosterone levels.

- Surgical versus medical intervention:
  - Higher CV events, mortality, and atrial fibrillation may be associated with medical therapy compared with surgical intervention in longitudinal studies. Patient selection bias may be contributory to findings.
  - Worse CV outcomes appear to correlate with persistently suppressed PRA < 1 µl/l/h rather than the degree of bp control. mra titration to achieve pra > 1 µL/L/h rather than to target BP has been suggested.
  - 2015 meta-analysis revealed that reduction of left ventricular mass is not different in patients treated with adrenalectomy or MRAs.
- Genetic testing: Patients with disease onset < 20 years of age and patients with a family history of pa or stroke at age <40 years should undergo testing for gra (fh-i) and germline mutations in kcnj5.
- For other conditions with the clinical triad of hypokalemia, metabolic alkalosis, and HTN, see **Fig. 2.18**.

Acute intermittent porphyria (AIP)

- Rare autosomal dominant disorder with deficiency of porphobilinogen deaminase, the third enzyme in heme biosynthesis. AIP is associated with the accumulation of porphobilinogens (PBGs) and δ-aminolevulinic acid (ALA) and increased urinary excretion of ALA, PBG, and porphyrins.

Clinical manifestations

- More commonly affect women from the second to fourth decades of life
- Most affected individuals are asymptomatic.
- AIP may be activated following puberty during menstrual cycles (progesterone) or use of drugs such as rifampin, progestins, anticonvulsants, barbiturates.
- Symptoms may include intermittent severe colicky abdominal pain, constipation (may be misdiagnosed as intestinal obstruction), dystonic bladder with urinary retention/incontinence, reddish brown urine when

exposed to sunlight, autonomic dysfunction with increased circulating catecholamine levels, resulting in HTN, tachycardia, sweating, restless and tremors, peripheral neuropathy, proximal muscle weakness, neuropsychiatric disorders (hallucinations, delirium, flaccid paralysis, seizures), SIADH (syndrome of inappropriate antidiuretic hormone secretion) with hyponatremia. Skin rash is not a typical manifestation compared to other forms of porphyria.

- Attacks may be brought on by infections, hormonal or dietary changes/starvation, drugs, severe illness, infections, surgery, smoking, alcohol.

Diagnosis

- Elevated urinary PBGs (urine spot test)

Management

- Mild attacks: high-dose oral glucose (400 g/d) or IV dextrose 10% solution
- Severe attacks, severe neurologic symptoms: hematin (hemin) 4 mg/kg/d for 4 days
- Pain control with narcotics as needed
- Laxatives, softeners for constipation, particularly if narcotics are used
- Gabapentin for seizures

Miscellaneous

- Klotho gene deficiency has been suggested to play a role in HTN associated with aging. The decline in Klotho expression is associated with upregulation of adrenal CYP11B2 expression, a key rate-limiting enzyme for aldosterone synthesis.
- Shorter sleep duration and frequent interrupted sleep may be at increased risk for HTN.
- Coarse particulate from air pollution has been suggested to play a contributory role in HTN via interaction with pulmonary receptors and associated heightened SNS activity.

hypertensive emergencies

General Considerations

Definition

- Severe HTN, typically but not always with BP > 180/120 mm Hg, accompanied by acute and ongoing end-organ damage

Evaluation

- Underlying cause: acute head injury or trauma, complete (prescribed, over-the-counter, recreational) drug ingestion history, recent withdrawal of short-acting antihypertensive agents with known rebound phenomenon (e.g., clonidine, BBs), pregnancy state
- Signs and symptoms associated with end-organ injury: nausea/vomiting (increased ICP), dyspnea, chest pain, discomfort, acute severe back pain
- Physical examination: focus on CV and neurologic examinations, fundoscopy
- Laboratory testing:
  - Routine: ECG, urinalysis, routine chemistry with SCr, cardiac biomarkers (e.g., troponin I)
  - Imaging studies as indicated by signs/symptoms, including chest/abdominal CT, brain CT or MRI (transesophageal), echocardiogram

Clinical manifestations

- Eye: hypertensive retinopathy Grade III: Soft cotton wool exudates and flame-shaped hemorrhages. Grade IV: Grade III changes plus bilateral optic nerve edema
- Cerebrovascular: hypertensive encephalopathy, stroke, intracerebral or subarachnoid hemorrhage (cerebral infarction is the most common presentation ~40%)
- Cardiac: acute aortic dissection, left ventricular failure, or MI
- Pulmonary: pulmonary edema (~25%)
- Renal: microangiopathic hemolytic anemia, AKI
- Eclampsia (~2%)

Management of hypertensive emergency

General recommendations

- *Gradual* BP reduction is *generally* recommended:
  - MAP reduction by ~10% to 20% in the first hour, then by
  - An additional 5% to 15% over the next 23 hours, with
  - Total 24-hour BP reduction <25%.

Exceptions to gradual BP reduction over the first day

- Acute phase of ischemic stroke:
  - BP should *not be* lowered unless ≥185/110 mm Hg in candidates for reperfusion therapy.
  - BP should *not be* lowered unless ≥ 220/120 mm Hg for nonreperfusion therapy candidates.
- Acute aortic dissection: SBP should be lowered to target of 100 to 120 mm Hg **within 20 minutes** and heart rate reduced to <60 beats/minute to reduce aortic shearing.
- Acute intracranial hemorrhage:
  - For SBP ranging between 150 and 220 mm Hg, acute lowering of SBP to 140 mm Hg is suggested.
  - For SBP > 220 mm Hg, aggressive SBP lowering to 140 to 160 mm Hg is reasonable.

Maintain euvolemia

- Keep patient euvolemic to reduce further activation of the RAAS, with caution not to worsen HTN with excess sodium load.

Antihypertensive Medications Used in Hypertensive Emergencies

Nitrates: nitroglycerin, nitroprusside

- NO induces arteriolar and venous vasodilatation by activation of calcium-sensitive potassium channels (via cyclic guanosine monophosphate [cGMP]) in cell membranes.

Nitroglycerin

- Low antihypertensive effect
- Consider in patients with symptomatic coronary disease or following coronary bypass

- Limitations: methemoglobinemia possible with prolonged use (i.e., >24 hours); no cyanide accumulation

Sodium nitroprusside

- Onset of action: <1 minute; activity loss within 10 minutes of discontinuation
- Limitations: cyanide/thiocyanate toxicity: altered mental status, lactic acidosis that may occur within 4 hours
- Risks for adverse effects: high dose, prolonged use >24 hours, poor kidney function
- For high doses (i.e., 10 µg/kg/min):
  - Do *not* use longer than 10 minutes.
  - Add sodium thiosulfate as sulfur donor to detoxify cyanide into thiocyanate.
  - *Caution*: may lead to reduced coronary, renal, and cerebral perfusion

NOTE Sodium nitroprusside and nitroglycerin can potentially increase ICP and reduce cerebral perfusion.

Calcium channel blockers (CCBs)

Clevidipine

- Ultra-short–acting dihydropyridine CCB (half-life 1 minute)
  - Direct arterial vasodilator without altering venous capacitance that does not cause clinically tachycardia
  - Metabolized in blood and intravascular tissues by esterases, safe for both kidney and liver failure patients
  - Contraindicated in patients with aortic stenosis (potential severe hypotension), dyslipidemia (mixed in lipid-laden emulsion), and known allergies to soy or eggs

Nicardipine

- Longer onset of action and longer elimination half-life (3 to 6 hours)

Selective dopamine-1 agonist: fenoldopam

- Antihypertensive that can maintain or increase renal perfusion

- Avoid in patients with glaucoma and sulfite sensitivity
- Consider in patients with acute renal hypertensive emergencies

β-Blockers (BBs)

Labetalol

- Combined β- and α-adrenergic blocker, good for patients with acute coronary syndrome. Nonetheless, prior administration of α-blockers (e.g., phentolamine) should be done before using labetalol in patients with increased adrenergic states (e.g., PHEO, methamphetamine overdose, tyramine ingestion in patients on MAO inhibitor).
- Avoid in patients with asthma, chronic obstructive pulmonary disease (COPD), acute HF, 2° or 3° degree heart blocks and bradycardia

Esmolol

- Cardioselective BB with short half-life and duration of action (9 and 30 minutes, respectively)

Others

Hydralazine

- IV form (arteriolar vasodilator, with possible reflex sympathetic stimulation, i.e., tachycardia)
- Avoid in patients with coronary artery disease or aortic dissection

Enalaprilat

- IV form of enalapril, ACEI
- May cause excessive hypotension in hypovolemic patients

HTN in Special Situations

Reversible posterior leukoencephalopathy syndrome (PRES)

- Hypertensive syndrome associated with cerebral edema and symptoms of headaches, vomiting, confusion, seizures, cortical blindness
- Acute rise in BP results in dilatation of cerebral arteries and arterioles and increase in blood–brain barrier permeability, leading to brain edema.

Underlying causes

- Vasculitis (lupus), pregnancy (eclampsia), kidney failure, severe HTN.

PRES may occur in patients without elevated BP, as seen in some patients receiving immunosuppressive therapy or those with sepsis and multiorgan failure.

Diagnosis

- MRI revealing cortico-subcortical areas of hyperintensity involving the occipital and parietal lobes on T2-weighted images.

Management

- BP control and treatment of underlying diseases or withdrawal of offending agents
- Condition may be reversible, but blindness may persist.

Head trauma

- Treat if cerebral perfusion pressure (MAP − ICP) is >120 mm Hg and ICP is >20 mm Hg.

Hypertensive encephalopathy

- Diagnosis of exclusion when mental status improves following BP control
- BP may be lowered by 10% to 20% during the first hour, with a total of 25% lowering within the first 24 hours.
- Consider clevidipine, nicardipine, fenoldopam, nitroprusside.
- Goal: Decrease MAP by 15% to 20%.

Acute ischemic stroke

- Consider labetalol or nicardipine.
- Goal: Decrease MAP by 15% to 20%.

Acute hemorrhagic stroke

- Consider labetalol, nicardipine, or shorter acting drugs.
- See **Management** under **BP Goals** above.

Subarachnoid hemorrhage

- Consider labetalol, nicardipine, or esmolol.
- Goal: SBP < 160 mm hg or map < 130 mm hg

Acute HF

- Consider use of IV sodium nitroprusside, nitroglycerin, or enalaprilat to reduce afterload.
- Avoid hydralazine (can increase cardiac work) or BBs, such as labetalol (can decrease cardiac contractility).
- IV furosemide as needed for hypervolemia

Acute coronary syndrome

- Consider IV nitroglycerin, clevidipine, nicardipine, or esmolol/metoprolol to reduce myocardial oxygen consumption/ischemia.

Acute hypertensive nephrosclerosis, renal emergencies

- Renal ischemia activates the renin–angiotensin system, thus exacerbates the underlying HTN.
- Consider labetalol, nicardipine, or fenoldopam.

NOTE Fenoldopam is associated with a temporary improvement in renal function and may be useful in renal hypertensive emergencies.

- BP lowering may lead to worsening kidney function, particularly with the use of potent CCBs due to the potential vasodilating effect on afferent arterioles and subsequent transmission of systemic HTN into glomeruli.

Acute aortic dissection

- Administer an IV BB (e.g., esmolol, labetalol, metoprolol) to reduce HR to below 60 beats/min.
- Add a vasodilator (e.g., nitroprusside, clevidipine, or nicardipine) following HR control as necessary to achieve BP goal.

Ingestion of sympathomimetic agents

- Ingestion of tyramine-containing foods in patients on chronic MAO inhibitors, cocaine, amphetamine) or severe autonomic dysfunction (e.g., Guillain–Barré, Shy–Drager syndromes), acute spinal cord injury:
  - Administer IV phentolamine or nitroprusside.
  - Goal: symptomatic relief
  - The use of BBs is traditionally contraindicated due to unopposed α-adrenergic vasoconstriction and worsening of HTN. However, some

studies have suggested that mixed α/β blockers such as labetalol and carvedilol may be effective and safe in the setting of ingestion of sympathomimetic agents. Nonetheless, risks and benefits must be weighed for individual cases, and close monitoring is required. The nonselective BBs labetalol and carvedilol have predominant β-blocking activity with β-to-α blocking ratio of 7:1 or greater.

Autonomic dysfunction

- Guillain–Barré, multiple system atrophy syndromes, or acute spinal cord injury
- Consider phentolamine, nitroprusside, or labetalol.

Acute postoperative HTN

- Manage pain, anxiety; evaluate acute bleed at surgical site.
- Consider nicardipine, labetalol, or esmolol.
- Goal: Achieve preoperative BP.

pregnancy and hypertension

BP in normal pregnancy

Physiologic changes in BP during pregnancy

- DBP decreases by 7 to 10 mm Hg in early pregnancy, by as much as 20 mm Hg in mid-pregnancy. DBP returns to baseline by the third trimester. Nondippers during mid-pregnancy may indicate risk for preeclampsia.
- SBP only decreases slightly due to concurrent 30% to 40% increase in cardiac output and decrease in peripheral resistance.

BP categorization in pregnancy

- Normal BP: <140/90 mm hg
- Mild-to-moderate HTN: 140–159/90–109 mm Hg
- Severe HTN: ≥160/110 mm Hg
- Of note, SBP > 30 mm Hg or DBP > 15 mm Hg increase compared with BP prior to pregnancy, but <140/90 should be considered and managed as high-risk patients per us national high bp education program.

HTN in pregnancy

Chronic HTN

- Occurs before 20 weeks of gestation
- May be primary or secondary HTN

Gestational HTN

- Occurs de novo *after 20 weeks* and normalizes within 3 months postpartum
- Gestational HTN may or may not present as preeclampsia/eclampsia.

Preeclampsia/eclampsia

- Preeclampsia is a severe form of gestational HTN with end-organ dysfunction. The presence of neurologic complication with seizures defines eclampsia. This is thought to be due to a form of posterior reversible encephalopathy syndrome (PRES).
- The underlying pathogenesis of preeclampsia/eclampsia is discussed in **Chapter 11**.
- Of interest, a fall in uric acid clearance is a key feature of preeclampsia. Serum uric acid levels >5.5 mg/dL has been suggested to be a strong indicator of preeclampsia, and levels >7.8 mg/dL may be associated with increased maternal morbidity.
- Histopathology (**Fig. 5.4**) of kidney injury associated with preeclampsia/eclampsia: Glomerular tufts are described as “bloodless”; capillary lumina are narrowed due to endothelial cell swelling, referred to as “endotheliosis.” In contrast, capillary loops are wide open in normal glomeruli. Foam cells with lipid vacuoles may also be seen in this condition.

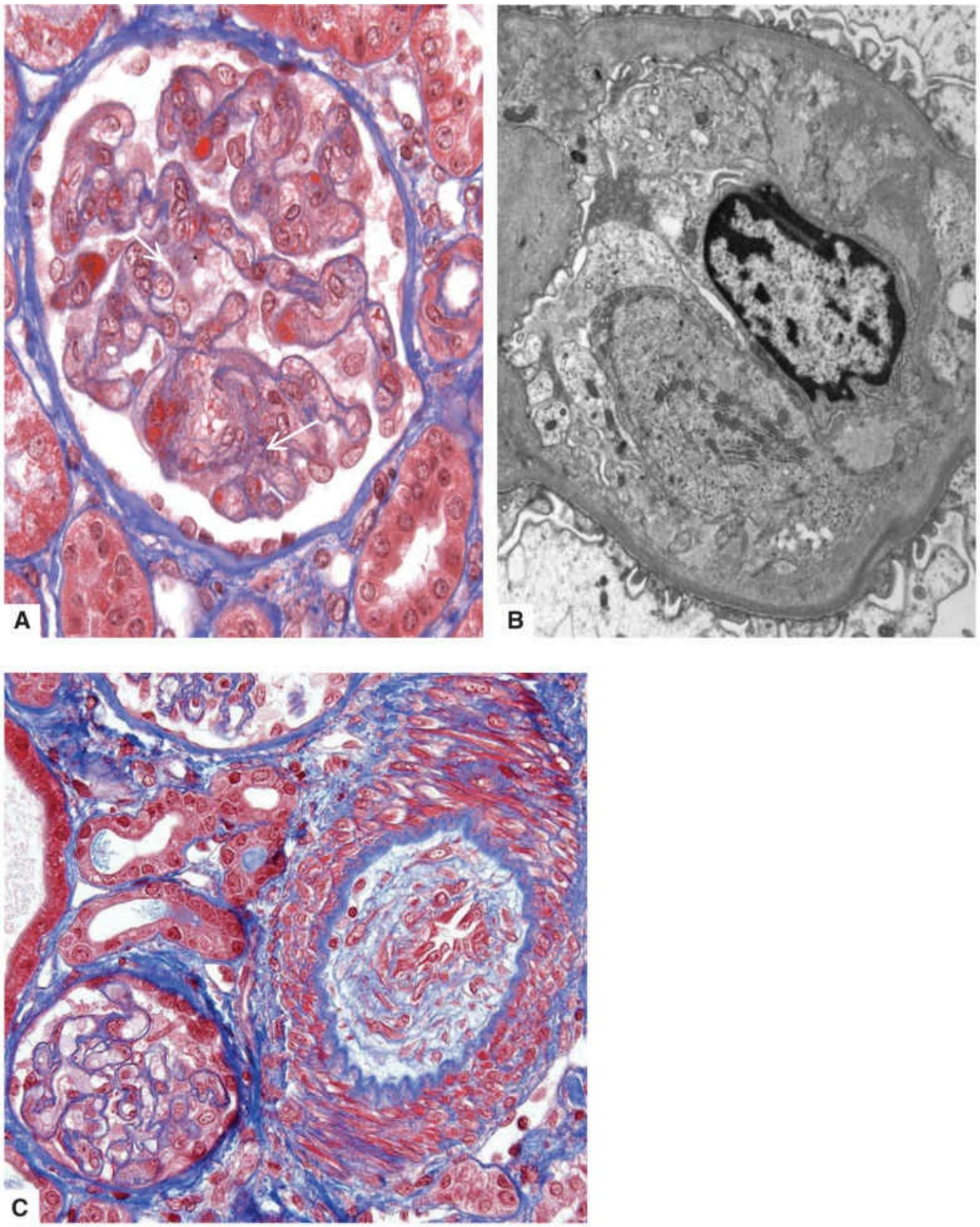


FIGURE 5.4 Histopathology of preeclampsia/eclampsia. **A.** Glomerular capillaries are filled with swollen endothelial cells, and, segmentally, there is luminal fibrin deposition (*arrows*). There is mild podocyte hypertrophy, and the adjacent arteriole is normal (Masson's trichrome ×500). **B.** Glomerular capillary with swollen endothelial cytoplasm resulting in luminal occlusion. Podocyte foot processes

are preserved, but may be effaced (×14,000). **C**. Large interlobular artery with marked loose mucoid intimal thickening, endothelial cell swelling, and luminal narrowing (Masson's trichrome ×250).

- Various forms/combinations of HTN seen during pregnancy are summarized in Table 5.3. Also see **Chapter 11**.

Table 5.3 Hypertension during pregnancy

	Onset	Proteinuria	Other Abnormalities	Comments
Chronic HTN	Prior to 20 wk gestational age	±Yes, prior to 20 wk	ECG or echocardiographic evidence of LVH	Absence of BP nadir during second trimester or presence of secondary HTN increase risk of preeclampsia/eclampsia
Preeclampsia/ eclampsia	After 20 wk gestational age	±Yes, after 20 wk[a]	↑LFT, ↑LDH, ↑uric acid, ↓serum albumin, hemolysis, thrombocytopenia	Worse prognosis with BP >160/110 mm Hg, oliguria, platelet count $<100 \times 10^9$/L, LDH > 600 IU/L, elevated LFT, pulmonary edema, neurologic symptoms, uric acid > 7.8 mg/dL increased risk of maternal morbidity
Chronic HTN with superimposed preeclampsia/ eclampsia	HTN throughout pregnancy, worse after 20 wk	±Yes, prior to 20 wk, worse after 20 wk[a]	Same as with preeclampsia	
Transient/ gestational HTN	During or within 24 h postpartum, resolves within 3 mo	Minimal if present	No evidence of acute end-organ damage	May predict increased risk of permanent HTN

[a]Patients most often will develop new proteinuria with preeclampsia. New-onset hypertension in the absence of proteinuria is diagnosed as preeclampsia if patients present with any of the following severe features: thrombocytopenia (platelet count < 100,000 × 10^9/l); impaired liver function (transaminitis to twice upper limit of normal range); severe persistent right upper quadrant or epigastric pain not accounted for by alternative diagnoses; reduced kidney function (serum creatinine > 1.1 mg/dL or doubling of serum creatinine in the absence of other kidney disease); pulmonary edema; new-onset headache unresponsive to medication and not accounted for by alternative diagnoses; visual disturbances.

Abbreviations: BP, blood pressure; ECG, electrocardiogram; HTN, hypertension; LDH, lactate dehydrogenase; LFT, liver function test; LVH, left ventricular hypertrophy.

Management of Hypertension in Pregnancy

See **Figure 5.5**.

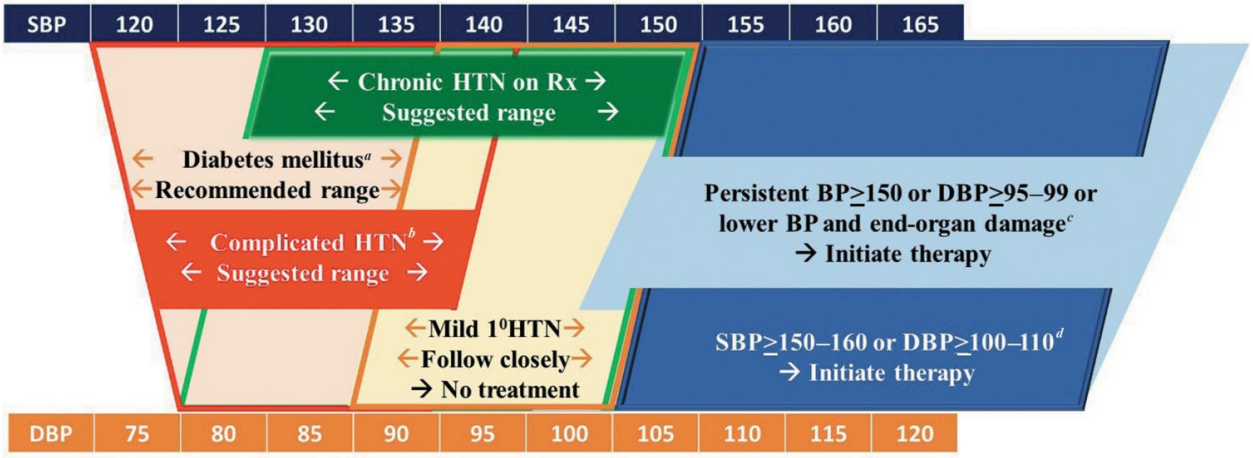


FIGURE 5.5 Blood pressure goals in pregnancy.

[a]Per American Diabetes Association.

[b]Complicated HTN include secondary HTN or HTN with increased cardiovascular risks.

[c]For chronic hypertension not yet on antihypertensive therapy.

[d]For new-onset HTN during pregnancy: Higher BP range (160/110 mm Hg) for initiation of antihypertensive therapy is per recommendation by The American College of Obstetricians and Gynecologists. Lower BP range (150/100 mm Hg) is per expert opinion.

Abbreviations: 1° HTN, primary hypertension; BP, blood pressure; DBP, diastolic blood pressure; HTN, hypertension; Rx, antihypertensive medications; SBP, systolic blood pressure.

Unless otherwise indicated, suggested ranges are based on August P. Use of antihypertensive drugs during pregnant and postpartum women. *UpToDate*. www.uptodate.com/contents/management-of-hypertension-in-pregnant-and-postpartum-women. Accessed March 12, 2020.

Chronic HTN

- For patients with uncomplicated HTN and already receiving antihypertensive medications:
  - Goal BP is in the range of 130–150/80–100 mm Hg.
  - Continue prepregnancy antihypertensive medications, except ACEI/ARB.
  - Diuretics continuation is acceptable, especially in salt-sensitive patients.
  - Adjust medications to achieve goal BP range.
- For patients with uncomplicated mild primary HTN, BP in the range of 140–150/90–100 mm Hg, follow closely without initiating medical therapy.
- For patients with persistently elevated SBP ≥150, DBP in the range of 95 to 99 mm Hg, or lower BP but with evidence of end-organ damage, initiate medical therapy.

- For patients with complicated HTN, secondary HTN, or HTN and increased CV risks, treatment goal is in the range of 120–140/80–90 mm Hg.
- For patients with DM, the American Diabetes Association suggests treatment for BP persistently elevated >135/85 mm Hg with treatment goal not dipping below 120/80 mm Hg.

New-onset HTN

- Rationale for treatment:
  - Treatment of severe HTN reduces maternal stroke risk.
  - Benefits of treating mild-to-moderate HTN developed over the short duration of pregnancy are not clear but may be associated with reduced placental perfusion and increased risk for fetal harm.
  - When to treat:
    - Treat when SBP ≥ 160 mm Hg or DBP ≥ 100 to 110 mm Hg, even with SBP < 160 mm hg.
    - For moderate HTN, individualize therapy based on maternal risk for cerebrovascular complications or evidence of target organ damage.
  - BP goals for patients receiving antihypertensive therapy: 130–150/80–100 mm Hg
- Common agents to treat nonsevere HTN in pregnancy:
  - Methyldopa: 250 to 500 mg bid to qid, maximum 2 g/d
  - Labetalol: 100 to 400 mg po bid to tid (maximum 1,200 mg/d)
  - Nifedipine, extended release, 30 to 60 mg po daily to bid
- Common agents used to treat severe HTN, BP ≥ 160/100 mm Hg
  - Labetalol (IV, then switch to oral): Avoid in asthma or HF. Inform neonatologist regarding possible neonatal bradycardia, risk of hypoglycemia.
  - Hydralazine (IV or intramuscular): may increase risk of maternal hypotension
  - Nifedipine (oral): associated with reflex tachycardia
- Other treatment options for severe HTN:
  - Nitroglycerin

- Diazoxide (1.5 mg IV) may be comparable to hydralazine (5 mg IV). Note however, a Cochrane systematic review published in 2013 suggested that diazoxide should probably be avoided, given higher risk of hypotension and cesarean section compared with labetalol.

Preeclampsia

- Control BP with agents suggested for HTN in pregnancy above
- Goal BP is in the range of 130–150/80–100 mm Hg.
- Diuretics should *not* be used in preeclampsia/eclampsia. Similarly, salt restriction is not recommended in preeclampsia/eclampsia.
- Magnesium sulfate:
  - May lead to a transient decrease in BP at 30 minutes following 2 to 5 g IV dose
  - **Note:** Magnesium has a synergistic hypotensive effect with CCB (e.g., nifedipine): This effect may be reversed with IV calcium (i.e., 10 to 20 mL of 10% calcium chloride over 10 minutes, repeat up to four times every 20 minutes as needed).
- Hemoadsorption of sFLT-1 in the management of preeclampsia/eclampsia remains undefined at the time of this writing. (see **Chapter 11**).

Eclampsia

- Magnesium sulfate as suggested for preeclampsia
- Treat HTN with agents that do not cause cerebral vasodilation. Labetalol is acceptable. Nicardipine has favorable cerebral hemodynamic effects. Both hydralazine and nifedipine vasodilate cerebral vasculature. However, this should not be the sole criteria for antihypertensive medication selection.
- Captopril may be used for severe postpartum HTN if *no* breastfeeding.

Postpartum HTN

- Treat as per nonpregnant population with care to adjust medications based on breastfeeding safety.
- **Note:** The use of VEGF inhibitors (e.g., bevacizumab and sunitinib) may give rise to a clinical entity reminiscent of preeclampsia with severe HTN.

genetic causes of hypertension

Liddle syndrome

Pathogenesis

- Autosomal dominant, gain-of-function mutation in the β- and γ-subunits of ENaC in the collecting tubules
- The mutation is in the PY motif of ENaC, which is the peptide segment necessary for Nedd4-2-ligase enzyme to target for ubiquitination, a process required for ENaC cytosolic internalization and degradation. Mutations affecting the PY motif of ENaC interfere with ubiquitination by Nedd4-2. This results in an increase in the number of functioning ENaC on the apical membranes and increased Na^+ reabsorption.

Clinical manifestations

- Average age of onset is 15 years old but may occur in adulthood
- Affected patients present with HTN due to increased Na^+ retention, hyporenin/hypoaldosterone due to volume expansion, but with *hypokalemia* and *metabolic alkalosis*. The latter is due to facilitated renal K^+ and H^+ secretion in the collecting tubules via the favorable electrochemical gradient generated by enhanced ENaC activity. Not all patients present with HTN.
- Complications of long-standing HTN: kidney failure, CVD, stroke
- Family history may be notable for sudden death or stroke prior the age of 40 years.

Treatment

- Dietary sodium restriction and direct ENaC inhibitors such as amiloride and triamterene. Spironolactone is suboptimal indirect therapy and likely *ineffective* because Liddle syndrome is not due to aldosterone-induced upregulation of ENaC.

Familial hyperkalemic hypertension (FHH), also known as pseudohypoaldosteronism type II and Gordon syndrome

- This condition may be suspected in patients with spontaneous HTN in association with hyperkalemia, and metabolic acidosis with or without

hypercalciuria and osteoporosis.

- Rare autosomal dominant, heterogeneous syndrome
- Implicated mutations include with-no-lysine kinases 1 and 4 (WNK1, WNK4), Kelch-like 3 (KLHL3), and Cullin 3 (CUL3).

Clinical manifestations

- Electrolyte abnormalities occur as early as infancy and include hyperkalemia, metabolic acidosis, hypercalciuria (osteoporosis).
- HTN may not be detected until second to fourth decades. All patients will eventually develop HTN in adulthood.
- Kidney function is normal in most cases of FHH.
- Patients with FHH present with low plasma renin and low-to-normal serum aldosterone levels despite having normal adrenal function.

Pathogenesis

- Mutations involving WNK1, WNK4, KLHL3, or CUL3 can result in:
  - ↑NCC activity and ↑paracellular Cl^- reabsorption → ↑Na^+ reabsorption → *HTN*, volume expansion–induced hyporenin/hypoaldosteronism → *hyperkalemia*, *metabolic acidosis*
  - ↓ROMK apical expression and ↑paracellular Cl^- reabsorption → ↓K^+ secretion → *hyperkalemia*, reduced ammoniagenesis, *metabolic acidosis*
  - ↓TRPV5 expression and activity → ↓Ca^{2+} reabsorption in DCT/CT → *hypercalciuria* → *osteoporosis*
- The associated hyperkalemia and metabolic acidosis may be due to:
  - Both WNK1 and WNK4 affect paracellular Cl^- reabsorption. The increased paracellular Cl^- reabsorption with WNK1 or WNK4 mutations reduces lumen electronegativity beneficial for optimal K^+ secretion.
  - Increased NaCl reabsorption via NaCl cotransporter (NCC) in DCT leads to volume expansion, which inhibits RAAS thus hyporenin/hypoaldosterone. Hypoaldosteronism reduces K^+ and H^+ secretion.
  - Increased NaCl reabsorption in DCT leads to reduced Na^+ delivery to cortical collecting tubule, hence reduced Na^+ reabsorption via ENaC, followed by reduced K^+ and H^+ secretion.

- For interested readers, see **Suggested Readings** list for a review on the molecular genetics of FHH.

Treatment

- Chronic low dietary sodium restriction
- Thiazide diuretics

MISCELLANEOUS

Scleroderma Renal Crisis

Epidemiology

- Scleroderma renal crisis (SRC) occurs in 2% to 4% with limited disease (skin involvement *below* elbows and knees only).
- SRC occurs in ~5% to 10% of diffuse scleroderma (skin involvement *below and above* elbows and knees).

Clinical manifestations

- Typically presents early, that is, at diagnosis of scleroderma or 3 to 5 years after disease onset
- Predominant presentations:
  - Acute onset of moderate-to-severe hypertensive urgency/emergency and oliguric kidney failure
  - Accompanying features: hyperrenin, thrombotic microangiopathy (TMA), anemia, CHF, and/or hypertensive encephalopathy and retinopathy
  - 10% of SRC occurs without HTN. This may reflect low baseline BP, underlying cardiac dysfunction, or other reasons to be hypotensive at baseline. “Normotension” at SRC presentation could already be hypertensive for some of these patients.

Risks

- Older age, African American ethnicity, systemic HTN
- Positive anti-RNA polymerase III antibodies or antinuclear antibody speckled pattern (*not* anti-Scl70 or anti-U3RNP antibodies)
- Early diffuse scleroderma, rapidly progressive skin disease, arthralgia,

synovitis, and tendon friction rubs, pericardial effusion
- Glucocorticosteroid exposure

Diagnosis

Hypertensive SRC

- SBP > 140 mm Hg or DBP > 90 mm Hg, or a rise in SBP > 30 mm Hg or DBP > 20 mm Hg from baseline, *and*
- One of the following features: increase in SCr > 50% from baseline or > 120% of upper normal limit; proteinuria > 2+ by dipstick; hematuria > 2+ by dipstick or >10 red blood cells per high-power field (RBC/HPF); thrombocytopenia <100,000 platelets/μl; hemolysis; or hypertensive encephalopathy

Normotensive SRC

- Increase in SCr > 50% above baseline or SCr > 120% of upper normal limit, *and*
- One of the following features: proteinuria 2+; hematuria >2+ by dipstick or >10 RBC/HPF; thrombocytopenia <100,000 platelets/μl; hemolysis; renal biopsy with microangiopathy consistent with src; or hypertensive encephalopathy

Management of SRC

- ACEIs are first-line therapy. ARBs are *not* adequate as first line to control BP. Other agents may be added to achieve BP goal. BBs are preferably avoided, given the theoretical risk of reduced cardiac output during the state of high peripheral vascular resistance.
- Goal: Reduce SBP/DBP by 20/10 mm Hg/24 hours as needed.
- Risk reduction: Avoid prolonged (e.g., >3 months) high-dose (e.g., prednisone >7.5 to 15 mg qd) glucocorticoid
- Prophylaxis therapy:
  - None proven effective
  - Although ACEIs are first-line therapy for SRC, *prophylactic ACEI* may lead to *worse* outcome, including two times increased risk of death and higher likelihood or dialysis dependency. The reason for this

discrepancy remains undefined.

- ARB is *not* effective. There have been reports of patients developing SRC while receiving ARB.

Renal transplantation

- Effective and improve survival
- Patients should be on ≥2 years on dialysis before consideration for transplant due to high recovery rates.
- Recurrence of SRC <5% and more common in those with early native kidney loss due to src.
- Onset of SRC with microangiopathic features in patients receiving CSA has been reported. Whether this is CSA-associated TMA independent of SRC is not known.

Calcineurin Inhibitor–Induced HTN

- Calcineurin inhibitor (CNI)–induced HTN is thought to be multifactorial and includes afferent arterial vasoconstriction, leading to reduced GFR thus sodium retention, reduction of endothelium-derived relaxing factor and NO activity, increased production of the potent vasoconstrictor endothelin-1, activation of RAAS, and increased expression of the phosphorylated (active) form of the thiazide-sensitive NCC.
- CNI-induced salt-sensitive HTN in mice revealed increased NCC activity with phenotype similar to FHH/Gordon syndrome. Clinical manifestations include renal sodium retention (HTN) and potassium retention (hyperkalemia), renal tubular acidosis, hypomagnesemia, and/or hypercalciuria. Treatment with thiazide diuretics may be beneficial.

Orthostatic HTN

- SBP rise of > 20 mm Hg when standing (opposite of orthostatic hypotension)
- Prevalence estimated at 5% among older hypertensive patients from SPRINT data.
- Pathogenesis: Autonomic dysfunction with possible overlap with primary (essential) hypertension.

- Management:
  - No specific recommendations given due to lack of data.
  - Consider nighttime α-blocker doxazosin or central-acting α-agonist clonidine. α-blocker is used to inhibit the α-adrenergic vascular overactivity that is, at least in part, responsible for orthostatic HTN. Clonidine has central sympatholytic properties.
  - Use of daytime venous stock compression may be considered to prevent venous pooling and fluctuation in central venous return.

Orthostatic Hypotension

- SBP fall of > 20 mm Hg with standing from supine or > 15 mm Hg from sitting position
- Management goal: Maintain functioning patient, not achieving specific BP number.
  - Nondrug: increase fluid and salt intake, avoid getting up quickly or prolonged motionless standing, use of compressive waist-high stockings, raise head of bed by 6 to 9 inches, maintain active lifestyle.
  - Drug options: midodrine, fludrocortisone, and pseudoephedrine
    - If supine HTN: consider midodrine as-needed basis (prn).
    - If not supine HTN: consider fludrocortisone or midodrine prn. Combination therapy if necessary.
    - Droxidopa, a precursor of norepinephrine, is an oral vasopressor agent that has been approved by the US Food and Drug Administration in 2014 for the treatment of neurogenic orthostatic hypotension. Action onset and duration of action are 1 and 6 hours, respectively. Nighttime HTN may be significant in some patients.
- Both orthostatic hypotension and HTN are associated with an increased risk for CV events.

CHAPTER 6

Tubular, Interstitial, and Cystic Disorders

Phuong-Chi T. Pham, Monica Deshmuk, Cynthia C. Nast, Phuong-Truc T. Pham, Phuong-Thu T. Pham

RENAL TUBULAR DISORDERS AND FANCONI SYNDROME

Fanconi Syndrome

Proximal tubular dysfunction causing renal wasting of low-molecular weight (LMW) proteins, glucose, bicarbonate, phosphate, uric acid, carnitine, and others

Clinical Manifestations of Fanconi Syndrome

- Polyuria, polydipsia, tendency for volume depletion
- Glucosuria in the absence of hyperglycemia
- Low-level proteinuria due to inability of proximal tubules to reabsorb LMW proteins that are normally filtered
  - LMW proteinuria is known as “tubular proteinuria,” which typically totals <1.0 to 2 g/d and comprises of less than 25% albumin.
  - Examples of LMW proteins: amino acids, β2-microglobulin, cystatin C, retinol-binding protein, α1-macroglobulin
- Metabolic acidosis due to reduced bicarbonate reabsorption
- Hypophosphatemia (Phosphaturia is typically only seen in early disease.

Once new steady state has been achieved, the degree of phosphaturia matches intake.)

- Hypokalemia (likely due to high distal sodium delivery to ENaC and subsequent potassium loss; high potassium filtered load associated with acidemia)
- Hypouricemia due to hyperuricosuria
- Carnitine deficiency (Carnitine is required for the transport of fatty acids from cytosol into mitochondria during the breakdown of lipids for the generation of metabolic energy. Carnitine deficiency has been implicated in poor fatty acid metabolism, reduced antioxidant activities, poor glucose control, and osteoporosis.)
- Rickets, osteomalacia, and growth failure due to reduced proximal tubular $1,25(OH)_2D_3$ production due to reduced 1-α hydroxylase activity, chronic metabolic acidosis, and electrolyte disturbances related to calcium, phosphate, and magnesium

Conditions Associated With Fanconi Syndrome

Inherited conditions

- Cystinosis: Most common inherited condition associated with Fanconi syndrome; associated with defective tubular reabsorption of **C**ysteine, **O**rnithine, **L**ysine, and **A**sparagine, known as COLA. Two cysteine molecules can dimerize via a disulfide bond to form cystine, a poorly soluble molecule that can easily crystalize in tubular lumen to form stones.
- Others: galactosemia, hereditary fructose intolerance, tyrosinemia type 1, glycogenosis, Wilson disease (inherited disorder involving copper metabolism), oculocerebrorenal syndrome (i.e., Lowe syndrome, X-linked mutation involving the enzyme phosphatidylinositol-4,5-bisphosphate 5 phosphatase in the trans-Golgi network, associated with severe bilateral cataracts and hypotonia at birth), mitochondrial cytopathies

Acquired conditions

- Heavy metals: lead, cadmium, mercury, platinum
- Drugs: cisplatin, ifosfamide, imatinib, gentamicin, rifampin, expired tetracycline, tenofovir, adefovir, azathioprine, valproic acid, suramin,

streptozocin, ranitidine, nucleoside reverse transcriptase inhibitors including abacavir, didanosine, and lamivudine and both formulations of tenofovir (tenofovir disoproxil fumarate, tenofovir alafenamide)

- Other exogenous agents: glue sniffing, diachrome, some herbal medicines
- Dysproteinemias: multiple myeloma/light-chain nephropathy (most common condition associated with Fanconi syndrome in adults), amyloidosis, Sjögren
- Others: acute tubular necrosis (ATN), nephrotic syndrome, kidney transplantation

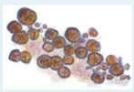
Crystalluria

Crystal nephropathy

- Drug precipitation/crystallization within renal tubules leads to microtubular obstruction and associated tubulointerstitial nephritis.
- Risk factors for drug crystallization: supersaturation of drug level in urine, volume depletion (low urine flow), urine pH, reduced levels of inhibitors for crystallization

Common inciting agents (Table 6.1)

Table 6.1 Drug-induced crystalluria

Crystals	Comments	Crystals	Comments
	**Sulfadiazine** • Resemble "shock of wheat," "bow tie" • Risks: dose > 4–6 g/d, urine pH < 5.5, volume depletion • Management: alkalinize urine > 7.15		**Methotrexate** • Risks: low urine pH, low urine flow • May also be nephrotoxic • Management: alkalinize urine to pH > 6.0, fluid support
	**Ciprofloxacin** • Needles, stars, fan-shaped crystals • Risks: older age, urine pH > 7.0 • Management: avoid use in older patients and concurrent use with alkalinizing agents		**Triamterene** • Risks: low urine pH • Spherical, brown crystals, may resemble Maltese crosses under polarized light • Management: use low dose with fluid support, alkalinize urine
	**Acyclovir** • Needles • Risks: rapid intravenous bolus therapy, volume depletion • Management: use low dose, slow infusion, normal saline support		**Calcium phosphate** • Oral sodium phosphate (bowel preparation) • Risks: volume depletion, use of RAAS inhibitors, diuretics, NSAIDs, high urine pH • Avoid use in CKD and the elderly
	**Indinavir (protease inhibitor)** • Other protease inhibitors also reported to cause crystal nephropathy **(darunavir, atazanavir)** • Management: fluid support		**Calcium oxalate crystals** • Crystals may take octahedral, dumbbell, or picket-fenced shape • Orlistat (inhibitor of gastric and pancreatic lipase, induces fat malabsorption), vitamin C, star fruit, rhubarb leaves, cranberry juice
	**Ampicillin** • Risks: high dose, acidic urine • Management: fluid support particularly with high dose		**Hippurate** • May be seen with toluene ingestion

Abbreviations: CKD, chronic kidney disease; NSAIDs, nonsteroidal anti-inflammatory drugs; RAAS, renin–angiotensin–aldosterone system.

- Drugs: sulfadiazine, ciprofloxacin, acyclovir, indinavir, atazanavir, darunavir, methotrexate, triamterene, orlistat, oral sodium phosphate, ampicillin, foscarnet, pseudoephedrine
- Natural sources: star fruit, rhubarb leaves, cranberry juice (oxalate); ma huang (ephedrine); djenkol beans (needle like)
- **Figure 6.1** shows tubular injury due to intraluminal crystals.

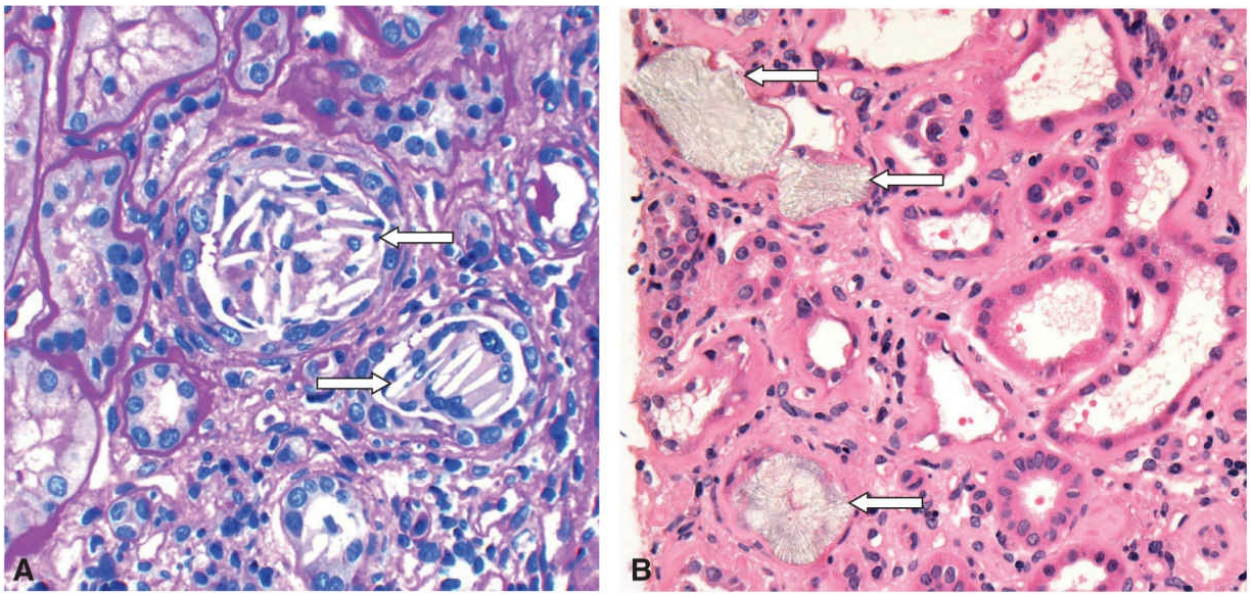


FIGURE 6.1 Tubular injury due to intraluminal crystals: **A.** Indinavir crystals are within the lumina of tubules (*arrows*) admixed with sloughed epithelium (periodic acid–Schiff ×400). **B.** There are clear to yellow crystalline aggregates of oxalate within tubular lumina (*arrows*) with tubular cell flattening, simplification and attenuation, and relative dilatation of tubular lumina (hematoxylin and eosin ×250).

- Most drug-induced crystal nephropathy resolves with drug withdrawal and supportive fluid support.

TUBULOINTERSTITIAL NEPHRITIS

Acute Interstitial Nephritis

Epidemiology of acute interstitial nephritis

- Acute interstitial nephritis (AIN) may be due to infections, drugs, or autoimmune diseases. Drug-induced AIN predominates all forms of AIN since the advent of antibiotics.
- Biopsy-proven AIN in all kidney biopsies reported globally ranges from 1% to 10%.
- Biopsy-proven AIN performed for acute kidney injury (AKI) ranges from 6.5% to 35%.

Pathogenesis of AIN

- Suggested role of the inciting agent:
  - Hapten: The inciting agent (i.e., drug [or infection]) binds to an otherwise nonimmunogenic native kidney protein (e.g., albumin or host

amino acid) and renders it immunogenic.
    - Prohapten: The inciting agent is a prohapten that becomes a hapten after it has been digested or metabolized by the host.
    - Pharmacologic interaction: The inciting agent binds to the host HLA molecules and is presented to T cells.
- Circulating immune complexes formed against the inciting agent deposit into the kidney interstitium and induce an inflammatory immunologic response that is:
    - Predominantly cell mediated: Kidney biopsy typically reveals predominant T-cell infiltrates in interstitium.
    - Less commonly antibody mediated:
        - Most biopsies do not reveal immune complex deposits.
        - In some cases, however, immune complex deposits may be seen in tubular basement membranes (TBMs).
- Of note, drug-induced AIN is idiosyncratic, unrelated to drug dose, host dependent, and recurs with re-exposure.

Clinical manifestations of AIN

- Classic triad of skin rash, leukocyturia, and fevers:
    - Not common, seen in <10% of cases
    - Classic triad is uncommonly seen in nonsteroidal anti-inflammatory drugs (NSAIDs)–induced AIN but may be commonly seen with antibiotic-induced AIN.
- AKI and subacute kidney injury:
    - Onset of kidney injury typically occurs within 10 to 20 days of exposure to the inciting agent but may occur within 2 to 3 days with re-exposure.
    - Kidney injury may be subacute and occurring over months.
    - De novo kidney injury from a medication previously tolerated may be observed.
- Abnormal urine sediment: leukocytes (50% to 60%), microscopic or gross hematuria (~50%), eosinophils (<50%), white blood cell casts (<5%), granular casts (<50% to 70%), low-grade tubular proteinuria <1 to 2 g/d (~90%)

- Eosinophiluria:
  - Eosinophiluria is not a sensitive marker for AIN:
    - Eosinophils may not shed into urine and/or lyse prior to visualization.
    - Not all causes of AIN have eosinophils in renal interstitium.
  - Eosinophiluria is not specific to AIN. It may also be seen with urinary tract infections, prostatitis, bladder malignancy, and glomerulonephritis.
  - The use of urine eosinophils to diagnose suspected AIN is not recommended, given its poor sensitivity and specificity.
- Proteinuria:
  - Non-nephrotic range
  - LMW proteinuria predominance
  - May be nephrotic if associated with NSAIDs use/concurrent glomerular disease
- Blood tests: elevated serum creatinine (S_{Cr}), leukocytosis with increased eosinophilia, anemia, elevated erythrocyte sedimentation rate, transaminitis. Antineutrophil cytoplasmic antibody (ANCA) may be positive without associated glomerular disease.

Histopathology of AIN (Fig. 6.2)

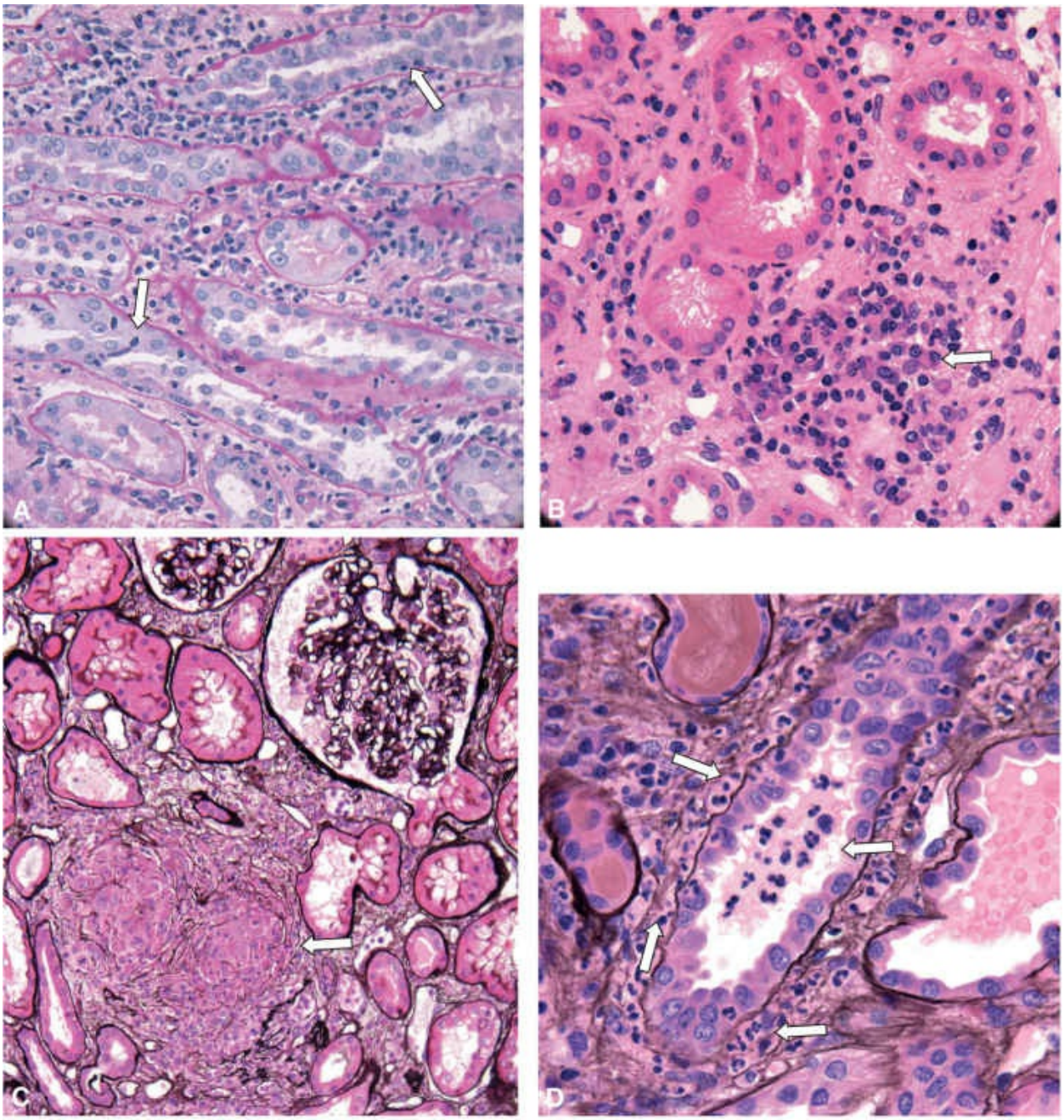


FIGURE 6.2 Acute tubulointerstitial nephritis. **A.** Lymphocytes are in the edematous interstitium and walls of tubules (*arrows*) with acute tubular cell injury (periodic acid–Schiff ×250). **B.** Interstitial edema and inflammation with prominent plasma cells (*arrow*) admixed with lymphocytes and plasma cells (hematoxylin and eosin ×350). **C.** Granulomatous interstitial nephritis. There is a non-necrotizing granuloma (*arrow*) in the interstitium composed of epithelioid histiocytes and multinucleated giant cells (periodic acid methenamine silver ×200). **D.** Neutrophils are in the interstitium (*arrows*) and tubular walls and lumen in infection (pyelonephritis) (periodic acid methenamine silver ×425).

Light microscopy

- Inflammatory infiltrates within the interstitium: Infiltrative lesions can be

diffuse, but are often patchy, predominating in the deep cortex and outer medulla. Inflammatory cells are primarily T cells and monocytes, macrophages, plasma cells, some eosinophils, and a few neutrophilic granulocytes.

- Tubulitis may be seen in AIN. Tubulitis refers to leukocytes and lymphocytes infiltration into tubular epithelium.
- Granulomas may be seen in AIN or chronic interstitial nephritis (CIN) associated with sarcoidosis, Sjögren syndrome, granulomatous polyangiitis, infections (e.g., tuberculosis, leprosy, histoplasmosis, xanthogranulomatous pyelonephritis), crystals/foreign bodies (e.g., urate, oxalosis, recreational drug impurities), medications (e.g., sulfas, synthetic penicillins, NSAIDs, thiazides, levofloxacin, checkpoint inhibitors; see **Causes of AIN: Drug-Induced** below).

Immunofluorescent (IF) microscopy and electron microscopy (EM)

- IF and EM are typically negative for immunoglobulins and C3.
- In some instances, antibodies may be formed linearly against antigens or drugs bound to TBM (e.g., methicillin, NSAIDs, phenytoin, allopurinol).
- Kidney biopsies from patients with AKI from Hantavirus infection may reveal granular immune deposits along the TBM and within glomeruli in 50% of cases.

Diagnosis of AIN

- Gold standard: kidney biopsy
- Urinalysis with abnormalities above
- Gallium scan:
  - Gallium binds to lactoferrin on white blood cells, originally thought to be specific to AIN, but later found to be positive in other conditions as well (e.g., glomerular diseases, pyelonephritis, atheroembolic disease).
  - Poor sensitivity and specificity and *not* recommended for the diagnosis of AIN
- *Future direction: measurement of urinary T-cell–derived cytokines (e.g., urine interleukin 19 [IL-9], tumor necrosis factor α [TNF- α]).*
  - *Elevated IL-9 levels may be seen in allergic conditions, including*

dermatitis, allergic asthma, food allergy.

- *IL-9 is produced from Th9 cells and leads to mast cell accumulation. Of interest, mast cells are seen in kidney biopsies of patients with AIN.*

Causes of AIN

Etiologies of AIN

- 70% to 75% is due to drugs.
- 10% is related to infections (more common in children and developing countries).
- 10% to 20% is due to autoimmune diseases, for example, sarcoid, Sjögren, systemic lupus erythematosus.
- 5% is associated with anti-TBM disease, tubulointerstitial nephritis and uveitis, and immunoglobulin G4 (IgG4)–related disease.
- <5% involves other causes including hereditary/toxic/metabolic conditions such as hyperoxaluria, heavy metal toxicity, hyperuricemia, hypercalcemia.

Drug induced

- Well-described drugs associated with AIN: antibiotics (β-lactams, sulfas , quinolones), NSAIDs including cyclooxygenase-2 (COX-2) inhibitors, proton-pump inhibitor (PPI), check point inhibitors, diuretics (with sulphonamide moiety, such as furosemide and thiazides).
- **NSAIDs and COX-2 inhibitors may induce kidney injury via various mechanisms:**
  - ATN due to acute afferent arteriolar vasoconstriction and resultant reduction in intraglomerular filtration pressure
  - Interstitial nephritis that may present as acute, chronic, or granulomatous disease
  - Papillary necrosis in patients with underlying ischemic renal disease (e.g., diabetes mellitus and associated arteriosclerosis, sickle cell disease)
  - Three-fourths of NSAIDs-induced AIN is associated with nephrotic syndrome and glomerular lesions, including minimal change disease, membranous nephropathy, and, less commonly, focal segmental

glomerulosclerosis (FSGS), membranoproliferative glomerulonephropathy. Risks include older age, chronic use, and use of fenoprofen.

- **Rifampin:**
  - Likely the *leading cause* of AIN/AKI among patients receiving therapy for antituberculosis, although pyrazinamide and isoniazid may also induce AIN
  - Patients may present with AIN and/or ATN.
  - Consider switching to levofloxacin (consult infectious disease specialist)
- **Allopurinol:**
  - Thought to be due to immunologic reactions between the metabolite oxypurinol with purines, ribonucleoproteins, and nucleic acids. Accumulation of oxypurinol increases with reduced kidney function. Dose reduction in chronic kidney disease (CKD) is recommended.
  - Clinical manifestations:
    - In addition to AIN and/or granulomas, patients may also develop toxic epidermal necrolysis, exfoliative dermatitis, or diffuse maculopapular rash, hepatic necrosis, and cholangitis.
- **Antihistamines:**
  - Suggested pathogenesis: Histamine stimulates a subset of suppressor T cells via H2 receptors. Blockage of H2 receptors may lead to increased cell-mediated responses.
  - Antihistamines associated with AIN include cimetidine, ranitidine, famotidine.
  - Of interest:
    - Cimetidine-induced AIN has also been reported to be associated with positive ANCA (against both MPO and PR3) serology.
    - Famotidine-induced AIN has been suggested to be due to autoantibody formation against carbonic anhydrase II.
- **5-Aminosalicylates (sulfasalazine, mesalamine, olsalazine):** AIN typically occurs within the first year of use.
- Aristolochic acid nephropathy (i.e., Chinese herb nephropathy):

First reported in Belgium where the use of slimming regimens containing aristolochic acid was used
- Balkan nephropathy is also thought to be associated with aristolochic acid.
- Affected patients may develop rapidly progressive interstitial nephritis, which can progress to end-stage kidney disease (ESKD).
- Associated with uroepithelial malignancy

- **Oxalate nephropathy:** ascorbic acid (vitamin C), star fruit, orlistat (induces malabsorptive state that promotes gastrointestinal [GI] oxalate absorption), rhubarb leaves
- **Checkpoint inhibitors:**
  - Checkpoint proteins are T-cell surface proteins that serve to dampen immune responses from T cells upon interaction with antigen-presenting cells. Checkpoint ***inhibitors*** allow T cells to remain "unchecked" in their active state to attack foreign antigens or tumor cells. Two checkpoint proteins that have been targeted in oncology include the cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and the programmed cell death protein 1 (PD-1). Inhibitors against these checkpoint proteins allow T cells to remain in their active state to fight tumor cells. The unchecked active T cells, however, can mount a more aggressive and/or sustained response to any presenting antigen including AIN-prone drugs or self- antigens associated with autoimmune diseases. That is, a subclinical AIN from a drug such as PPI may be unmasked as overt AIN during checkpoint inhibitor therapy for underlying malignancy.
  - AIN and/or granulomatous features have been reported with the use of CTLA-4 and PD-1 inhibitors:
    - CTLA-4 antagonist ipilimumab: AIN presents within 6 to 12 weeks after initiation of therapy and/or associated podocytopathy.
    - PD-1 inhibitors: nivolumab and pembrolizumab: AIN presents within 3 to 12 months following initiation of therapy.
  - Inflammatory responses involving other organs (e.g., thyroiditis, hepatitis, colitis, dermatitis, pancreatitis) may also occur with the use of checkpoint inhibitors.

- **Other reported drug-induced AIN:** liraglutide, varenicline, rosuvastatin, kudzu root (Japanese arrowroot) juice ingestion, B-rapidly accelerated fibrosarcoma oncogene inhibitors vemurafenib and dabrafenib (used for BRAF V600E mutation-positive melanoma, lung, colorectal carcinoma), linezolid, clindamycin
- **Drug reaction with eosinophilia and systemic symptoms (DRESS):**
  - Clinical manifestations: fevers, facial edema, skin lesions (diffuse macular/papular erythematous lesions with lymphocytic infiltrates, exfoliative dermatitis), lymphadenopathy, multiorgan inflammatory response (e.g., pneumonitis, hepatitis, AIN)
  - Laboratory findings: eosinophilia, lymphocytosis, elevated aminotransferase (ALT)
  - Reported responsible agents: phenytoin, phenobarbital, allopurinol, sulfonamides, dapsone, vancomycin, minocycline, raltegravir, vemurafenib, lenalidomide, β-lactams
  - Treatment: drug withdrawal, supportive care, steroids
- Infection related:
  - May involve various bacteria, viruses, parasites, atypical microorganisms, fungi
  - Granulomatous AIN may be seen, particularly with fungal, mycobacteria, and parasites.
  - AKI during treatment of infections may result from infection-related AIN, independent of antibiotic/treatment.

Glomerular disease–associated tubulointerstitial nephritis

- Nonselective proteinuria involving proinflammatory proteins and growth factors may induce peritubular inflammatory response, complement activation, and progressive interstitial fibrosis.
- Immunologic or autoimmune-mediated AIN:
- Associated with systemic diseases: sarcoid, Sjögren, tubulointerstitial nephritis and uveitis, (TINU), IgG4-related disease (see **Chronic Interstitial Nephritis** section), systemic lupus erythematosus, ANCA-associated disease, IgM plasma cell interstitial nephritis, primary biliary cirrhosis, others

- Tubulointerstitial nephritis and uveitis (TINU):
  - Inflammatory disease involving dysregulated T cells that affect both the eyes and the kidneys
  - Mechanism of disease is not known.
  - Commonly seen in young women
  - Clinical manifestations: painful red eyes (uveitis), AIN, possibly transaminitis
  - Treatment: prednisone 1 mg/kg/d × 3 to 6 months with slow taper. Addition of cytotoxic agent may be necessary (e.g., mycophenolate, calcineurin inhibitor).
- Primary renal AIN with tubulointerstitial immune complex deposits:
  - Anti-brush border antibody (ABBA) disease (also known as LRP2 nephropathy):
    - Rare ABBA condition with autoantibody directed against low-density lipoprotein (LDL) receptor–related protein 2 (LRP2 or megalin)
    - Abundant IgG4-positive plasma cells may be seen.
  - Idiopathic hypocomplementemic tubulointerstitial nephritis
  - Giant cell tubulitis with TBM immune deposits
- Primary renal AIN without immune complex deposits: anti-TBM nephritis

- Kidney transplant setting
  - AIN may occur due to acute rejection in allograft, immunosuppressive therapy, and infections, particularly polyomavirus BK nephropathy and adenovirus nephritis.
- Other causes of AIN
  - Heavy metals, herbal products, idiopathic

Prognosis of AIN

- Recovery depends on duration of drug exposure, duration of AKI, and severity of interstitial fibrosis and tubular atrophy.
- Recovery may take several weeks. 50% recover fully, whereas the other 50% will have elevated S_{Cr}.

Management of AIN

- Supportive, dialysis as needed
- Prompt removal of offending agent
- Role of glucocorticoids:
  - Optimal benefits:
    - Early initiation <7 days is most important.
    - Lower degree of fibrosis is associated with better response.
      - Expert opinion: Avoid steroids if >75% tubulointerstitial fibrosis on biopsy.
  - Optimal dose:
    - No consensus
    - Consider pulse intravenous (IV) methylprednisolone, 250 to 1,000 mg every day (qd) × 3 days, followed by prednisone 1 mg/kg/d (maximum 80 mg qd) × 3 months (ASN Annual Scientific Meeting, 2019, AIN session)— taper per response/discretion of treating physician due to side effects of high-dose steroids
    - May lead to prompt recovery *if given early*, but not necessarily overall outcome
  - Consider systemic glucocorticoids if severe systemic involvement (e.g., DRESS)

Chronic Interstitial Nephritis

Background

- CIN is characterized by tubulointerstitial scarring and fibrosis, tubular atrophy, with or without significant macrophage and lymphocytic infiltration.

Clinical manifestations of CIN

Patients are typically asymptomatic with incidental abnormal laboratory findings:

- Mild proteinuria <1.5 to 2.0 g/d
- Proteinuria predominantly consists of LMW proteins.
- “Bland” urinalysis: no (or rare granular) casts, minimal white and/or red

blood cells

- Anemia severity is out of proportion to the degree of kidney injury due to damage of peritubular erythropoietin–producing cells in chronic tubulointerstitial nephritis (CTIN).
- Other signs of tubular injury may be present: sodium wasting, metabolic acidosis, Fanconi syndrome, nephrogenic insipidus

Histopathology of CTIN (Fig. 6.3)

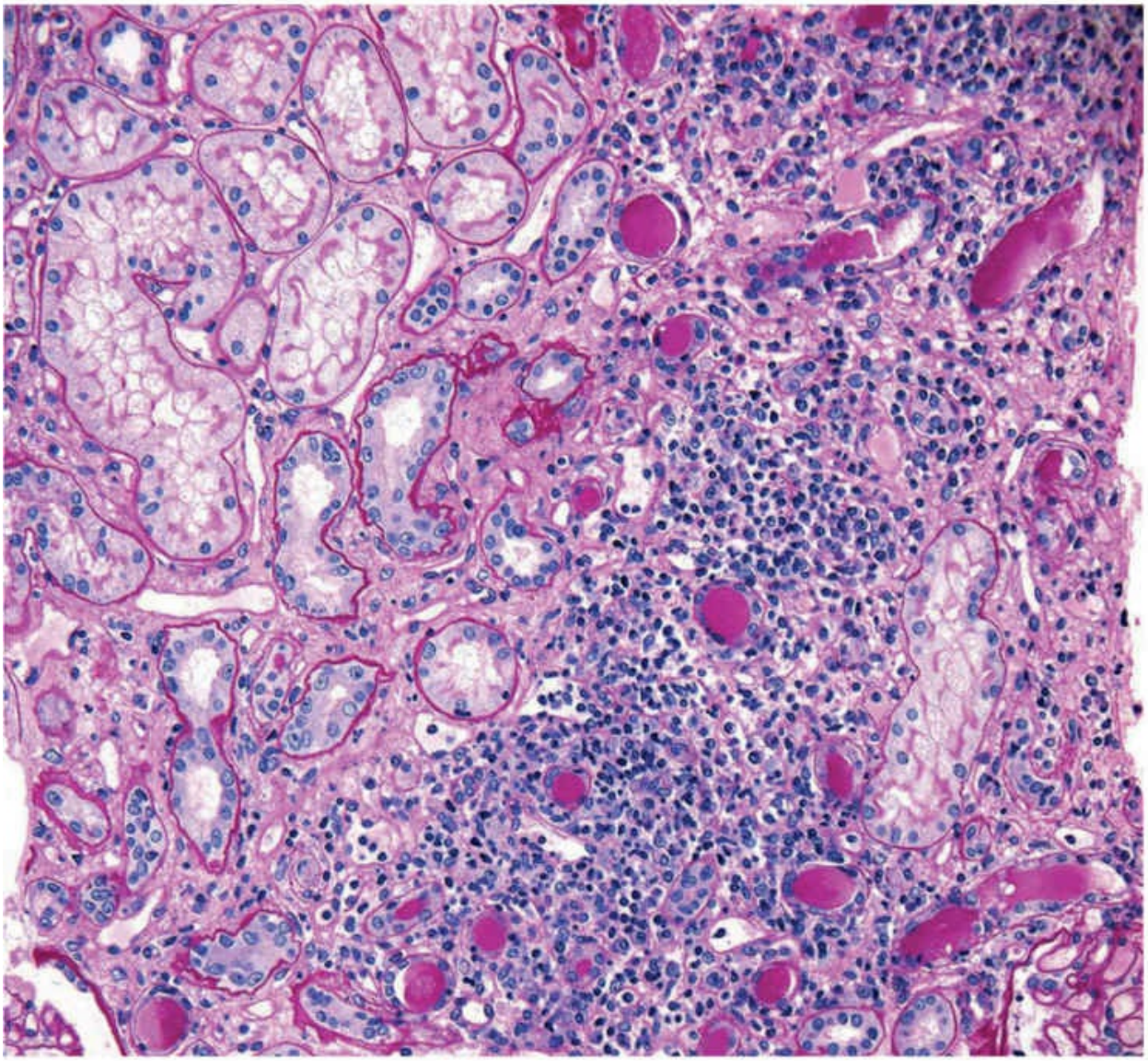


FIGURE 6.3 Chronic tubulointerstitial nephritis. The interstitium contains a lymphocytic infiltrate that is restricted to the area of interstitial fibrosis and tubular atrophy. Note the adjacent preserved tubulointerstitium in the upper left corner, in which there is no inflammation (periodic acid–Schiff ×250).

- Fibrotic hypocellular interstitium
- Tubular atrophy

Causes of CTIN

- Common causes (drugs, crystals [e.g., calcium phosphate, uric acid, oxalate], infections, autoimmune, obstruction, chronic ischemia, heavy metals)

Drug-induced CTIN

- Analgesic nephropathy:
  - Traditionally, analgesic nephropathy referred to the chronic use of the drug mixture containing [phenacetin, paracetamol, or acetaminophen] plus [salicylate] plus a potentially addicting agent [caffeine or codeine]. Any of the drugs belonging to the first group can be metabolized to acetaminophen and its toxic metabolites, which require glutathione for detoxification. Accumulation of these toxic metabolites may form covalent bonds with kidney tissue and induce tissue injury and vascular endothelial damage. Salicylate is a glutathione depletor that limits the neutralization process of toxic acetaminophen metabolites.
  - Analgesic nephropathy affects predominantly the medulla and papillary tip. Characteristic presentations include CKD, computed tomography (CT) revealing papillary necrosis and calcifications, or kidney ultrasound revealing small echogenic kidneys (**Fig. 6.4**).

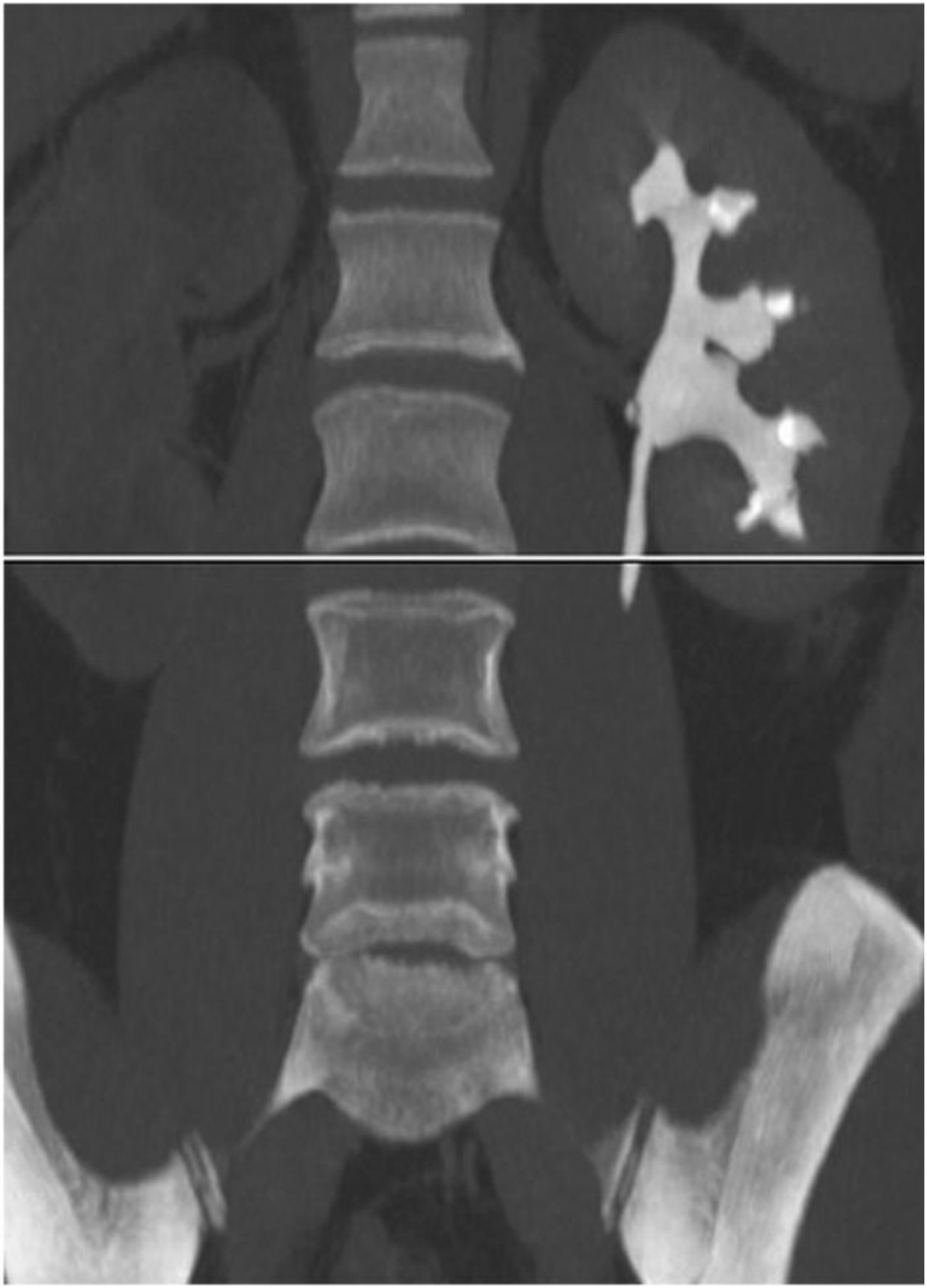


FIGURE 6.4 Papillary necrosis. Coronal postcontrast excretory phase maximum intensity projection images showing classic appearance of papillary necrosis.

  - Single analgesic use may also lead to analgesic nephropathy.
- **Acetaminophen**:
  - Physicians' Health Study (11,000 healthy men): no increased relative risk of CKD with exposure ≥2,500 pills over a period of 11 years
  - Nurses' Health Study (~1,700 healthy women), follow-up over 11 years: >3,000 g of acetaminophen gave an odds ratio of 2.04 for a decrease in glomerular filtration rate (GFR) of >30 mL/min/1.73 m^2 compared to <1,000 g use.
- **Salicylates:** Most studies suggest that the long-term use of daily therapeutic dose of aspirin (ASA) alone (i.e., without concurrent use of acetaminophen) do not lead to kidney injury.
- **NSAIDs:**
  - High dose of NSAIDs may induce CKD in those with underlying or high risk for kidney injury, but not in healthy individuals.
  - Physicians' Health Study (healthy men): no increased risk of CKD with ingestion of ≥2,500 pills
  - Nurses' Health Study (healthy women): no association with decline in GFR over lifetime use
- **Lithium-induced kidney injury:**
  - CIN: characterized by cortical and medullary distal and collecting tubular dilatations/cysts, tubular atrophy, and interstitial fibrosis
  - Toxic intracellular lithium levels are thought to alter primary cilia function and lead to tubular cyst formation.
  - Commonly associated glomerular lesions: global sclerosis, FSGS, minimal change disease
  - Lithium may also be associated with nephrogenic diabetes insipidus, distal renal tubular acidosis (RTA), hypercalcemia, and hypothyroidism.
  - Histopathology (**Fig. 6.5**): severe lithium-associated tubulointerstitial nephropathy with diffuse interstitial fibrosis, tubular cysts, dilations, and tubular atrophy (flattened tubular epithelial cells) and relative sparing of glomeruli. Tubular cysts may be evident on CT imaging.

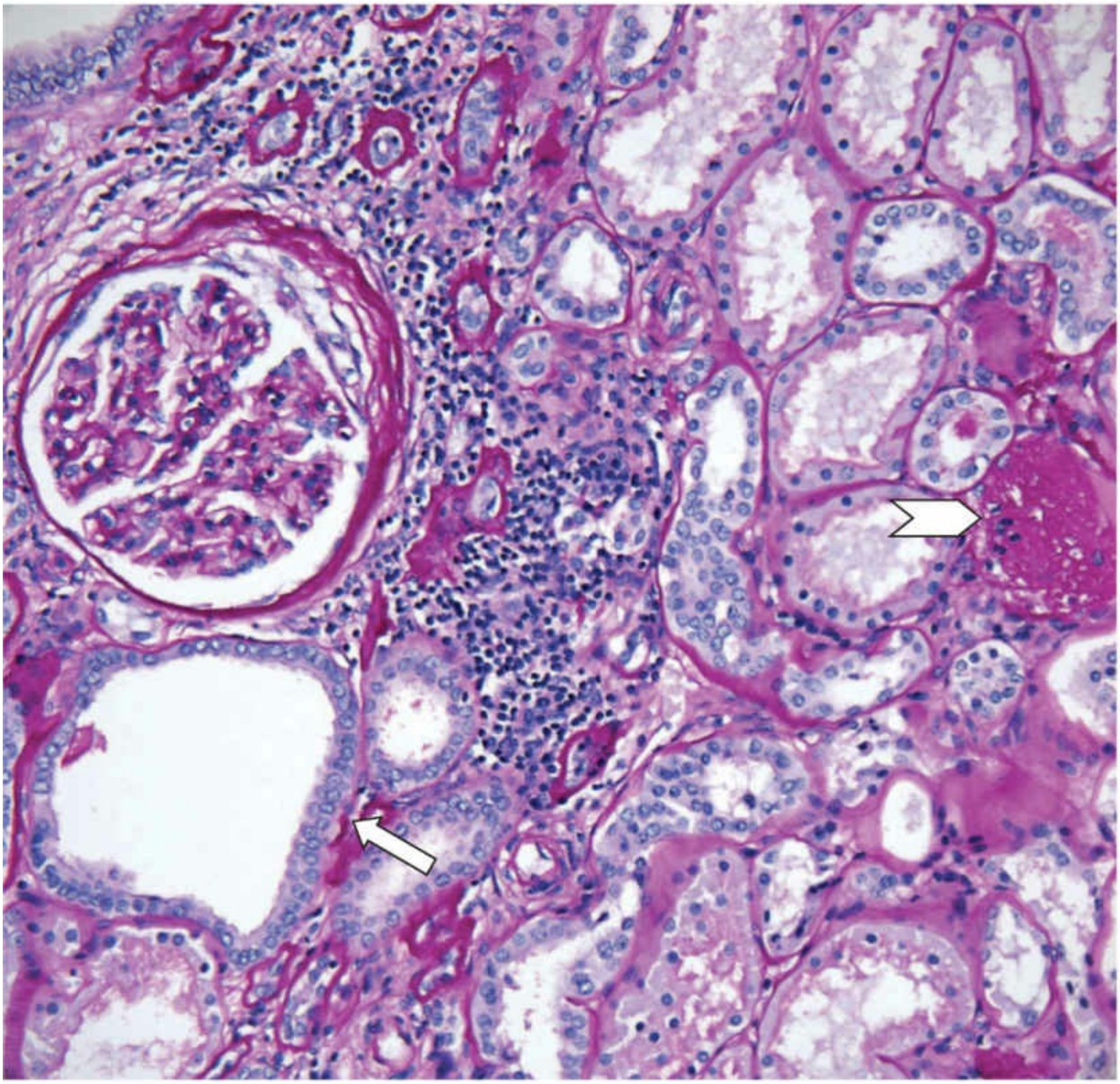


FIGURE 6.5 Lithium-induced chronic tubulointerstitial nephritis. There are focal tubular atrophy and interstitial fibrosis with associated lymphocytic inflammation. Microcystic dilatation of distal tubule (*arrow left lower corner*) and a globally sclerotic glomerulus are also seen (periodic acid–Schiff ×200).

- Management:
  - Discontinue lithium if safe and possible. There are reports of patients committing suicide with lithium discontinuation.
  - Routine CKD management to slow GFR decline
  - Amiloride may be considered during lithium use to reduce reabsorption of the drug at the collecting tubules.
  - Thiazides may be considered in the treatment of nephrogenic

diabetes insipidus.

- **Proton-pump inhibitors (PPIs):**
  - More commonly reported in older patients
  - Tend to present as subacute rather than AIN (i.e., slow rise in S_{Cr} over months)
  - Kidney biopsy reveals interstitial nephritis and/or granulomatous changes.

Infection-related CTIN (Table 6.2)

Table 6.2 Infection-related chronic tubulointerstitial nephritis

	Characteristics	Radiologic and Histologic Findings	Management
Emphysematous pyelonephritis	• ***Life-threatening necrotizing acute pyelonephritis*** and/or obstruction; predominantly seen in patients with ***diabetes mellitus*** • Commonly caused by gas-forming organisms including *Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Proteus mirabilis*	• Plain abdominal radiograph, ultrasound, or CT: presence of gas pockets • Histology: interstitial nephritis may be present	• Antibiotic specific to microorganism involved • Relief of obstruction • Surgical resection as needed
Xanthogranulomatous pyelonephritis	• Condition ***associated with chronic obstruction*** (e.g., staghorn calculi) and urinary tract infections	• CT: low-density masses with calcifications resembling renal malignancy • Histology: granulomatous inflammation with diffuse cellular infiltrate of lipid-laden foam cells replacing normal renal parenchyma	• Antibiotic specific to microorganism involved • Relief of obstruction • Surgical resection as needed
HIV immune restoration inflammatory syndrome	• IRIS refers to a disease- or pathogen-specific inflammatory response that may be triggered after antiretroviral therapy (ART) initiation, reinitiation, or intensification/modification. • IRIS may present as worsening of a diagnosed disease (e.g., ongoing opportunistic infection) or unmasking of an undiagnosed disease.	• Ultrasound: Kidneys may be slightly enlarged due to acute inflammatory response • Histology: chronic interstitial nephritis and/or granulomas	• Treat opportunistic infections, provide supportive and symptomatic care • Severe IRIS: • Consider holding ART • If IRIS is not caused by cryptococcal meningitis or Kaposi sarcoma, treat with 1–2 mg/kg prednisone for 1–2 wk followed by taper; monitor for other opportunistic infections
Malakoplakia	• Rare granulomatous disease of infectious origin • Pathogenesis: ***defective macrophage function*** • Characterized by presence of Michaelis–Gutmann (MG) bodies that are lysosomes filled with partially digested bacteria and/or calcium and iron deposits	• Ultrasound/CT: mass-like lesions mimicking renal carcinoma • Histology: notable for sheets of histiocytes with basophilic inclusions of concentric laminations (MG bodies) and calcium and iron deposits	• Surgical resection • Antibiotics (quinolones, trimethoprim–sulfamethoxazole, rifampicin)

Abbreviations: CT, computed tomography; IRIS, immune restoration inflammatory syndrome.

- **Emphysematous pyelonephritis (Fig. 6.6):**

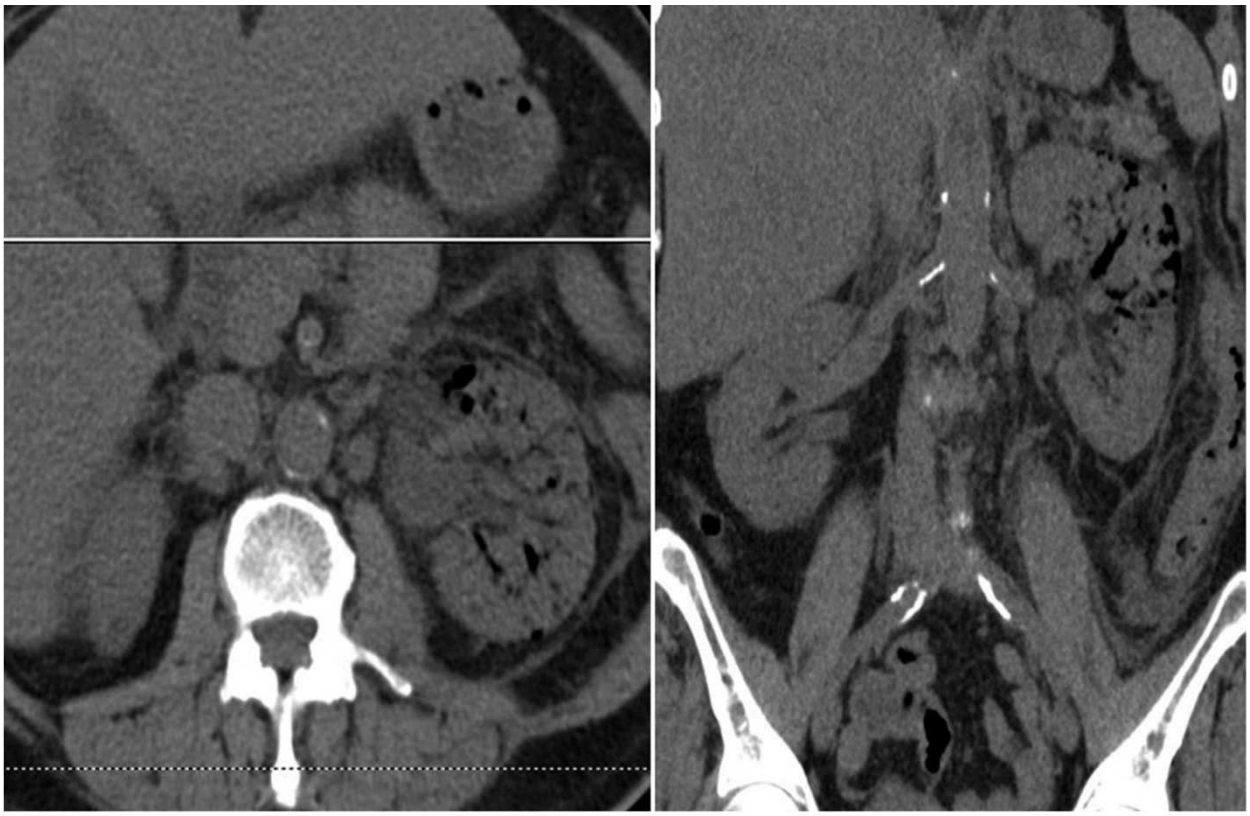


FIGURE 6.6 Emphysematous pyelonephritis. Axial and coronal noncontrast computed tomography images showing crescentic collection of gas within Gerota fascia (indicative of infection within the perinephric spaces) consistent with emphysematous pyelonephritis.

- Life-threatening necrotizing acute pyelonephritis and/or obstruction, predominantly seen in diabetic patients
- Commonly caused by gas-forming organisms such as *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *Proteus mirabilis*
- Gas pockets may be detected on plain abdominal radiograph, ultrasound, or CT.
- Management: organism-specific antibiotics, relief of obstruction, and surgical resection as needed

- **Xanthogranulomatous pyelonephritis (Fig. 6.7):**

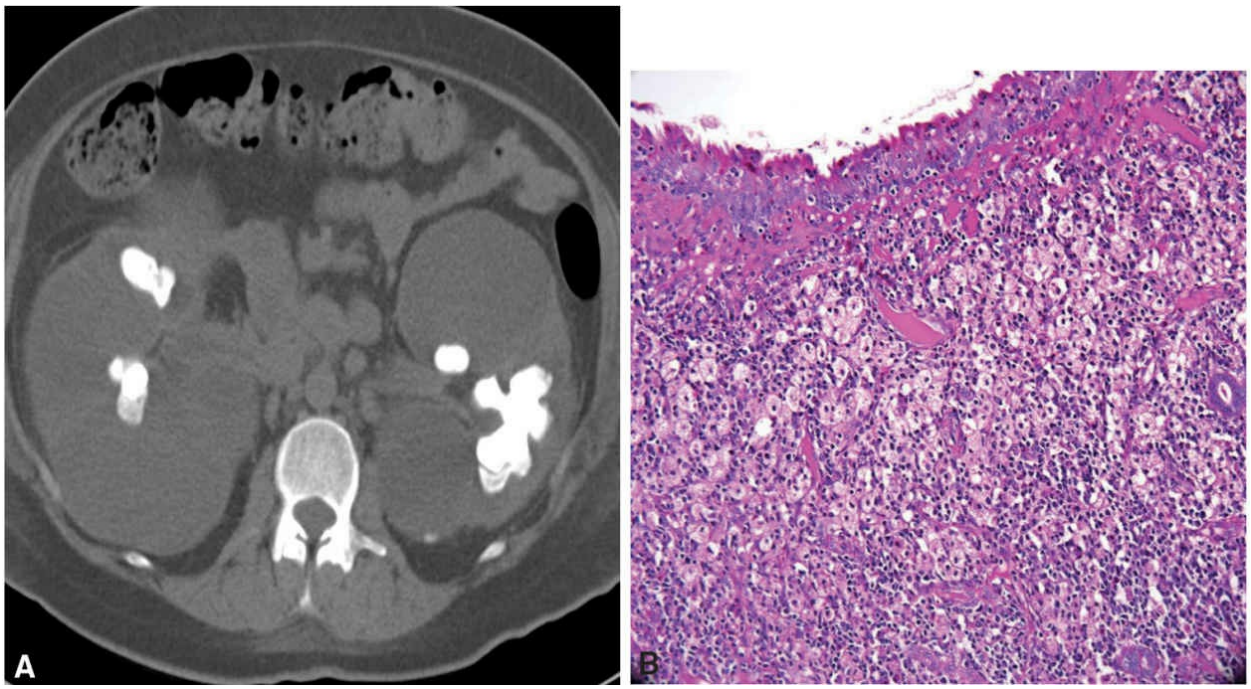


FIGURE 6.7 Xanthogranulomatous pyelonephritis. **A.** Axial and coronal noncontrast computed tomography (CT) images showing enlarged kidneys containing staghorn calculi with resulting contraction of the renal pelvises and associated ballooning of the renal calyces and inflammation of the perinephric fat. The appearance of xanthogranulomatous pyelonephritis on CT has been compared to a "bear claw" with the ballooned renal calyces representing the paws. **B.** The renal pelvis and medulla are diffusely infiltrated with foamy (xanthomatous) cells, which are lipid-laden macrophages, and lymphocytes obliterating the normal renal parenchyma (hematoxylin and eosin ×200).

  - Condition associated with chronic obstruction (e.g., staghorn calculi) and urinary tract infections with resulting granulomatous inflammation
  - CT: low-density masses with calcifications mimicking renal malignancy
  - Histology: granulomatous inflammation with diffuse cellular infiltrate of lipid-laden foam cells replacing normal renal parenchyma
  - Clinical manifestations: commonly affect middle-aged women who may present with fevers/chills, chronic flank pain, and, possibly, palpable mass. Urine cultures may reveal gram-negative organisms such as *E. coli*, *Klebsiella*, or *Proteus* and, less commonly, *Staphylococcal species*.
  - Management: organism-specific antibiotics, relief of obstruction, surgical resection as needed
- **HIV immune restoration inflammatory syndrome (IRIS):**
  - IRIS refers to a disease- or pathogen-specific inflammatory response that may be triggered after antiretroviral therapy (ART) initiation,

reinitiation, or intensification/modification. IRIS may present as worsening of an ongoing disease (e.g., ongoing opportunistic infection) or unmasking of an undiagnosed disease.

- Kidney involvement may manifest as interstitial nephritis and/or granulomas.
  - Management
    - Treat opportunistic infections and provide supportive and symptomatic care.
    - ART should not be interrupted unless ongoing IRIS is life-threatening.
    - Severe IRIS:
      - Consult infectious disease specialist regarding possibility of holding ART.
      - If IRIS is not caused by cryptococcal meningitis or Kaposi sarcoma, treat with 1 to 2 mg/kg prednisone or equivalent for 1 to 2 weeks followed by taper; monitor for development of other opportunistic infections, including cytomegalovirus retinitis and tuberculous disease, while receiving prednisone.

- *Malakoplakia:*
  - Background:
    - Rare granulomatous disease of infectious etiology (bacterial, fungal, tuberculosis, etc.)
    - Presents as friable yellow plagues that may involve genitourinary tract, GI tract, other visceral organs, skin (erythematous nodular lesions, ulcerations, fistulas/abscesses)
    - Reported in immunocompromised hosts and patients with asthma
  - Pathogenesis: thought to be due to defective macrophage function
  - Diagnosis: urine culture and biopsy
    - Imaging studies may reveal mass-like lesions, mimicking renal tumor.
    - Histopathology (**Fig. 6.8**):

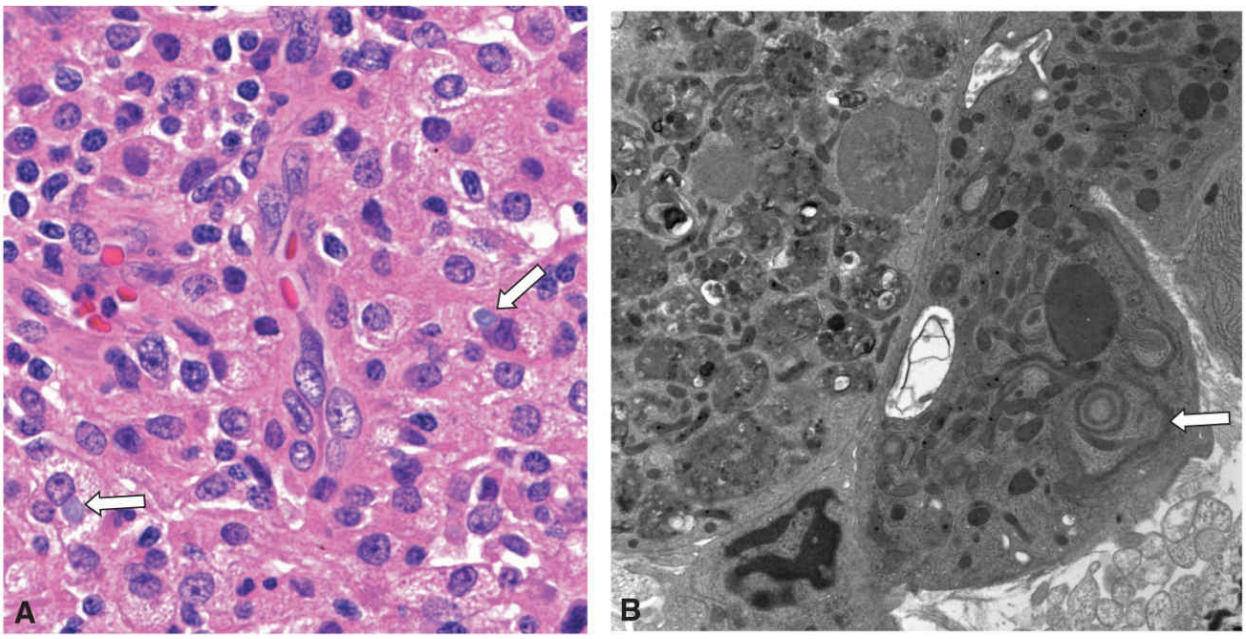


FIGURE 6.8 Malakoplakia. **A.** Interstitial macrophages with abundant granular cytoplasm containing rounded calcifications (Michaelis–Gutmann bodies, *arrows*) (hematoxylin and eosin ×600). **B.** Electron micrograph of a macrophage showing forming calcospherule (Michaelis–Gutmann body, *arrow*) (×12,000). Hematoxylin and eosin staining reveals sheets of histiocytes with basophilic inclusions of concentric laminations called Michaelis–Gutmann (MG) bodies. MG bodies are lysosomes filled with partially digested bacteria with calcium and iron deposits on residual bacterial glycolipids. The presence of MG body is considered pathognomonic for malakoplakia.

- FIGURE 6.8 Malakoplakia. **A.** Interstitial macrophages with abundant granular cytoplasm containing rounded calcifications (Michaelis–Gutmann bodies, *arrows*) (hematoxylin and eosin ×600). **B.** Electron micrograph of a macrophage showing forming calcospherule (Michaelis–Gutmann body, *arrow*) (×12,000). Hematoxylin and eosin staining reveals sheets of histiocytes with basophilic inclusions of concentric laminations called Michaelis–Gutmann (MG) bodies. MG bodies are lysosomes filled with partially digested bacteria with calcium and iron deposits on residual bacterial glycolipids. The presence of MG body is considered pathognomonic for malakoplakia.

- EM: MG bodies consist of lysosomes filled with partially digested bacteria. Identification of the responsible organism may be possible with bacterial gram staining or immune staining with antibody against *Mycobacterium bovis* if such is the pathogenic

organism.

- Management: surgical, antibiotics (e.g., quinolones, trimethoprim–sulfamethoxazole, rifampicin)

Heavy metal-associated CTIN

- Lead (Pb):
  - Pathogenesis: chronic lead deposition and associated toxicity in proximal tubules, hyperuricemia, and hypertension (HTN)
  - Clinical manifestations:
    - Chronic: anemia with basophilic stippling, gout, CKD, peripheral motor neuropathies, perivascular cerebellar calcifications, small shrunken kidneys
    - Acute lead intoxication: encephalopathy, abdominal pain, hemolytic anemia, Fanconi syndrome, and peripheral neuropathy
  - Management: Consider Pb chelation therapy.
- Mercury:
  - Found in alloy and mirror plants, batteries
  - Mercury dichloride ($HgCl_2$) may induce CTIN and ATN.
- Cadmium:
  - Found in glass/metal alloy plants, electrical equipment
  - Outbreak of cadmium toxicity in Japan due to industrial contamination leads to itai itai (i.e., “ouch ouch”) disease because of significant bone pain associated with condition. Kidney involvement includes hypercalciuria, kidney stones, proximal tubular dysfunction, anemia, and CTIN.
- Arsenic:
  - Found in poison gas, insecticides, weed killers, paints
  - Proximal RTA and CTIN

IgG4-related disease

- A condition characterized by dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, with or without associated elevated serum IgG4 concentrations.
- Mass lesions in various organs, including pancreas, autoimmune

pancreatitis, enlarged (submandibular) salivary glands, kidneys (tubulointerstitial nephritis), lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid, pericardium, skin, and even bone (destructive lesions resembling granulomatous polyangiitis)

- Renal involvement: tubulointerstitial nephritis, membranous nephropathy, IgG4 plasma cell arteritis, obstructive uropathy from retroperitoneal encasement/fibrosis
- Patient characteristics:
  - Male predominance (60% to 80%)
  - Older age (>50 years)
  - Up to 40% with history of allergic diseases (e.g., bronchial asthma or chronic sinusitis)
- Clinical diagnosis:
  - Elevated serum IgG4 (although 30% have normal values), hypocomplementemia (~50%), peripheral eosinophilia (~30%)
  - Affected tissue biopsy is characterized by (**Fig. 6.9**):

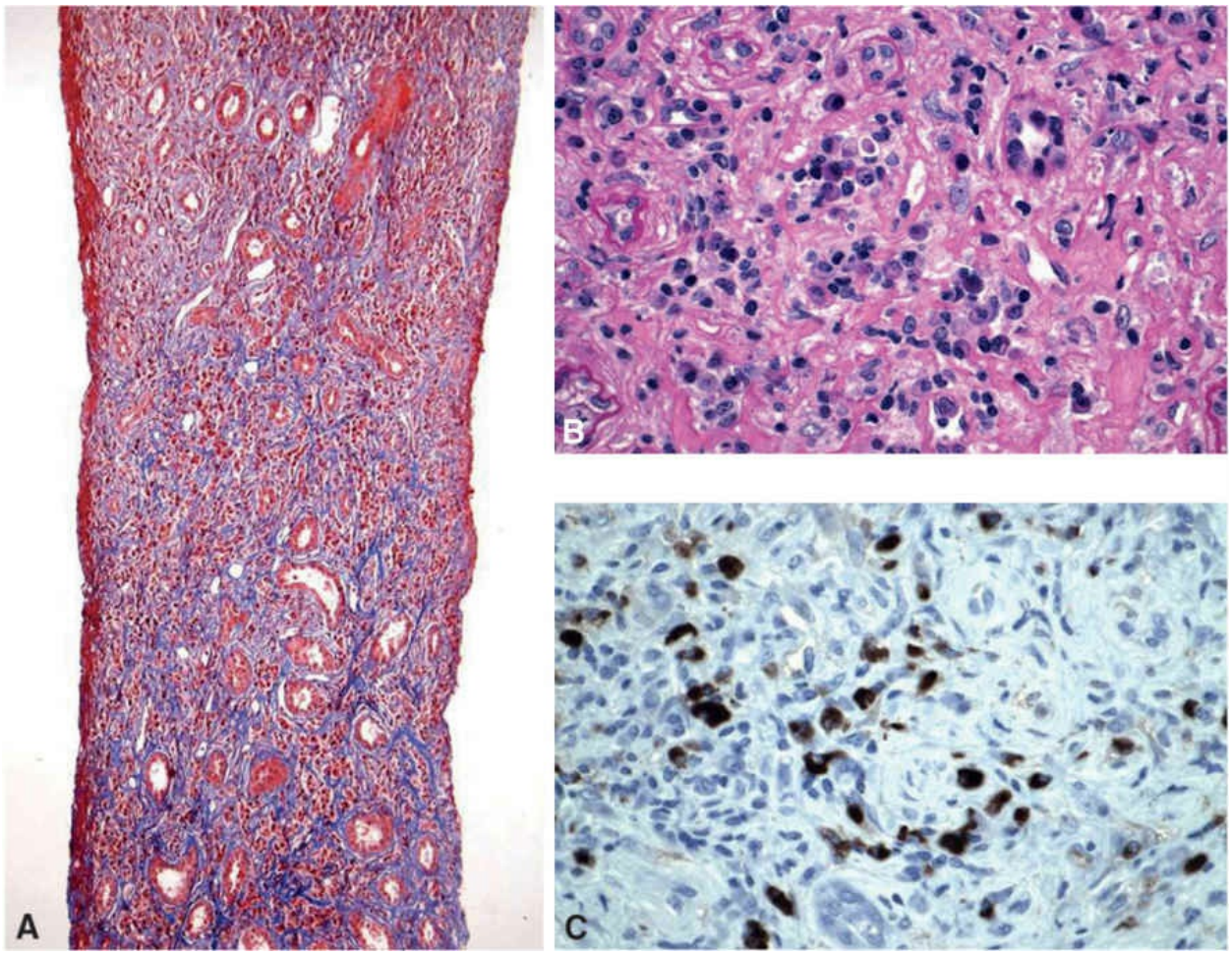


FIGURE 6.9 Immunoglobulin G4 (IgG4)–related disease. **A.** There is widespread interstitial fibrosis with varying degrees of tubular atrophy and a heavy inflammatory infiltrate (Masson trichrome ×100). **B.** There are small aggregates of lymphocytes and plasma cells with surrounding collagen (hematoxylin and eosin ×400). **C.** IgG4 immunohistochemical stain showing positive staining in >50% of the plasma cells (×400).

    - Dense lymphoplasmacytic infiltrates consisting of lymphocytes, plasma cells, eosinophils, and fibroblasts
    - Ratio of IgG4-bearing plasma cells to IgG-bearing plasma cells >50% is highly suggestive of IgG4-related disease.
    - Obliterative phlebitis
    - Storiform fibrosis (likened to cartwheel pattern)
  - Imaging:
    - Abnormal findings in >50% of patients
    - Common findings: masses, enlargement, perinephric stranding
- Pathogenesis is thought to involve:

- Autoimmune process or presence of an infectious agent that triggers an immune response driven predominantly by type 2 helper T (Th2) cells and activation of regulatory T (Treg) cells. The influx of inflammatory cells leads to multiorgan enlargement, cytokine release, eosinophilia, elevated IgG4 and IgE levels, and eventual progression to fibrosis of affected organs.

- Treatment of IgG4-related disease:
  - Glucocorticoids:
    - Suggested regimen: prednisolone 0.6 g/kg body weight/d for 2 to 4 weeks, tapered over 3 to 6 months to 5 mg/d and maintain for up to 3 years
    - Response occurs even in the presence of severe interstitial fibrosis and tubular atrophy.
  - Others: rituximab, AZA, MMF, and methotrexate have been suggested as glucocorticoid-sparing agents.
  - Relapse:
    - Common up to 70%
    - Predictors of relapse: elevated baseline serum IgG4, IgE, and circulating eosinophils

Mesoamerican nephropathy

- Described in Central America
- Affects predominantly males, often sugarcane field workers
- Underlying etiology is thought to be due to repeated exposures to severe dehydration and rehydration, hyperosmolality-stimulated aldose reductase activity leading to conversion of glucose to sorbitol and fructose with subsequent metabolism by fructokinase to oxidant mediators. Exacerbating or contributing factors may include concurrent high intake of fructose and/or NSAIDs, contaminated drinking water (e.g., arsenic, pesticides), leptospirosis, and/or genetic susceptibility.
- Typical manifestations: mild proteinuria, hyperuricemia, *hypokalemia*
- Kidney biopsy is characterized by *extensive glomerulosclerosis*, tubular atrophy, and interstitial fibrosis. Of note, glomerulosclerosis is a prominent

feature of this condition, which is thought to reflect glomerular ischemic injury.

Inflammatory bowel disease is associated with an increased risk of CTIN, independent of exposure to 5-aminosalicylates

Granulomatous (noncaseating) CTIN: Common causes

- Drugs: sulfas, synthetic penicillin, NSAIDs, thiazides, quinolones, intravesical BCG therapy
- Infections: tuberculosis, leprosy, xanthogranulomatous pyelonephritis, BK virus–associated nephropathy, adenovirus nephritis after kidney transplant, histoplasmosis, glandular fever
- Systemic diseases: granulomatous polyangiitis, sarcoidosis, chronic lymphocytic leukemia
- Others: urate, oxalosis

Karyomegalic interstitial nephritis

- Rare, adult onset
- Disease noted for bizarre, enlarged nuclei in proximal tubular cells
- Slowly progressive
- Unknown treatment

Diagnosis of CTIN

- Urinalysis is typically bland with minimal tubular proteinuria
- Kidney biopsy is the gold standard

RENAL CYSTIC DISEASES

Table 6.3 summarizes major renal cystic diseases.

Table 6.3 Renal tubulointerstitial and cystic diseases

Tubulointerstitial and Cystic Diseases	
[a]**Nephronophthisis (small kidneys)**	**AD Tubulointerstitial Kidney Disease (small kidneys)**
• AR CTIN, urinary concentrating defect, corticomedullary cysts • ESKD by ~30 years of age • Accounts for 2.4-15% of ESKD in children	• AD CTIN, urinary concentrating defect, corticomedullary cysts • Generally progresses to ESKD in adulthood

• >25 genes implicated • Associated findings: retinitis pigmentosa, liver fibrosis, bronchiectasis, situs inversus, polydactyly, neurologic abnormalities; volume depletion	• Mutations of UMOD, MUC1, HNF1b, REN, or SEC61A1 • Associated findings: gout, hyperuricemia with UMOD, REN; anemia with REN; volume depletion

Medullary Sponge Kidney (normal-sized kidneys)

- Mostly sporadic but familial clustering as autosomal dominant inheritance with variable penetrance is possible
- Characterized by dilatation of collecting ducts due to cystic damage in medullary and papillary portions of kidneys
- Manifestations: nephrocalcinosis (calcium phosphate or oxalate), dRTA, hypocitraturia, urinary concentrating and acidification defect, hematuria, UTI, rarely hyperparathyroidism
- Usually does not lead to ESKD

Autosomal Recessive Polycystic Kidney Disease (large kidneys)

- Mutation of PKHD1 (fibrocystin/polyductin) leading to abnormal fusiform/saccular dilation of collecting ducts (renal cystic disease) and remodeling of biliary system (progressive portal fibrosis, hepatic fibrosis)
- Imaging studies: radially arrayed dilated collecting ducts spanning from cortex to medulla; “striated nephrogram”
- Complications: ESKD in >60% by age 10; hepatic fibrosis, ascending cholangitis, cholangiocarcinoma

Autosomal Dominant Polycystic Kidney Disease (kidney size can be very large)

- Mutation of PKD1 (polycystin 1), PKD2 (polycystin 2), or GANAB (α-subunit of glucosidase II)
- PKD1 have more cysts, larger kidneys, worse prognosis compared with PKD2; All 3 mutations above are associated with liver cysts
- Complications: aneurysms, stones (uric acid and calcium oxalate), mitral valve prolapse, diverticulosis, hypertension (avoid CCB)
- FDA-approved therapy: tolvaptan

Cystic Kidney Diseases with Kidney Tumor Syndromes

- Commonalities of cystic kidney diseases with kidney tumor syndromes:
- Cystic kidney disease with RCC at young age and/or bilateral RCC
- Pathogenesis: Germ-line mutation of 1 copy of a disease-specific gene with subsequent somatic mutation of the normal gene copy later in life

[b]Tuberous Sclerosis Complex (TSC)

- Germ-line mutation: TSC1 (hamartin), TSC2 (tuberin), or both
- Associations: hamartomas of brain (seizures, developmental delay), eyes, heart, lung, liver, kidney, skin
- Renal: angiomyolipomas (worse in pregnancy, rupture/bleeding potential if >3cm), cysts, RCC, lymphangioleiomyomatosis
- Skin: angiofibromas, ash leaf spots, Shagreen patches

von Hippel Lindau Syndrome (VHL)

- Germ-line mutation: VHL (VHLp)
- Associated tumors: retinal or CNS hemangioblastomas, RCC, pheochromocytomas, pancreatic or endolymphatic sac tumors, renal and pancreatic cysts, epididymal or broad ligament cystadenomas
- Normal kidney size with small number of small cysts in >50% of cases; Although not all cysts become malignant, all cysts must be considered preneoplastic.

ᶜBirt Hogg Dube Syndrome (BHD)

Germ-line mutation: FLCN (folliculin) Manifestations: fibrofolliculomas (white popular lesions on nose, cheeks), pulmonary cysts RCC only occurs if there is also a somatic mutation of the normal copy of FLCN

Other Cystic Diseases

Simple cysts

- Typically asymptomatic, solitary, unilateral
- Large cysts may be associated with hypertension and erythrocytosis
- Cyst growth rate is not affected with transplant whether it be in the donor or recipient.

Multicystic Kidney Disease

- Irregular cysts replace renal cortex in utero
- Cysts commonly involute, affected kidney atrophies and becomes nonfunctional with age
- 30% have other CAKUT (congenital abnormality of kidney and urinary tract, e.g., vesicoureteral reflux in contralateral kidney, neurogenic bladder, duplicating collecting system, ectopic kidney)
- Complications: vesicoureteral reflux, albuminuria, possibly secondary FSGS

Benign (Multifocal) Cystic Nephroma

- Benign mixed mesenchymal and epithelial neoplasm
- Typically Bosniak III, well-circumscribed cystic mass
- Bimodal age: 4-year old boys & postmenopausal women
- Surgical resection
- *Generally benign but RCC has been reported in ~3-4%*
- Management: surgical resection

Acquired Cystic Kidney Disease

- Associated with CKD
- Risks: CKD and dialysis vintage
- *May transform into malignancy*
- Screening in patients with advanced CKD, G5D, and G5T is recommended.
- May also be associated with chronic hypokalemia: cysts typically localize in medulla, resolve with correction of hypokalemia

Glomerulocystic Kidney Disease

- Familial or sporadic condition

- Cystic dilation of Bowman space and proximal tubules; Ultrasound: increased echogenicity of cortex with minute cysts
- May present as an isolated condition, infantile manifestation of ADPKD, part of heritable syndrome (e.g. TSC, VHL), or hypoplastic kidneys
- *May be associated with RCC as part of malignant syndrome*

[a]Nephronophthisis is previously known as medullary cystic kidney disease.
[b]TSC/PKD1 continuous gene syndrome also belongs to syndromes with kidney tumors.
[c]In BHD, pulmonary cystic disease and fibrofolliculomas may occur without the somatic mutation, but RCC requires somatic mutation of the second FLCN copy.
Abbreviations: AD, autosomal dominant; ADPKD, autosomal dominant polycystic kidney disease; AR, autosomal recessive; BHD, Birt–Hogg–Dubé; CCB, calcium channel blocker; CKD, chronic kidney disease; CNS, central nervous system; CTIN, chronic tubulointerstitial nephritis; dRTA, distal renal tubular acidosis; ESKD, end-stage kidney disease; FDA, Food and Drug Administration; FSGS, focal segmental glomerulosclerosis; G5D, CKD stage 5 on dialysis; G5T, CKD stage 5 in transplant recipients; HNF1β, gene encoding hepatic nuclear factor 1β; MUC1, gene encoding mucin 1; RCC, renal cell carcinoma; REN, gene encoding prorenin; SEC61A1, gene encoding the α1-subunit of SEC61 translocon pore; TSC, tuberous sclerosis complex; UMOD, gene encoding uromodulin; UTI, urinary tract infection; VHL, von Hippel–Lindau; VHLp, von Hippel–Lindau protein.

Multicystic Dysplastic Kidney Disease

Background

Multicystic dysplastic kidney disease (MCDK) is a congenital abnormality of the kidney and urinary tract (CAKUT) where irregular cysts of various sizes replace the normal renal cortex, leading to a nonfunctional kidney.

Epidemiology

0.1%; male-to-female ratio: 1.3 to 1.9:1

Pathogenesis

- Known mutations account for <20% of cases and predominantly include genes involved in glomerular development, ureteric branching, and metanephric mesenchyme.
- May be seen with fetal alcohol syndrome

Clinical manifestations of MCDK

- Age of onset: in utero, may present with oligohydramnios
- MCDK is a unilateral disease.
- 30% of patients have other CAKUT: vesicoureteral reflux in contralateral kidney, neurogenic bladder, duplicating collecting systems, ectopic kidney

- Ultrasound: Typically, only involves one kidney that may be seen as an enlarged kidney in utero due to multiple cysts without normal renal parenchyma. Spontaneous involution with cystic collapse may occur in utero. Higher rate of involution by 10 years is seen with kidney size <5 cm and more commonly for right than left kidney. adults may present with an atrophic kidney and a single functioning kidney, which may be confirmed with a renal nuclear scan study.
- MCDK is not associated with HTN or malignancy.
- Long-term follow-up for vesicoureteral reflux, albuminuria, and kidney injury is recommended.

Hereditary Tubulointerstitial Disease

- Mode of inheritance may be autosomal dominant or recessive.
  - Autosomal dominant form is referred to as autosomal dominant tubulointerstitial kidney disease (ADTKD).
  - Autosomal recessive tubulointerstitial disease is known as nephronophthisis (NPHP).
- Common histologic features of inherited tubulointerstitial disease: TBM irregularities, tubular atrophy with cystic formation, interstitial cell infiltration with fibrosis

Autosomal Dominant Tubulointerstitial Kidney Disease

Background

ADTKD is a rare kidney disease characterized by tubular damage and interstitial fibrosis with normal glomeruli that progress to ESKD in adulthood. Subclassification of ADTKD is based on the underlying gene mutation, involving UMOD, MUC1, REN, HNF1β, or SEC61A1. ADTKD is previously known as medullary cystic kidney disease.

Epidemiology

- Not accurately determined, given rarity and under-recognition of disease
- Prevalence estimated to be 0.3% to 1% of patients with CKD stages 3 to 5, and 2% of patients with ESKD have ADTKD-UMOD.

Pathogenesis of ADTKD

ADTKD-UMOD

- Mutation of UMOD, encoding uromodulin = previously known as Tamm–Horsfall glycoproteins. Mutated uromodulin proteins are trapped in tubular epithelial cells, which lead to tubular cell apoptosis, reactive interstitial fibrosis, and cyst formation.
- ADTKD-UMOD is associated with defective function of thick ascending limb of Henle loop, salt-wasting, volume depletion, hyperuricemia, gout, and ESKD early in the third decade of life.

ADTKD-MUC1

- Mutation of MUC1, encoding Mucin-1, which normally functions to protect epithelial mucus barrier and maintain immunomodulatory properties and signal transduction
- ADTKD-MUC1 may present with ESKD by the sixth decade of life.

ADTKD-HNF1a

- Mutation of HNF1β, encoding the hepatocyte nuclear factor-1β, a transcription factor involved in the early development of neural tube, lung, kidney, and GI and genital tracts
- ADTKD-HNF1β is associated with maturity-onset diabetes mellitus of the young type 5, renal cyst, hypomagnesemia, and diabetes syndrome.

ADTKD-REN

- Mutation of REN, encoding preprorenin. Mutated preprorenin results in defective translocation to endoplasmic reticulum (ER) and lysozymes for processing into renin. Cytoplasmic accumulation of preprorenin in renin-producing cells leads to tubular dilation and fibrosis.
- ADTKD-REN is associated with anemia, hyporenin, hypovolemia, early-onset hyperuricemia, gout.

ADTKD-SEC61A1 (most rare of all ADTKD)

- Mutation of SEC61A1, encoding the α1-subunit of SEC61 translocon pore —The translocon complex mediates transport of signal peptide–containing precursor polypeptides across the ER.

ADTKD-SEC61A1 is associated with small, dysplastic kidneys and/or
- simple cysts, congenital anemia, intrauterine or postnatal growth retardation, neutropenia with recurrent cutaneous abscesses.

Clinical manifestations common to ADTKD subtypes

- Small kidneys with or without corticomedullary cysts
- Renal insufficiency, bland urine; ESKD by the third decade of life with UMOD and sixth decade of life with MUC1 mutations
- Hyperuricemia and gout may be seen, particularly in ADTKD-UMOD and ADTKD-REN.
- HTN is uncommon prior to ESKD. Because this is a chronic tubulointerstitial disease with concentrating defects, these patients tend to have volume depletion.
- Genetic testing is indicated for living-related kidney donors.

Management

- No specific treatment: Follow guidelines established for the management of CKD.
- Consider losartan and/or xanthine oxidase inhibitors in patients with gout.
- Use diuretics with caution, given potential for volume depletion and hyperuricemia.
- Low-salt diet is not recommended, given concerns for potential volume depletion.
- Anemia and hypotension/hyperkalemia may be treated with erythropoiesis-stimulating agents and fludrocortisone, respectively.

Autosomal Recessive Tubulointerstitial Disease: NPHP

Background

NPHP is an autosomal recessive tubulointerstitial disease characterized by urinary concentrating defect, CTIN, cyst formation, and progression to ESKD, typically by the age of 30.

Epidemiology

- One of the most common genetic disorders leading to ESKD in children

- Accounts for up to 2.4% to 15% of ESKD in this age group

Pathogenesis

- Mutations of more than 25 different genes have been implicated in the pathogenesis of NPHP. Responsible genes are those encoding the nephrocystin protein involved in the function of primary cilium, basal body, and centrosome in tubular epithelial cells. Causal gene is not known in two-thirds of NPHP cases.

Clinical manifestations

- Age of onset: in utero
- Polyuria, polydipsia requiring fluid intake at night, secondary enuresis, anemia, growth retardation
- Extrarenal manifestations reflecting a ciliopathy syndrome occur in 10% to 20% of cases and include retinal defects (retinitis pigmentosa, ocular apraxia, nystagmus, coloboma), liver fibrosis, cardiac malformation, situs inversus, bronchiectasis, ulcerative colitis, skeletal abnormalities (polydactyly), and neurologic abnormalities (encephalocele, vermis aplasia, hypopituitarism).
- ESKD by the third decade of life, but may range from the first few years to the fifth decade of life depending on the affected gene.
- Ultrasound findings are similar to those seen in ADTKD: Kidneys are small to normal size with increased echogenicity and loss of corticomedullary differentiation. Corticomedullary or medullary cysts may be present. Thin-section CT may identify corticomedullary junction cysts.
- Histolopathology: tubular atrophy, interstitial fibrosis, and corticomedullary microcystic dilation of renal tubules (**Fig. 6.10**)

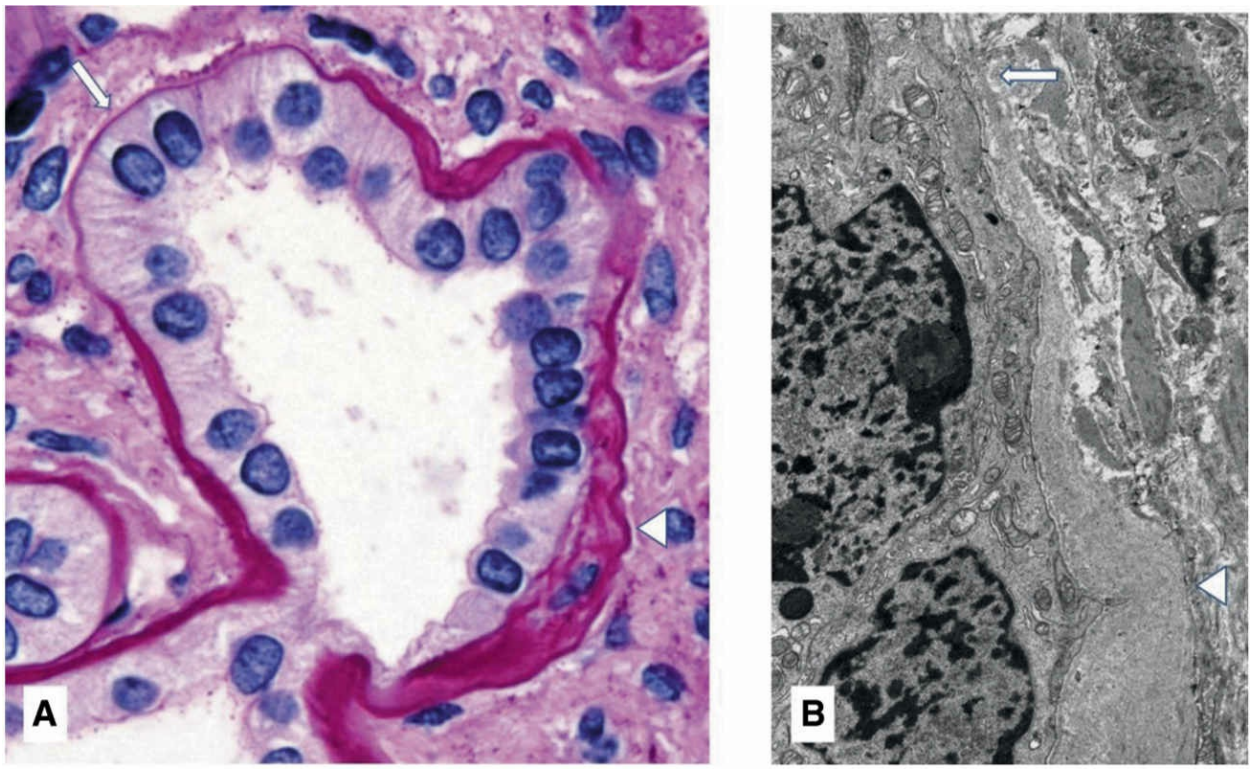


FIGURE 6.10 Nephronophthisis. **A.** Irregularly shaped tubule with a thin (*arrow*) and thickened multilayered (*arrowhead*) basement membrane (periodic acid–Schiff). **B.** Electron micrograph showing a thin (*arrow*) to thickened and layered (*arrowhead*) tubular basement membrane in a single tubule.

Diagnosis

- Presence of clinical syndrome and genetic testing
- Genetic testing may be performed, but a causative single-gene mutation is detected in only up to 60% of cases depending on the composition of the cohort studied.

Management

- No specific treatment: Follow guidelines established for the management of CKD.
- Consider salt, fluids, with or without fludrocortisone if hypotension/hypovolemia.

Autosomal Dominant Polycystic Kidney Disease

Epidemiology

- Incidence estimated to be 1 in 500 to 1,000 live births.
- Autosomal dominant polycystic kidney disease (ADPKD) affects 12.5

million people worldwide, both genders, and all ethnic groups equally.
- ADPKD accounts for 5% to 10% of patients with ESKD and is the fourth leading cause for renal replacement therapy (RRT) worldwide.

Pathogenesis

Factors implicated in the pathogenesis of ADPKD

- Full or partial loss of functional polycystin (PC) *and*
- Somatic inactivation of the normal PKD allele and/or the presence of mutated modifier genes leading to defective processing of PC or an imbalance in the expression of PC

Responsible genes identified in ADPKD include PKD1, PKD2, and GANAB

- PKD1 and PKD2 encode for PC1 and PC2, respectively.
- See **Figure 6.11** for simplified pathogenesis of ADPKD.

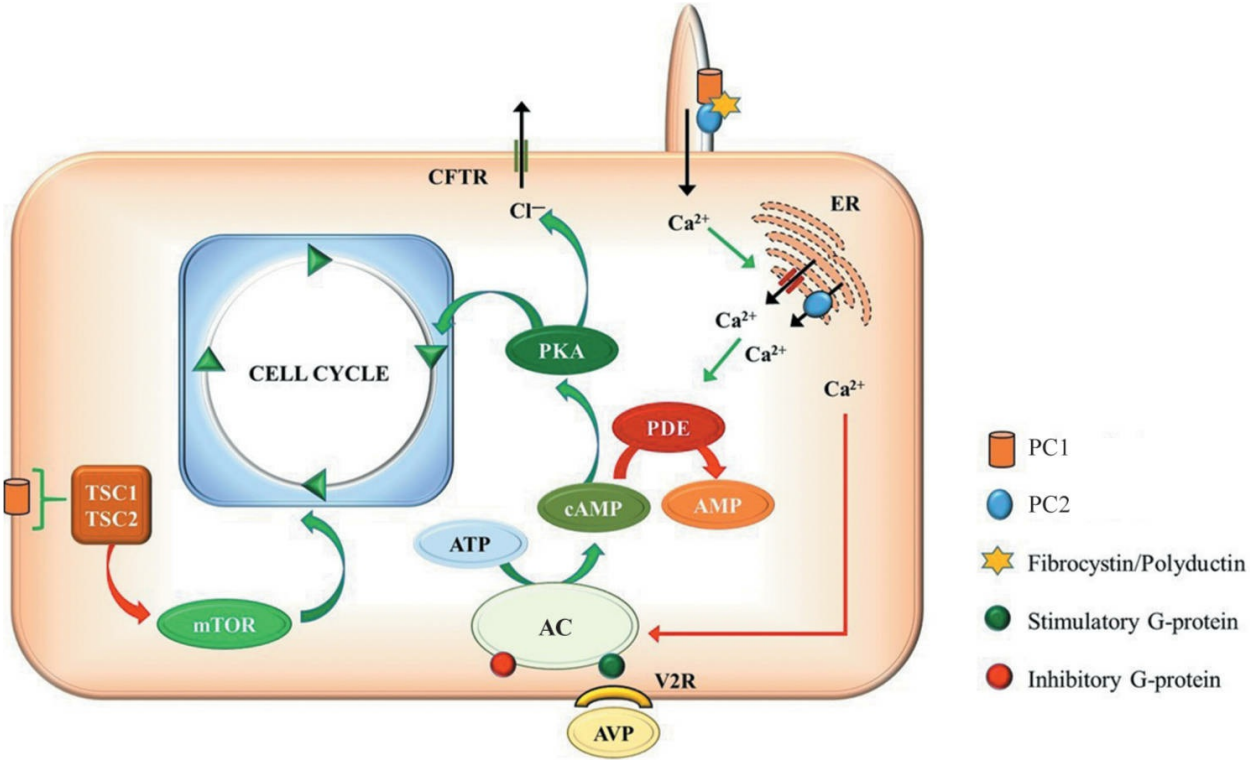


FIGURE 6.11 Pathogenesis of autosomal dominant polycystic kidney disease. PC1 and PC2 form a PC complex on primary cilium on the apical surface of renal tubular and biliary epithelial cells. The normal PC complex functions as a mechanosensor that regulates flow-mediated Ca^{2+} entry into cells, which, in turn, triggers Ca^{2+} release from the ER into the cytoplasm. PC2 is also present in the ER, where it interacts with inositol triphosphate and ryanodine receptors to signal ER Ca^{2+} release into the cytoplasm. Mutations of PC1 or PC2 interfere with flow-mediated increase in cytoplasmic Ca^{2+} level, which leads to accumulation of cAMP. (*Intracellular cAMP level is determined by the net activity of AC and PDE. Whereas AC increases cAMP production, PDE breaks down cAMP. High intracellular Ca^{2+} activates PDE and inhibits AC. In the case of low intracellular Ca^{2+} associated with PC1 or PC2 mutation, AC activity is stimulated, whereas PDE is inhibited, thereby favoring cAMP accumulation.*) cAMP activates PKA, which stimulates chloride-driven fluid secretion into the lumen of formed cysts by the phosphorylated CFTR and in the presence of low intracellular Ca^{2+}, PKA promotes cellular proliferation. Vasopressin binding to its receptor V2R increases cAMP levels via activation of AC. PC1 on the cell surface also interacts with tuberin (TSC2). A disrupted tuberin–PC1 interaction causes a loss of downstream inhibition of mTOR. Uninhibited or unregulated mTOR activity leads to increased protein synthesis and cell proliferation. Mutations involving fibrocystin/polyductin is associated with autosomal recessive polycystic kidney disease. All *green arrows* and *red arrows* indicate stimulatory and inhibitory activities, respectively. *Black arrows* indicate direction of electrolyte movement. Abbreviations: AC, adenylyl cyclase; AMP, adenosine monophosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; CFTR, cystic fibrosis transmembrane conductance regulator; ER, endoplasmic reticulum; mTOR, mammalian target of rapamycin; PC1/PC2, polycystin 1/polycystin 2; PDE, phosphodiesterase; PKA, phosphokinase A; TSC1/TSC2, hamartin/tuberin complex; V2R, vasopressin receptor 2.

- PC1 and PC2 form a polycystin complex on primary cilium on the apical

surface of renal tubular and biliary epithelial cells. The normal PC complex functions as a mechanosensor that regulates flow-mediated calcium entry into cells, which, in turn, triggers calcium release from the ER into the cytoplasm, a process known as “calcium-induced calcium release.” PC2 is also present in the ER, where it interacts with inositol triphosphate and ryanodine receptors to signal ER calcium release into the cytoplasm.

- Mutations of PC1 or PC2 interfere with flow-mediated increase in cytoplasmic calcium level, which leads to accumulation of cyclic adenosine monophosphate (cAMP), an important mediator of cystic growth. (*Intracellular cAMP level is determined by the net activity of adenylyl cyclase 6 [AC6] and phosphodiesterase-1 [PDE1]. Whereas AC increases cAMP production, PDE1 breaks down cAMP. High intracellular calcium activates PDE1 and inhibits AC6. In the case of low intracellular calcium associated with PC1 or PC2 mutation, AC6 activity is stimulated, whereas PDE1 is inhibited, thereby favoring cAMP accumulation*.)
  - cAMP activates protein kinase A (PKA), which stimulates:
    - Chloride-driven fluid secretion into the lumen of formed cysts by the phosphorylated cystic fibrosis transmembrane conductance regulator (CFTR) *and*
    - In the presence of low intracellular calcium, PKA promotes cellular proliferation via a multistep signaling pathway.
  - The proliferative effect of cAMP may be enhanced by epithelial growth hormone-like factors present in cyst fluid.
  - Note that vasopressin (ADH) can increase cAMP levels via activation of adenylate cyclase AD6.
- PC1 on the cell surface also interacts with tuberin. A disrupted tuberin–PC1 interaction causes a loss of downstream inhibition of the mammalian target of rapamycin (mTOR). Uninhibited or unregulated mTOR activity leads to increased protein synthesis and cell proliferation.
- Family history may be absent in 10% to 15% of patients with ADPKD due to de novo mutations, mosaicism, mild disease from PKD2,

nontruncating PKD1 mutations, or misdiagnosis.
    - Despite having large-sized kidneys, ADPKD cysts only involve <1% to 2% of all nephrons.
- GANAB encodes the α-subunit of glucosidase II. The heterodimeric enzyme glucosidase II is involved in protein folding and processing of immature glycoproteins in the ER. Mutation in this gene is associated with maturation and localization defects of PC1 and PC2, thus ADPKD and autosomal dominant polycystic liver disease (ADPLD) phenotypes.

Epidemiology

- Relative frequencies of PKD1 and PKD2 mutations in genetically identifiable cases of ADPKD are approximately 85% and 15%, respectively.
- GANAB mutation is thought to account for ~0.3% of total ADPKD.
- 7% to 10% of all ADPKD cases are genetically unresolved.

Clinical manifestations

- PKD1 has more cysts and larger kidneys compared with PKD2. Cystic growth rates are similar between PKD1 and PKD2. The lower number of cysts, that is, “lower cyst dose,” in PKD2 is thought to result in later development of ESKD in PKD2 compared with PKD1. See **Fig. 6.12**.

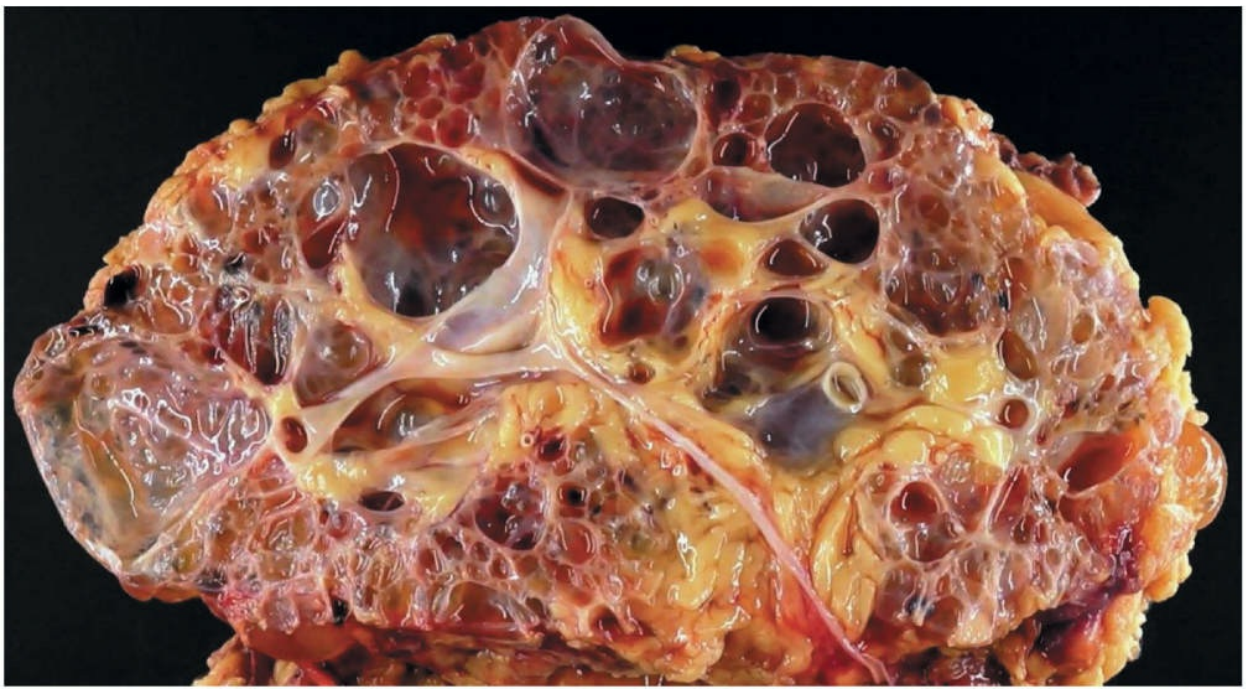


FIGURE 6.12 Autosomal dominant polycystic kidney disease. Kidney showing variably sized cysts in the cortex and medulla involving all segments of the nephron.

- Clinical findings from the Consortium for Radiologic Imaging Studies of PKD (**CRISP**):
  - The value of magnetic resonance imaging (MRI) in the study of PKD:
    - Cyst volume increase may be detected within 6 months.
    - Renal blood flow may be used as a marker of disease severity. The decline in kidney function and disease progression of ADPKD appears to be closely linked with the decline in renal blood flow.
  - PKD1 is a more severe disease compared to PKD2 because, in PKD1, more cysts develop earlier, not grow faster.
  - Cystic growth with increase in total kidney volume (TKV) is a continuous and steady process that is patient specific. At 3-year follow-up, the mean annual growth rate was 5% to 6%.
- GANAB mutations are associated with autosomal polycystic liver disease and mild ADPKD with few renal cysts. Liver involvement ranges from having no cyst to severe polycystic liver disease requiring surgical intervention.

Diagnosis

- Revised unified renal ultrasound diagnostic criteria for *at-risk individuals for ADPKD:
  - *At-risk individuals are defined as individuals with first-degree relative of an index case with unknown genotype.
  - 15 to 39 years old: ≥three cysts unilateral or bilateral
  - 40 to 59 years old: ≥two cysts in each kidney
  - ≥60 years old: ≥four cysts in each kidney
  - If positive family history, in utero presence of even one cyst confirms the diagnosis.
  - In the United States, presymptomatic screening for at-risk children is currently not recommended.
- Criteria for disease exclusion (i.e., for potential related living kidney donor):
  - Ultrasound based:
    - 30 to 39 years old: no cyst
    - ≥40 years old: ≤two renal cysts
    - <30 years old: absence of cyst by ultrasound does not exclude adpkd with certainty.
  - MRI based: <five cysts for patients younger than age 40
  - Obtain direct DNA sequencing for potential kidney donors at risk for ADPKD and age <40 years
- Preimplantation genetic diagnosis is available for ADPKD.

Complications

End-stage kidney disease (ESKD)

- ADPKD is the most common genetic cause of ESKD in adults.
- Prevalence of ESKD due to ADPKD is 5% to 10% in the dialysis population.
- PKD1 typically reaches ESKD by the fourth and PKD2 by the sixth decade of life.
- Risks for CKD progression:
  - Patients with TKV >600 mL/m height or kidney length >17 cm likely progress to stage 3 CKD within 8 years.

TKV/height = sum of (kidney length × width × depth [cm] × π/6) of both kidneys/height (m),

- Albuminuria
- HTN (particularly if onset prior to age 35)
- Male gender
- Low birth weight
- Higher plasma copeptin level is associated with higher TKV and urinary albumin excretion and reduced GFR and effective renal blood flow.
- Others: sickle cell trait, dyslipidemia

Stones

- Stones may occur in ~20% of patients with ADPKD.
- Cyst burden (high TKV) is associated with hematuria and nephrolithiasis.
- Uric acid and calcium oxalate stones are most common in ADPKD.
- Increased stone risk is thought to be due to urinary stasis from cyst compression, low urinary pH presumably due to defective ammonium excretion, hypocitraturia, and hyperuricosuria.

Hypertension (HTN)

- Occurs even prior to reduction in GFR in 60% of patients
- Absence of nocturnal blood pressure (BP) dipping is common (40% of patients).
- Implicated underlying etiologies:
  - Activated renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system due to cyst compression and associated renal parenchymal hypoxia
  - Impaired vascular tone: increased vascular smooth muscle contractility; reduced nitric oxide endothelium-dependent vasorelaxation
  - Others: increased circulating endothelin-1, erythropoietin, vasopressin, insulin resistance

Cardiovascular system

- Left ventricular hypertrophy
- Cardiac valvular abnormalities (mitral valve prolapse, aortic, mitral,

tricuspid regurgitation)
- Pericardial effusion
- Thoracic aortic and cervicocephalic arterial dissection, abdominal aortic and coronary aneurysm

Pain (back, abdomen, head, chest, legs)

- Back pain may be due to compression of enlarged kidneys, ruptured or infected cyst, stones, malignancy.

Cystic infections

- Common pathogens: *E. coli*, *Klebsiella*, *Proteus*, *Enterobacteriaceae*
- Antibiotics: fluoroquinolones or trimethoprim–sulfamethoxazole for better cystic penetration for 4 to 8 weeks, up to 3 months; vancomycin or erythromycin if streptococcal or staphylococcal infection, metronidazole or clindamycin if anaerobic organisms
- Drainage or surgical intervention may be necessary in case of poor response.
- Imaging: CT and MRI are generally adequate. Indium-labeled white blood cell scan or 18-fluorodexoyglucose positron emission tomography may be considered to identify infected cyst.

Renal cell carcinoma (RCC)

- The incidence of clinically significant RCC in patients with ESKD from ADPKD is not increased compared to that of patients with ESKD from other kidney diseases.

Polycystic liver disease

- Occurs in >85% of patients by age 25 to 34 and 94% by age 35 to 46 (CRISP study)
- Liver function is often preserved, but can be complicated with transaminitis, cyst infections, and hepatic venous outflow obstruction (Budd–Chiari).
- *Enterobacteriaceae* is the most common organism isolated in infected liver cysts.
- Progressive disease may be seen with pregnancies, oral contraceptives, and

hormonal replacement therapy.

Cerebral aneurysms

- Cerebral aneurysms most often affect the anterior circulation of circle of Willis
- Asymptomatic cerebral aneurysms may be detected in 5% of patients without a family history and up to 20% in those with a family history.
- High risk of rupture for aneurysms >10 mm in diameter
- Screening indications: family history of aneurysm, previous known aneurysms, high-risk occupations (e.g., pilots), kidney transplantation, pregnancy, elective surgery. Screening recommendations apply to those with good life expectancy.
  - Small unruptured aneurysms require regular follow-up at 6 to 24 months.
  - Patients with family history and negative screening should be rescreened in 5 to 10 years.
  - Screening study of choice is time-of-flight MRI without gadolinium.

Other associations

- Cysts in other organs: pancreas, prostate, epididymitis. Ovarian cyst is not associated with ADPKD.
- Asymptomatic bronchiectasis, inguinal/umbilical hernia, diverticulosis (increased risk of perforation in kidney transplant recipients), defective sperm motility (although infertility is rare)

Management

Dietary

- Moderate dietary sodium restriction <2.3 to 3.0 g/d: increased urine sodium correlates with increased tkv over time.
- Minimize caffeine intake. Caffeine is a methylxanthine that increases intracellular cAMP levels in cultured renal epithelial cells, which could potentially accelerate cystic growth.
- Adequate free water intake to minimize ADH secretion (goal urine osmolality <250 to 270 mosm/kg) with caution not to cause hyponatremia —note, however, although this practice is commonly suggested, its benefit

has not been proven. completion of a randomized controlled trial to determine the efficacy and safety of prescribed water intake to prevent kidney failure due to adpkd (prevent-adpkd trial) is expected by the end of 2020.

- Maintain normal body mass index (BMI); moderate caloric restriction

Cholesterol

- LDL < 100, high-density lipoprotein (hdl) >50 mg/dL; low threshold for statins

Control HTN

- Maintain BP goal ≤110/75 mm Hg if age of 18 to 50 years old and eGFR > 60 mL/min; otherwise ≤130/85 mm Hg.
- RAAS inhibitors:
  - HALT-PKD trial
    - Angiotensin-converting-enzyme inhibitor (ACEI) alone can adequately control HTN in most patients. The addition of angiotensin-receptor blocker (ARB) did not provide any additional benefits.
    - Lowering BP below goal (target 95–110/60–75 mm Hg) in young patients with good kidney function reduced rate of TKV increase by 14%, renal vascular resistance, urine albumin excretion, and left ventricular mass. The rate of decline in eGFR, however, was not significantly different.
- Diuretics in ADPKD:
  - ADPKD patients may have higher aldosterone levels and salt retention compared to those without the disease. Diuretic use may thus be beneficial. Care must be taken to avoid volume depletion, which could further activate RAAS.
  - DIPAK trial (Developing Interventions to Halt Progression of ADPKD 1) revealed that thiazide use was not associated with acceleration of renal function decline. Of note, however, 89% of thiazide users also used RAAS inhibitors.
- Calcium channel blockers (CCBs) in ADPKD:

    - There are concerns that CCB may accelerate cystic growth. CCB has been shown to worsen ADPKD progression in rats.
    - Clinical studies have also revealed worse kidney function outcome among ADPKD patients who received CCB:
        - A small retrospective study from Japan revealed worse kidney function among those receiving CCB compared to those receiving RAAS inhibition, with an average follow-up of 2.4 years.
        - Post hoc analysis of the DIPAK-1 trial also revealed worse eGFR outcome among CCB users compared to those not receiving CCB.
    - CCB should be reserved as third-line antihypertensive therapy.
- Data for safety and efficacy for other antihypertensive classes are lacking.

End-stage kidney disease/renal replacement therapy

- A 5-year survival of ADPKD patients undergoing hemodialysis (HD) is superior to those with other kidney diseases.
- Compared with arteriovenous grafts and fistulas, the use of catheters for HD in ADPKD is associated with an increased risk for renal and liver cyst infections.
- Peritoneal dialysis (PD) is not contraindicated. However, there is a higher risk of abdominal wall hernia. Overall survival rate and peritonitis rates are similar to those seen in nondiabetic PD patients.
- ADPKD patients have been reported to have higher hemoglobin levels and lower requirement for erythropoiesis-stimulating agents. This effect is thought to confer survival benefits among patients with ADPKD over those with other kidney diseases.
- Kidney transplantation:
    - There is no difference in patient or graft survival among patients with ESKD due to ADPKD or other kidney diseases.
    - Kidney volumes have been shown to decrease by 40%, whereas liver volumes increase by 20% at 3 years posttransplantation.
    - Deceased ADPKD kidneys with good function and relatively small size may still be considered for recipients who consent.
    - Notable posttransplant complications: new-onset diabetes, GI

complications (e.g., perforation from diverticulosis), erythrocytosis, urinary tract infections, thromboembolic complications, hemorrhagic strokes

Direct medical therapies of ADPKD

- Vasopressin receptor antagonists (AVR2 antagonists, tolvaptan)
  - Tolvaptan Efficacy and Safety in Management of ADPKD and its Outcomes 3:4 Trial (TEMPO 3:4 trial): Tolvaptan reduced kidney growth by 45%, and eGFR decline by 26% in early ADPKD over 3 years. “Early ADPKD” was defined as having creatinine clearance > 60 mL/min.
  - Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE trial): eGFR decline reduced by 35% in advanced ADPKD over 1 year. “Advanced ADPKD” was defined as having eGFR 25 to 65 mL/min/1.73 m^2.
  - Notable adverse effects from tolvaptan: transaminitis and severe hepatocellular toxicity, polyuria, renal potassium wasting, thirst, hyperuricemia (rarely gout), drug interactions (CYP3A inhibitors)
  - Tolvaptan was approved for use in adult patients with ADPKD by the Food and Drug Administration (FDA) in 2018.
    - Patients who most likely benefit from tolvaptan treatment may be identified as having all the following:
      - ADPKD Mayo Class 1C, 1D, or 1E (classification is based on kidney volume measurements,* calculator may be found at: www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754. Of note, Mayo Class 2 refers to atypical presentations (e.g., unilateral or segmental/asymmetric disease or bilateral disease with parenchymal atrophy). Patients with ADPKD Mayo Class 2 disease are only managed with conservative therapy.)
      - Rapidly progressive ADPKD
      - eGFR ≥ 25 mL/min/1.73 m^2
      - Age: 18 to 55 years old

      *Kidney volume may be measured by CT with contrast if eGFR >

60 mL/min/1.73 m^2 or MRI without gadolinium if eGFR < 60 ml/min/1.73 m^2.

- Due to the concerns for liver toxicity (transaminitis and liver failure), physicians prescribing tolvaptan must be well trained in its use, and patients receiving tolvaptan must be well informed of side effects and closely monitored. See www.jynarquehcp.com/rems-program.

- mTOR inhibitors:
  - Increased signaling of the mTOR complex is thought to enhance cystic growth in ADPKD. Two clinical studies involving sirolimus, however, have not shown benefits in TKV or kidney function at 18-month-follow-up. Notably, urine albumin-to-creatinine ratio was higher in the sirolimus group (Sirolimus for ADPKD [SUISSE] study).
  - Everolimus (mTOR inhibitor): slowed TKV increase but no slowing of eGFR decline detected over a 2-year study period
- Somatostatin analogs:
  - A Long-Acting Somatostatin on Disease Progression in Nephropathy due to ADPKD (ALADIN): Somatostatin analog octreotide-LAR resulted in a trend for smaller TKV increase and better secondary outcome of kidney function. However, this was a small study.
  - Not yet recommended due to lack of larger trials
- HMG-CoA reductase inhibitor (statin): The use of pravastatin in children treated with ACEI revealed slower rates of TKV growth and reduced rate of GFR decline.
- Other suggested/in-trial agents: src/bcr-abl tyrosine kinase inhibitor bosutinib (activation of tyrosine kinase receptors for multiple growth factors may activate cystic cell proliferation), multikinase inhibitor KD019, vitamin K_3, nicotinamide, metformin, pioglitazone, triptolide, dietary interventions

Management of ADPKD-associated complications

- Pain:
  - Sequential approach based on the World Health Organization’s pain relief ladder is recommended.

    - Others: celiac plexus blockade, radiofrequency ablation, spinal cord stimulation, laparoscopic or percutaneous transluminal catheter–based denervation
- Gross hematuria:
    - Observation, hospitalization if severe, fluid support as needed
    - Prolonged hematuria (i.e., >7 days) dictates further evaluation for neoplasm.
- Stones:
    - Maintain urine volume > 2.5 L/d, dietary sodium restriction
    - Supplement potassium citrate as needed for hypocitraturia and as tolerated per serum potassium level
- Polycystic liver disease:
    - For severe polycystic liver disease, aspiration, sclerotherapy, fenestration, partial or segmental liver resection, or liver transplantation may be considered.
    - Somatostatin analogs use is restricted to clinical trials or compassionate use.
    - Cystic infections are best treated with percutaneous drainage and prolonged therapy with fluoroquinolones.

Pregnancy

- Increased risk for progression of liver cysts
- Increased risk for pregnancy-induced HTN and preeclampsia
- Multiple pregnancies (>3) are associated with a higher risk for GFR decline.

TUMOR SYNDROMES WITH CYSTIC KIDNEYS

- Tumor syndromes associated with cystic kidneys include:
    - Tuberous sclerosis complex (TSC)
    - von Hippel–Lindau (VHL) syndrome
    - Birt–Hogg–Dubé (BHD) syndrome
- All three conditions are associated with increased risk of RCC.

NOTE The occurrence of bilateral RCC or RCC in young individuals should prompt consideration and evaluation for hereditary tumor syndromes. Unlike hereditary tumor syndromes, RCC in the general population is typically unilateral and focal and diagnosed later in life, in the sixth to eighth decades of life.

- Common pathogenesis of TSC, VHL, and BHD involves the inheritance of one copy of the mutated autosomal dominant gene (i.e., germline mutation) followed by somatic mutation of the normal gene copy later in life.
  - Germline mutation associated with hereditary tumor syndromes:
    - TSC: TSC1 or TSC2 (or both) encoding hamartin and tuberin, respectively
    - VHL: VHL, encoding VHL protein
    - BHD: FLCN, encoding folliculin
  - Somatic mutation of the normal gene copy that occurs later in life gives rise to the full phenotypic presentation associated with the inherited germline mutation.

Tuberous Sclerosis Complex

Background

TSC is an autosomal dominant (or sporadic) tumor suppressor gene syndrome associated with benign hamartomas of the brain, eyes, heart, lung, liver, kidney, and skin. Renal involvement includes formation of cysts, glomerulocystic kidney disease (GCKD), clear cell RCCs (often bilateral and multifocal), and FSGS with interstitial fibrosis.

Epidemiology

- 1 in 6,000 to 1 in 10,000 live births worldwide
- Sporadic mutations occur in approximately 70% of cases.

Pathogenesis

- In normal cell growth, hamartin and tuberin form a hamartin–tuberin complex that exerts an inhibitory effect on mTOR and effectively serves as a regulator of cell growth. Loss of function of the hamartin–tuberin complex results in dysregulated cell growth and formation of hamartomas, cystic disease, and RCC.

- Compared with TSC1, TSC2-linked disease is typically more severe. TSC2 mutations are five times more common than TSC1 with sporadic mutations. Familial mutations involve TSC1 and TSC2 equally.
- Genetic analysis is positive in 75% to 90%. Negative genetic testing may suggest de novo somatic mutations.
- Of interest, PC1 also interacts with tuberin and mTOR to regulate cell growth. The loss of PC1 function leads to the loss of regulated cell growth, hence cystogenesis in ADPKD1 (**Fig. 6.11**).

Clinical manifestations

- Classic Vogt triad (<30% of tsc): seizures, mental retardation, facial angiofibromas
- Common clinical findings:
  - Renal angiomyolipoma (AML) (60% to 70%), cysts (20% to 30%), and RCC (2% to 4%)
  - TSC-associated AML:
    - Typically, bilateral and multiple lesions (vs. single lesions in the general population) (**Fig. 6.13**).

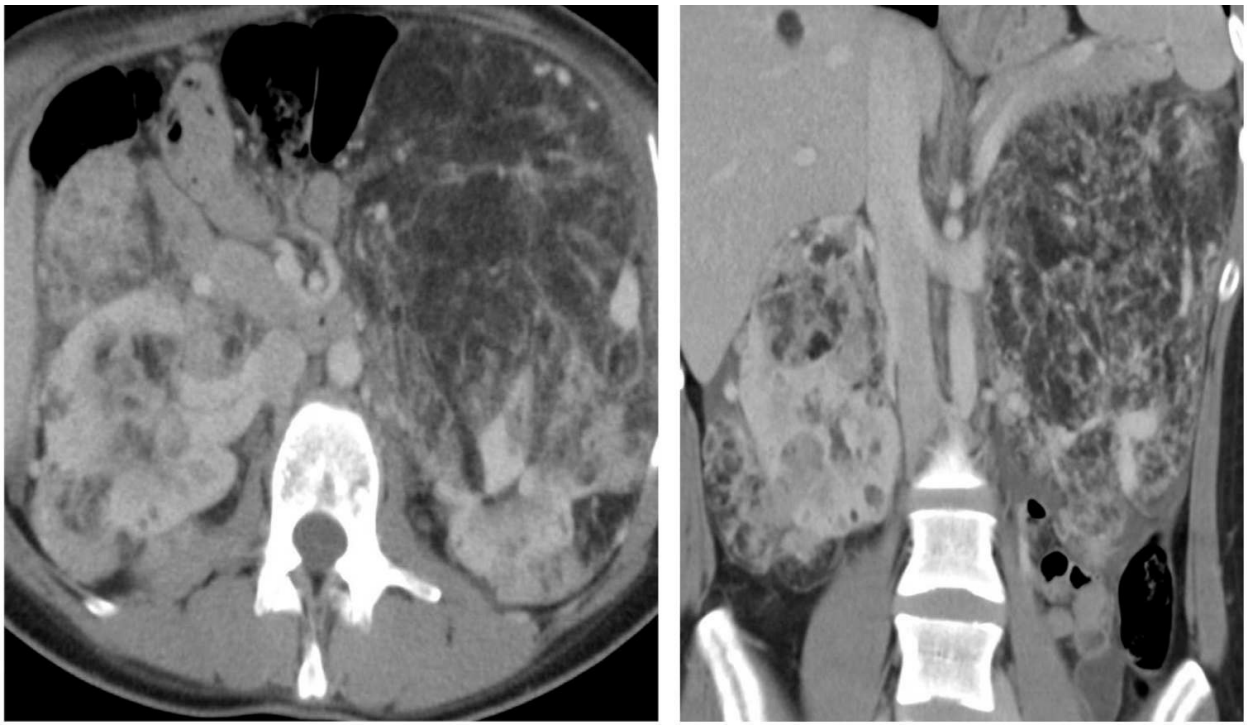


FIGURE 6.13 Renal angiomyolipoma (AML). Axial and coronal postcontrast computed tomography images show very large AML in both kidneys in a patient with known tuberous sclerosis complex. The left renal AML is very large and at risk for bleeding. Note a small AML in the liver.

  - May be more severe in women with increased rupture risk during pregnancy and length >3 cm. Prophylactic surgery or vascular coiling/thrombosis may be considered if >4 cm.
- Renal cysts may derive from any nephron segment. The presence of both AML and renal cysts is highly suggestive of TSC.
- TSC-associated RCC tends to be more slowly progressive than RCC in the general population.
- Lymphangioleiomyomatosis occurs almost exclusively in women and/or spontaneous pneumothorax.
- Others:
  - Brain: giant cell astrocytomas and other central nervous system (CNS) tumors, mental retardation, seizures, autism
  - Lungs: pulmonary lymphangioleiomyomatosis
  - Cardiac: cardiac rhabdomyomas
  - Skin: angiofibromas, periungual fibromas, hypomelanotic macules (ash leaf spots, Shagreen patches)

Diagnosis

- Genetic testing
- Clinical criteria for “definite diagnosis”: ≥two major features or one major with ≥two minor features
  - Major features: hypomelanotic macules, angiofibromas, ungual fibromas, Shagreen patch, multiple retinal hamartomas, cerebral cortical dysplasias, subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis, AMLs
  - Minor features: “confetti” skin lesions, dental enamel pits, intraoral fibromas, retinal achromic patch, multiple renal cysts, nonrenal hamartomas

Management

- Obtain abdominal CT or MRI every 1 to 3 years lifelong to assess AML and cystic progression as well as malignancy transformation.
- TSC-associated AML:
  - The mTOR inhibitors sirolimus and everolimus may be used.
  - Advise women with AML of potential accelerated AML growth and hemorrhagic complications with estrogen replacement therapy.
- Renal cell carcinoma (RCC):
  - Surgical decompression of large symptomatic cysts refractory to medical therapy
  - Nephron-sparing surgical resection of renal carcinoma is generally suggested due to the tendency for bilateral renal involvement.
  - Bilateral nephrectomies are recommended at ESKD (dialysis or transplant).

TSC/PKD1 Contiguous Gene Syndrome

- Deletion mutation involving both *TSC2* and *PKD1* genes results in severe PKD with TSC features.
- Occurs in 2% to 3% of patients with TSC; age of onset: first year of life; ESKD by age 20s
- Ultrasound: large kidneys similar to ADPKD

Von Hippel–Lindau Disease

Background

Multiorgan predisposition to malignancy due to a germline mutation of one VHL gene copy and a somatic mutation of the second copy later in life

Epidemiology

One in 36,000 live births involving all ethnicities

Pathogenesis

- Autosomal dominant mutation of *VHL* gene encoding the VHL protein. VHL protein is part of the ubiquitin-ligase complex involved in ubiquitination and subsequent degradation of the α-subunit of the hypoxia-inducible factors HIF-1 and HIF-2. Accumulated HIF-α binds to HIF-β, translocate to nucleus, bind to the hypoxia response element to induce transcriptions of vascular endothelial growth factor (VEGF), erythropoietin, tumor growth factor-β1, and platelet-derived growth factor, among others (see **Fig. 4.1**).
- Autosomal mutation occurs in 80% of cases and sporadic in 20%.

Clinical manifestations of VHL disease

- Onset of disease between the second and third decades of life, >90% by age 65
- Associated tumors: retinal or CNS hemangioblastomas, clear cell RCC, pheochromocytomas, pancreatic islet tumors, endolymphatic sac tumors, renal and pancreatic cysts, epididymal or broad ligament cystadenomas
- VHL-associated RCCs:
  - Lifetime risk ~70%
  - Tend to be clear cell RCC and slower growing than those seen in sporadic cases

Diagnosis

- Presence of one tumor (retinal or cerebellar hemangioblastoma, RCC, or pheochromocytoma) if positive family history, two tumors if no family history or genetic analysis
- Renal imaging: normal kidney size with cysts in >50% of cases. Cysts

typically present in small number and small size. Although not all renal tumors are preceded by cysts, all renal cysts must be considered preneoplastic and closely monitored.

- To evaluate for pheochromocytomas, obtain plasma norepinephrine.

Management

- Annual BP measurements, urine studies for pheochromocytomas, MRI or CT of kidneys and CNS.
- Renal-sparing surgery is appropriate for RCC < 3 cm in size due to multifocal nature of rcc. radioablative therapy is an option for multicentric lesions.
- Medical therapies with promising results include tyrosine kinase inhibitors (e.g., sunitinib, pazopanib), anti-VEGF antibody (e.g., bevacizumab), mTOR inhibitor (e.g., everolimus), and checkpoint inhibitors (e.g., anti-programmed cell death PD-1 [nivolumab], inhibitor of CTLA-4 [ipilimumab]).

Birt–Hogg–Dubé Syndrome

- Autosomal dominant mutation of the tumor suppression folliculin (*FLCN*) gene. Folliculin is involved in cell–cell adhesion, cell polarity, mTOR signaling pathways, and ciliogenesis. Loss of folliculin function can lead to dysregulated cell growth and tumor formation.
- Heterozygous inheritance of the mutated *FLCN* gene is enough to cause fibrofolliculomas and pulmonary cysts, but not enough to cause RCC. Random mutation of the normal FLCN copy later in life is required for dysregulated cell growth in the kidneys and RCC transformation.
- Clinical manifestations: RCC (30%), fibrofolliculomas (white papular lesions on nose and cheeks), cystic lung disease, recurrent spontaneous pneumothorax
- Diagnosis may be made by genetic testing.

NON-MALIGNANT CYSTIC KIDNEY DISEASES

Autosomal Recessive Polycystic Kidney Disease

Epidemiology

Occurs in 1 of 20,000 live births; carrier rate: 1 in 70

Pathogenesis

- Mutations of the polycystic kidney and hepatic disease 1 (*PKHD1*) gene encoding fibrocystin/polyductin (FCP), a transmembrane protein found in mitotic spindle, microtubules, and apical primary cilia in biliary and renal tubular epithelia. FCP interacts with PC2 in renal tubules and biliary ducts and is thought to play a central role in microtubule formation and function and epithelial proliferation and secretion.
- Mutations of FCP lead to abnormal fusiform or saccular dilation of the collecting ducts and abnormal remodeling of the biliary system, resulting in renal cystic disease and progressive portal fibrosis, respectively.

Clinical manifestations

- Majority of patients present in utero or at birth.
- In utero presentation includes enlarged echogenic kidneys, poor kidney function, and oligohydramnios. The latter may lead to abnormal fetal development, Potter phenotype consisting of pulmonary hypoplasia, characteristic facies, and spine and limb deformities.
- Children may present with urinary concentrating defect, volume depletion.
- Perinatal mortality is estimated to be 25% to 30%.
- ESKD is reached in >60% by age 10.
- Imaging studies:
  - Ultrasound:
    - Enlarged kidneys with poor corticomedullary differentiation due to the hyperechoic medulla, peaking in first 1 to 2 years of age, then reduce in size in subsequent years
    - Radially arrayed dilated collecting ducts spanning from the cortex to the medulla may be seen with high-resolution ultrasound.
    - Autosomal recessive polycystic kidney disease cysts are not discrete sacs as those seen in ADPKD, TSC, and VHL disease.
  - Computed tomography (CT):
    - Nephromegaly with renal attenuation values similar to water due to dilated collecting tubules

    - Striated nephrogram due to the stasis of contrast medium in dilated tubules
    - Pelvicaliectasis and renal calcifications
- Hepatobiliary complications: hepatosplenomegaly, portal HTN, hepatic fibrosis, ascending cholangitis, cholangiocarcinoma
- Patients may present with combined severe kidney and liver disease, mild disease of one organ and severe disease of the other, mild disease of both organs, or isolated hepatic fibrosis and nonobstructive dilation of intrahepatic bile ducts (Caroli disease).

Diagnosis

- Genetic testing
- Histology is notable for kidneys with cystic dilatation of the collecting ducts in a linear pattern perpendicular to the capsule extending from the medulla to the cortex. See **Figure 6.14**.

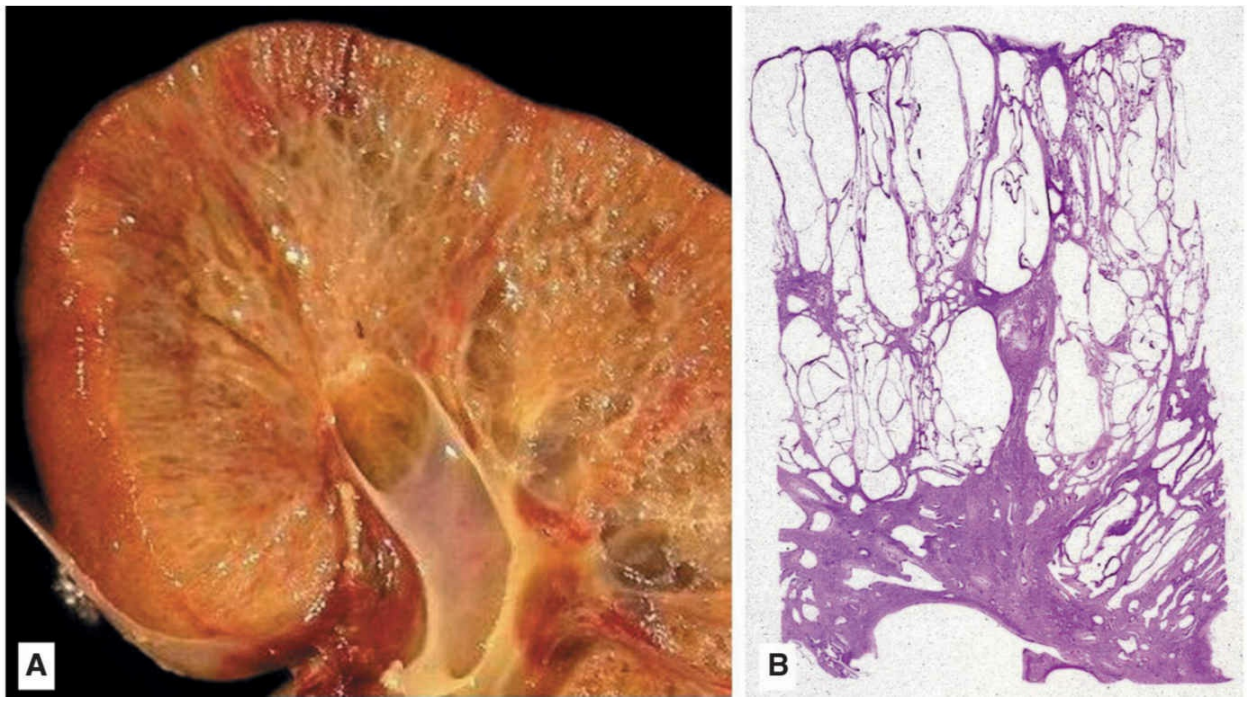


FIGURE 6.14 Autosomal recessive polycystic kidney disease. **A.** Kidney with cystic dilatation of the collecting ducts in a linear pattern perpendicular to the capsule. **B.** Collecting duct cysts extending from the medulla to the cortex with a linear arrangement (hematoxylin and eosin).

Management

- BP control with RAAS inhibitors.

- Thiazide diuretics may be considered for severe concentrating defect and polyuria.
- Maintain high index of suspicion for ascending cholangitis.
- Kidney transplantation is preferred in ESKD. Combined kidney liver transplantation should be considered in cases with extensive portal HTN. Parental organ donation is generally possible if normal imaging studies of kidneys and liver due to the recessive nature of disease.

Medullary Sponge Kidney

Background

Rare condition characterized by dilatation of collecting ducts due to cystic damage in medullary and papillary portions of kidneys. Clinically, patients may present with nephrocalcinosis, distal RTA, and hypocitraturia.

Epidemiology

- Prevalence is estimated between 5 in 10,000 and 5 in 100,000.
- Mostly sporadic but may rarely present with familial clustering as autosomal dominant inheritance with variable penetrance

Pathogenesis

- Thought to involve genes imperative for proper renal formation and distal nephron development of precalyceal and collecting ducts. Implicated genes include the glial cell–derived neurotrophic factor (GDNF) and receptor tyrosine kinase (RET).
- May occur in association with other developmental defects or tumors (e.g., PKD, Wilms tumor, horseshoe kidney, CAKUT syndrome, Caroli syndrome, Beckwith–Wiedemann syndrome, Rabson–Mendenhall syndrome)

Clinical manifestations

- Generally asymptomatic, incidental finding
- May be complicated by hematuria, urinary tract infections, nephrolithiasis (calcium phosphate or calcium oxalate), tubular mineral “plugs”
- May present with hyperparathyroidism
- Urinary concentrating and acidification defect resulting in incomplete

distal RTA with associated hypercalciuria and alkaline urine, bone mineralization defect

- Medullary sponge kidney usually does not lead to ESKD.

Histopathology

Bilateral multiple spherical or oval cysts (1 to 8 mm) in renal papillae that may communicate with the collecting system and contain calcium apatite concretions

Diagnosis (Fig. 6.15)

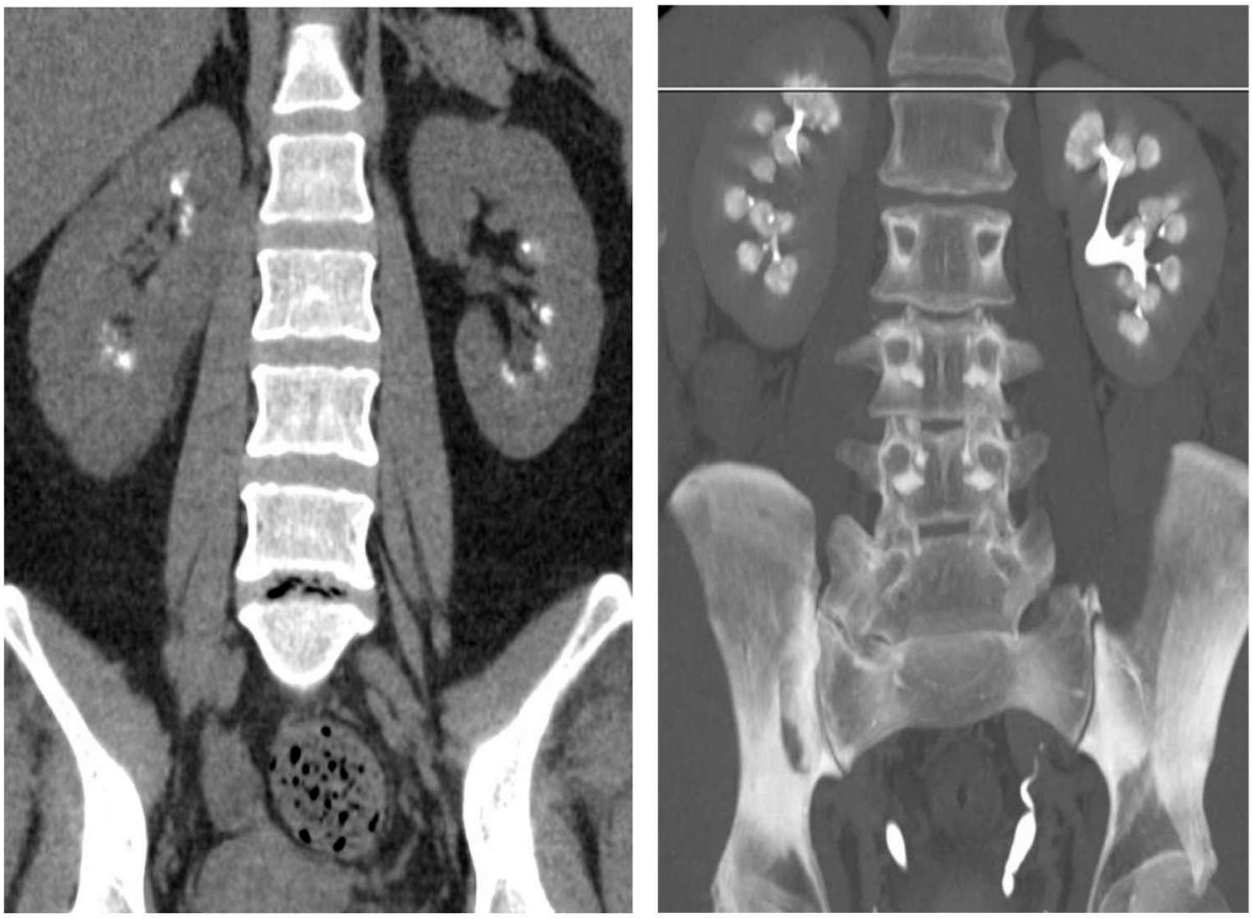


FIGURE 6.15 Medullary sponge kidney. Coronal noncontract computed tomography images showing amorphous and course pyramidal calcifications in both the kidneys. Postcontrast excretory phase maximum intensity projection images show a "paintbrush" like appearance to the renal calyces.

- Abdominal radiographs revealing radiopaque concretions (calcium stones)
- Excretory urography revealing spherical cysts or diffuse linear striations due to contrast retention by dilated medullary and papillary collecting ducts. These findings may also be described as "bouquet of flowers" or "paintbrush."
- Nonenhanced CT may reveal echogenic hyperdense foci in the medulla from stones/nephrocalcinosis.

Management

- Nephrolithiasis:
  - Potassium citrate and high fluid intake
  - Thiazides if recurrent stones
  - Inorganic phosphate if first two options fail or not possible. Avoid

phosphates in patients with struvite stones. Recall struvite stones are "triphosphates."

- Urinary tract infections:
  - Antibiotic selection per sensitivity
  - Aggressive and prolonged therapy is generally recommended.

Simple Cysts

- Simple cysts are typically asymptomatic solitary and unilateral cysts located in the renal cortex.
- Pathogenesis: thought to be related to an initial ischemic event that leads to an aberrant hypertrophic response with subsequent cystic growth
- Associated risks include increasing age, male gender, HTN, reduced renal mass, increased BMI, reduced kidney function, and, possibly, smoking.
- Similar to ADPKD, circulating levels of copeptin levels (validated surrogate for vasopressin) is associated with kidney length and function.
- Clinical manifestations:
  - Generally asymptomatic but may be associated with HTN and erythrocytosis. Association with HTN is thought to be due to increased renin release from epithelial cells lining the cyst. Large cysts associated with severe HTN may be considered for drainage.
  - Cysts may become infected with subsequent development of thickened walls and calcifications.
- Kidney transplantation: Growth rate of simple cysts does not increase with kidney donation whether they are in the donor or recipient. Simple cysts do not adversely affect renal outcomes.

Acquired Cystic Kidney Diseases

- Histology: cystically dilated tubule with epithelial cell hypertrophy and hyperplasia. See **Figure. 6.16**

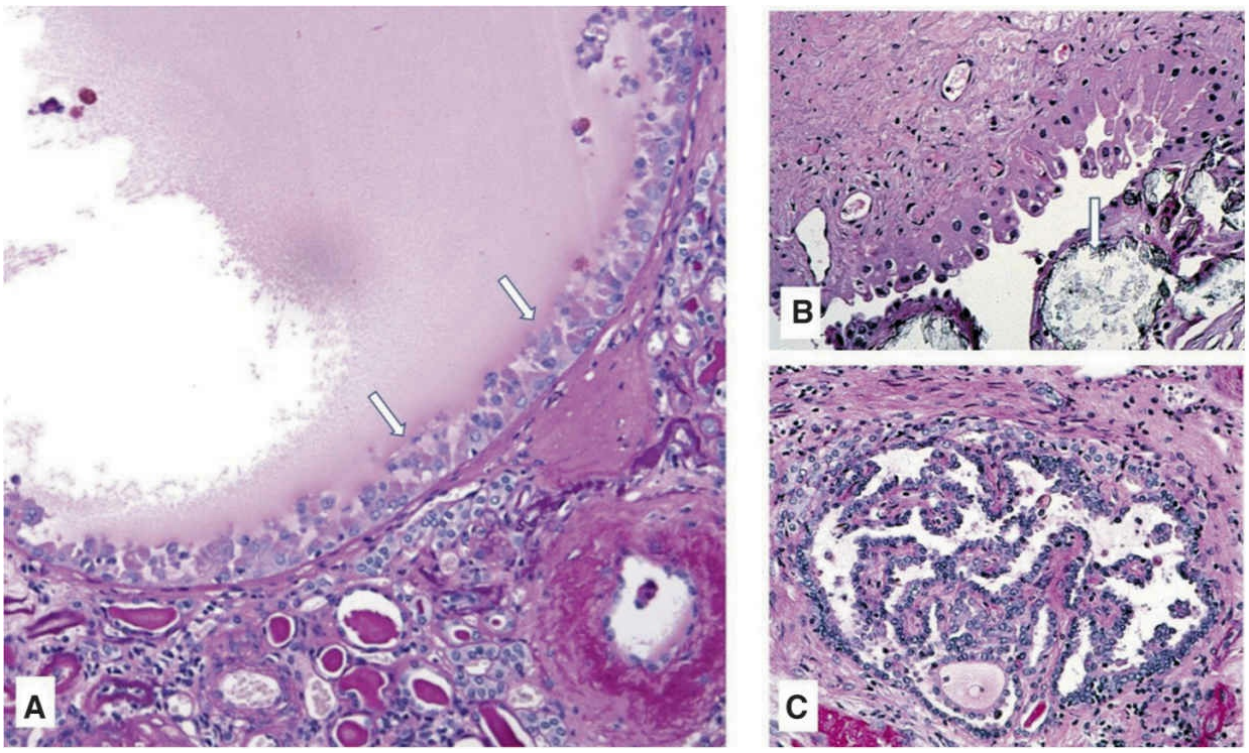


FIGURE 6.16 Acquired cystic kidney disease. **A.** Cystically dilated tubule with epithelial cell hypertrophy and hyperplasia (*arrows*) (periodic acid–Schiff). **B.** Cystically dilated tubule with epithelial cell hypertrophy and oxalate crystals (*arrow*) in the tubular wall (hematoxylin and eosin). **C.** Intrarenal small papillary tubular cell adenoma (neoplasm). These are commonly found in the setting of acquired cystic disease (periodic acid–Schiff).

- Conditions associated with acquired cystic kidney diseases (ACKD):

Chronic hypokalemia

- Cysts typically localize to renal medulla.
- Resolution of cysts is possible after correction of hypokalemia (e.g., adrenalectomy for functioning tumors).

CKD-associated ACKD

- Epidemiology: The incidence of ACKD is 50% to 80% among patients who receive dialysis for 10 years or more.
- Pathogenesis: similar to simple cyst above plus presumed contribution from uremic milieu
- Diagnosis: the presence of cysts in both the kidneys with a total of at least four cysts
- Risk: CKD and dialysis vintage

Clinical manifestations

- Cysts are typically <0.5 cm but may be up to 2 to 3 cm, generally asymptomatic.
- ACKD may transform into adenomas or RCC.
  - Unlike sporadic clear cell RCC, ACKD-associated RCC is typically multifocal and bilateral with lower proliferative activity and metastatic disease.
  - ACKD-associated RCC is histologically distinct with eosinophilic cytoplasm with calcium oxalate crystal deposits in cribriform, tubulocystic, and papillary architecture.

Screening of CKD-associated ACKD

- CKD, pre-ESKD: Screening in patients with pre-ESKD is controversial and not well established.
- Dialysis patients: Annual screening among patients who have received dialysis for 3 years or more with good life expectancy has been suggested. Ultrasound is generally accepted as a screening study. In the presence of cysts, annual follow-up with contrast-enhanced CT or MRI without gadolinium has been suggested.
- Kidney transplant recipients:
  - All patients: annual ultrasound screening of native kidneys
  - Bosniak I and II (see **Classification** below): ultrasound screening twice yearly or CT scan to evaluate for progression
  - Bosniak IIf: ultrasound evaluation four times a year; CT or MRI scan yearly; nephrectomy if progressive lesions, even if not reaching category III/IV
  - Bosniak III and IV: nephrectomy

Bosniak CT-based cyst classification

Class I

- Cyst with hairline thin wall; no septation, calcification, or solid component; no enhancement with contrast CT
- Benign cyst, no follow-up required

Class II

- Type 1:
  - Cyst with a few hairline thin septations and/or perceived (nonmeasurable) enhancement may be present; fine calcification in cyst wall or septae.
  - Benign simple cyst, no follow-up required
- Type 2:
  - Uniformly high attenuation lesion <3 cm, well-marginated, nonenhancing
  - Likely benign kidney mass, no follow-up required

Class IIF (F is for follow-up)

- Type 1:
  - Cysts with multiple hairline thin septa or minimally smooth thickening of wall or septa and/or perceived enhancement that may have thick or nodular calcification
- Type 2:
  - Intrarenal nonenhancing hyperattenuating renal masses > 3 cm
- Most Bosniak IIF masses are benign. When malignant, most are indolent. Follow-up at 6 and 12 months, then annually for 5 years to assess for changes.
- For kidney transplant recipients: ultrasound evaluation four times a year; CT or MRI scan yearly; nephrectomy if progressive lesions, even if not reaching category III/IV

Class III

- Cyst with thickened irregular or smooth wall/septa with measurable enhancement. (Contrast enhancement implies vascularized mass, thus possible malignancy.)
- Bosniak III masses have an intermediate probability of being malignant. Consult urologist.

Class IV

- Soft-tissue components/nodules with measurable enhancement
- A large majority of Bosniak IV cystic renal masses are malignant. Consult

urologist.

- For interested readers, a proposed detailed update of current Bosniak classification is reviewed in Silverman et al. (2019)

Multilocular Cystic Nephroma (i.e., Papillary Cystadenoma, Benign Cystic Nephromas) (Fig. 6.17)

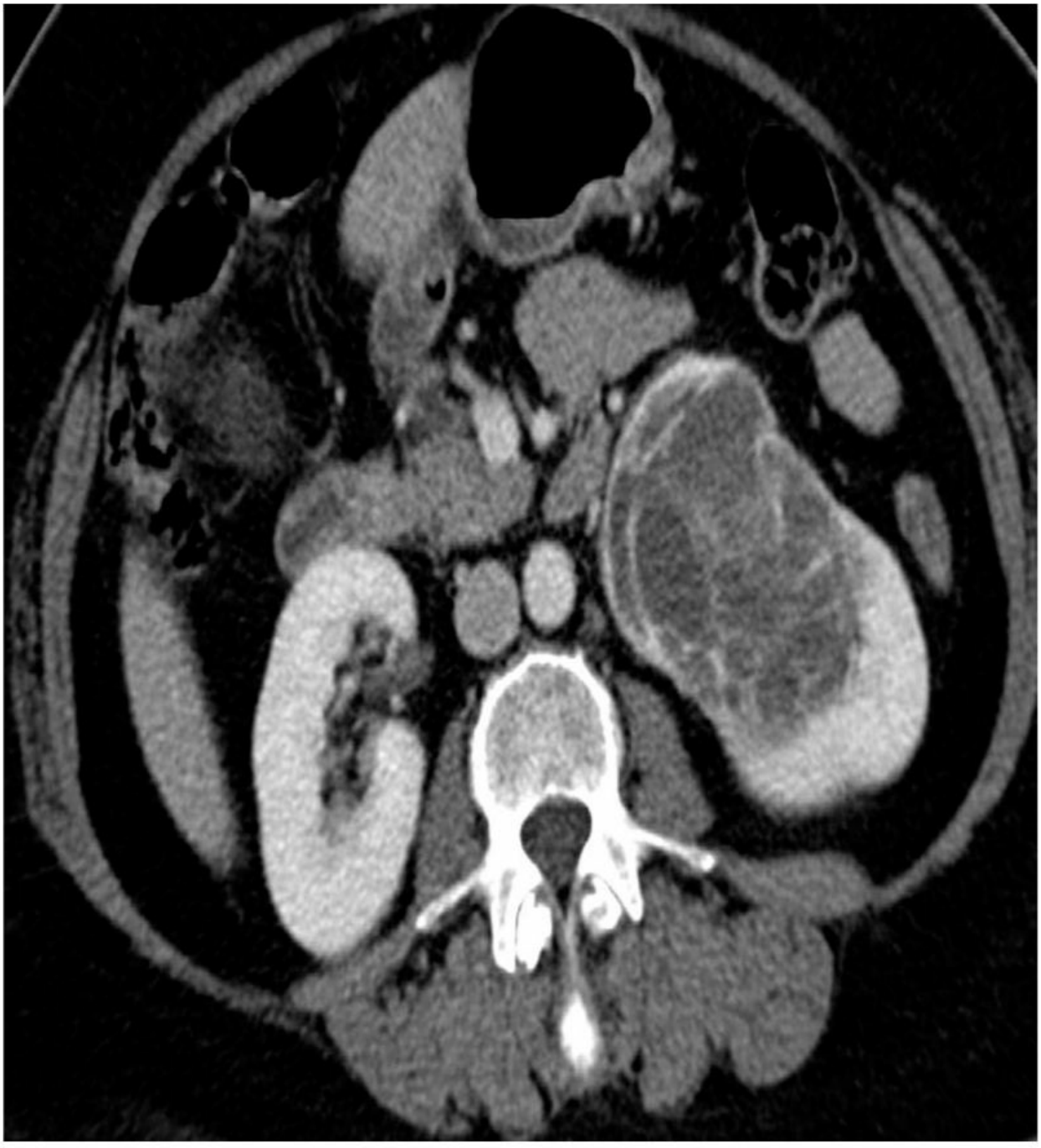


FIGURE 6.17 Multilocular cystic nephroma. Axial postcontrast computed tomography image showing a well-circumscribed multilocular cystic mass with septal enhancement. This lesion is indistinguishable from renal cell carcinoma on imaging.

- Benign mixed mesenchymal and epithelial slow-growing neoplasm in the kidney
- Diagnosis:

- Ultrasound findings:
  - Unilateral mass with irregular cysts and septa of variable thicknesses
  - Generally classified as Bosniak III that requires surgery to exclude malignancy
- CT findings:
  - Well-circumscribed cystic mass with hypoattenuated components with no contrast excretion into cystic components
  - Contrast enhancement of septa may be seen.

- Clinical manifestations:
  - Follows a bimodal age and sex pattern: boys 3 months to 4 years; postmenopausal women 40 to 60 years of age
  - Abdominal pain, palpable mass, hematuria, HTN
- Complications: flank pain, hematuria, calculi, urinary tract infections. Carcinomatous degenerations may occur.
- Management: surgical resection; malignant transformation was observed in 3.4% in a systematic literature review.

Glomerulocystic Kidney Disease

- GCKD may present as a familial dominant or sporadic condition or infantile manifestation of ADPKD.
- GCKD is characterized by cystic dilation involving Bowman space and proximal tubules.
- Ultrasound may be notable for increased echogenicity of renal cortex with minute cysts. Associated renal medullary dysplasia and biliary dysgenesis may be found in infants with familial or sporadic GCKD.
- GCKD can present as an isolated condition, infantile manifestation of ADPKD, part of a disease syndrome involving a heritable malformation syndrome (e.g., TSC, VHL), acquired and dysplastic kidneys, or familial hypoplastic kidneys. Familial hypoplastic GCKD presents with relatively small kidneys with medullocalyceal abnormalities and variable associations with gynecologic abnormalities and maturity-onset diabetes of the young type 5 (MODY5).

Table 6.3 summarizes major renal cystic diseases and important associated

clinical features.

Access the eBook for self-assessment questions.

CHAPTER 7

Glomerular and Vascular Disorders

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GENERAL PRINCIPLES IN THE MANAGEMENT OF GLOMERULAR DISEASES

Kidney Biopsy

- Kidney biopsy should be performed when results will change management and/or refine prognosis. See **Fig. 7.1** for kidney biopsy indications.

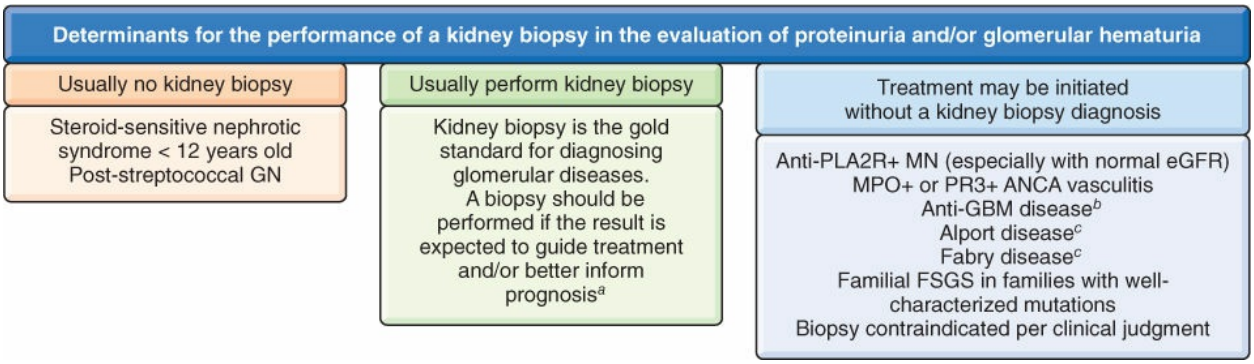

FIGURE 7.1 Kidney biopsy indications.

[a]A kidney biopsy may also be performed at the discretion of the nephrologist (e.g., new unexplained active urinary sediment or worsening proteinuria).

[b]In the presence of positive anti-GBM antibodies and classic presentation.

[c]Positive genetic analysis; Low α-galactosidase A activity in leukocytes of males with history in Fabry disease.

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; GN,

glomerulonephritis; MN, membranous nephropathy; MPO+, myeloperoxidase positive; PLA2R, phospholipase A2 receptor; PR3+, proteinase 3 positive.

- Repeat kidney biopsy indications:
  - Initial biopsy is inadequate for diagnosis.
  - Biopsy results will change management and/or refine prognosis.
    - Poor response to therapy
    - Unexpected deterioration of kidney function
    - Clinical or laboratory findings suggesting a change in severity of same disease (e.g., conversion of membranous to active diffuse lupus nephritis [LN])
    - Clinical or laboratory findings suggesting a new disease process
    - Unclear cause of glomerular filtration rate (GFR) deterioration, chronic progression versus active disease
    - Determination of disease chronicity for treatment decisions (stop, continue, or intensify therapy)
- Kidney biopsy adequacy:
  - Defined by sample size and location submitted for each microscopic method used (**Fig. 7.2**)

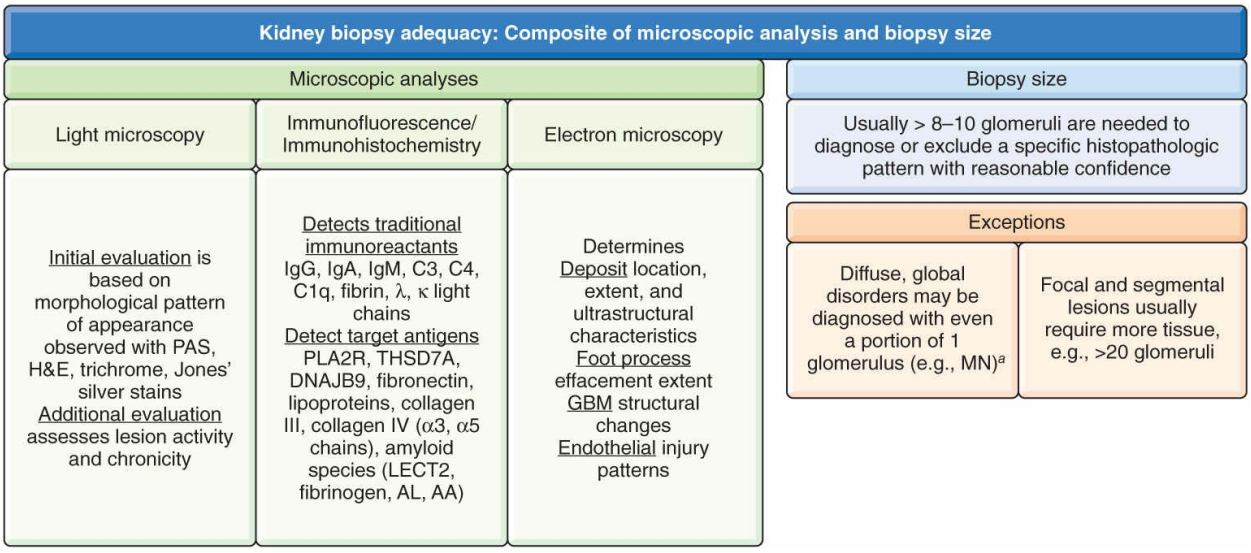

FIGURE 7.2 Kidney biopsy adequacy.

[a]While a limited diagnosis can be made, additional information (activity, chronicity, presence of secondary FSGS or crescents) will not be available when the specimen is suboptimal.

Abbreviations: AA, amyloid A; AL, amyloid light chain; DNAJB9, DnaJ homolog subfamily B

member 9; FSGS, focal segmental glomerulosclerosis; H&E, hematoxylin and eosin; LECT2, leukocyte chemotactic factor 2; MN, membranous nephropathy; PAS, periodic acid–Schiff; PLA2R, phospholipase A2 receptor; THSD7A, thrombospondin type 1 domain containing 7A.

- In general, a minimum of 8 to 10 glomeruli/biopsy; diffuse diseases can be diagnosed with one glomerulus (membranous nephropathy [MN], immunoglobulin A [IgA] nephropathy [IgAN]).
- However, activity, chronicity, and other findings require more biopsy tissue.
- Focal and/or segmental disease diagnosis requires more glomeruli (may need 20 glomeruli for focal segmental glomerulosclerosis [FSGS]).

General Management Considerations for Glomerular Diseases

Hypertension (HTN)

- Goal systolic blood pressure (SBP) is <120 mm hg using standardized office bp measurement in adult patients and <140/90 mm hg in pregnant patients with glomerular disease and proteinuria.
- Lifestyle modifications: salt restriction, weight optimization, exercise, smoking cessation
- Clinical data support angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB) as first-line therapy if safely tolerated:
  - Educate discontinuation for volume depletion (vomiting, diarrhea, sweating from high fever/strenuous exercise).
  - Monitor serum creatinine (SCr) and K^+ frequently: Discontinue if SCr rises >20% from baseline.
  - K^+-lowering medications may be considered if hyperkalemia limits ACEI/ARB tolerability. See Chapter 2.
- Second-line medical therapy:
  - Mineralocorticoid-receptor antagonist (e.g., spironolactone, eplerenone):
    - Useful antihypertensive and antiproteinuric agents, particularly in ACEI/ARB intolerant patients
    - May require discontinuation if hyperkalemia develops
    - Salvage therapy with K^+ binders may be feasible.
- Additional strategies:

- Reducing BP with antihypertensive agents without angiotensin blocking activity also reduces proteinuria.
- Loop and thiazide diuretics improve BP control, reduce hyperkalemia, and enhance the antiproteinuric effect of renin–angiotensin–aldosterone system inhibitor (RAASi).

Proteinuria

- First-line medical therapy:
  - ACEI or ARB may reduce proteinuria by 40% to 50%. ACEI/ARB may be delayed in normotensive patients with podocytopathy expected to be easily responsive to immunosuppression (e.g., minimal change disease [MCD], primary FSGS, or steroid-sensitive nephrotic syndrome [NS]).
  - Combination may result in additive antiproteinuric effect, but hyperkalemia and acute kidney injury (AKI) may also be additive and unacceptable.
- Others:
  - For patients who cannot tolerate ACEI or ARB, consider nondihydropyridine calcium channel blockers (e.g., diltiazem).
  - Intensify dietary sodium restriction (<2 g sodium) and consider using mineralocorticoid-receptor antagonists in patients who fail to achieve proteinuria reduction despite maximal medical therapy.
- Dietary protein intake in patients with proteinuria (emphasize plant sources):
  - For patients with nephrotic-range proteinuria, advise 0.8 to 1 g/kg ideal body weight/d; add an additional 1 g/g of urinary protein losses (up to 5 g/d).
  - For those with non–nephrotic-range proteinuria and estimated GFR (eGFR) < 60 ml/min/1.73 m^2, advise 0.8 g/kg/d.

Hyperlipidemia

- Statin (HMG-CoA reductase inhibitors) use should be per standard guidelines for those with increased atherosclerotic cardiovascular disease (ASCVD) risks. Note that reduced eGFR < 60 ml/min/1.73 m^2 not on dialysis and albumin to creatinine ratio (acr) > 30 µg/mg are independently

associated with increased risk of ASCVD.

- Statins have not been proven to reduce cardiovascular events (CVEs) in NS (particularly MCD).
- The renoprotective effect of statins in slowing GFR decline is not established.
- The role for nonstatins (e.g., ezetimibe, fibrates, or PSCK9 inhibitors) in NS remains to be defined.

Nephrotic edema

- Intravenous (IV) loop diuretics should be considered if anasarca is present because bowel wall edema limits oral medication absorption. Twice-daily administration is preferred.
- Furosemide-resistant edema:
  - Consider switching furosemide to torsemide or bumetanide for better bioavailability.
  - Add thiazide, thiazide-like diuretics (e.g., metolazone), and/or mineralocorticoid antagonists to loop diuretics.
  - For diuretic-resistant edema, consider amiloride, acetazolamide, IV loop diuretics, ultrafiltration, or hemodialysis. *In particular, consider adding amiloride in patients with high degree of proteinuria. Patients with proteinuria may have increased urinary plasmin level that directly stimulates sodium epithelial channel (ENaC) activity, thus sodium reabsorption.*
  - Consider albumin infusion with diuretics, although benefit remains unproven.
- Dietary sodium restriction < 2.0 g (<90 mmol) daily

Hypercoagulability

- Increased thromboembolism (TE) risk in patients with NS with serum albumin <2.5 g/dl
- Anticoagulation with heparin or warfarin (target international normalized ratio [INR] 2 to 3) if known arterial or venous thrombosis or pulmonary embolism for 6 to 12 months and/or for the duration of the NS
- Consider prophylactic full-dose anticoagulation if serum albumin <2.0 to

2.5 g/dl *and* one or more of the following: proteinuria >10 g/d, body mass index > 35 kg/m^2, family history of TE with documented genetic predisposition; New York Heart Association functional class III or IV congestive heart failure, recent abdominal or orthopedic surgery, or prolonged immobilization.

- During heparin anticoagulation, a higher-than-average dose may be required because part of heparin action depends on antithrombin III, which may be lost in urine in nephrotic patients.
- Aspirin may be used in lieu of heparin or warfarin in patients with high bleeding risk.
- Aspirin may also be used in patients with serum albumin between 2.5 and 3.2 g/dL and increased estimate arterial TE risk of > 20/1,000 person-year.
- Neither the efficacy nor safety of direct thrombin and factor Xa inhibitors has been systematically studied in patients with nephrotic-range proteinuria.

Risk of infection

- Spontaneous bacterial peritonitis (SBP) may occur in nephrotic patients with ascites. Empiric antibiotics should include benzylpenicillin (pneumococcal infection).
- In recurrent SBP, consider monthly IV Ig 400 mg/kg daily × 4 days to keep serum IgG >600 mg/dL (limited evidence).
- Screening and treatment for latent diseases should optimally be performed prior to or concomitant with the initiation of immunosuppression.
  - For most patients, screen for hepatitis B and C, human immunodeficiency virus (HIV), syphilis, and tuberculosis (TB).
  - For patients from a tropical climate, screen for Strongyloides.
- Latent TB should be treated concomitantly with immunosuppression. Four months of rifampin has been suggested to be noninferior to 9 months of isoniazid and pyridoxine. Note however, rifampin may decrease the bioavailability of corticosteroids.
- Prophylactic trimethoprim–sulfamethoxazole (dapsone or atovaquone if sulfa-allergic) should be considered as prophylactic therapy against *Pneumocystis jirovecii* (previously known as *Pneumocystis carinii*

pneumonia) when high-dose corticosteroids or other immunosuppressive agents are used.

- Pneumococcal vaccination with both heptavalent conjugate vaccine (7vPCV) and 23-valent polysaccharide vaccine (23vPPV), annual influenza vaccination, and recombinant herpes zoster vaccine should be given.
  - The effectiveness of the recombinant zoster vaccine may be diminished in patients taking corticosteroids.
  - Vaccination with both a meningococcal conjugate vaccine (MenACWY) and a serogroup B meningococcal vaccine (MenB) should be provided to patients receiving complement inhibitor medications (i.e., eculizumab). Since these may confer only partial protection, the Centers for Disease Control also recommends additional concomitant meningococcal antibiotic prophylaxis (cdc.gov/meningococcal/clinical/eculizumab.html).

NEPHRITIC GLOMERULAR DISORDERS AND VASCULITIS/VASCULOPATHY

Immunoglobulin A Nephropathy

Background

- Most common glomerulonephritis (GN) worldwide
- Highest incidence in Eastern Asians; common in South Indians, Native Americans, and Mediterranean Europeans; very low incidence in African Americans
- 15% to 25% reach end-stage kidney disease (ESKD) within 10 years, and 20% to 40% by 20 years
- Comprises 10% to 20% of ESKD due to high prevalence

Pathogenesis (multistep model, steps 1 to 5)

1. Initial mucosal inciting event/pathogen exposure:
   - Naïve mucosal B cells switch class to become IgA antibody-secreting cells through T-cell–dependent (cytokine-mediated) and T-cell–independent (Toll-like–receptor ligation) pathways.

Mucosal types IgA are **IgA1 with galactose deficient at hinge region *(Gd-IgA1)***.

 Normal circulating IgA1  Mucosal type galactose deficient at hinge region of IgA1 (Gd-IgA1)

2. Due to genetic and/or other undetermined factors, some mucosal Gd-IgA1 ***secretory B cells "mis-home" or "mis-traffic" and enter systemic compartments*** while continuing to secrete Gd-IgA1 systemically.
3. ***Antibodies directed against the underglycosylated hinge region of Gd-IgA1 are produced***, likely driven by molecular mimicry.

 IgA or IgG antibodies directed against Gd-IgA1 are produced.

4. ***The immune complexes [ICs] deposit in the mesangium in the kidneys***
   - ICs are preformed in circulation or formed in situ when circulating IgA or IgG antibodies bind to previously deposited IgA1 in the mesangium.
   - ICs deposition in the mesangium is likely driven by mesangial trapping and increased affinity for Gd-IgA1 by mesangial matrix.
5. Deposited ICs ***activate complement and other pathways and lead to mesangial cell proliferation, matrix deposition, glomerular injury, and tubulointerstitial fibrosis***.

Clinical manifestations

IgAN may present as primary GN, a GN secondary to a systemic disease, or a systemic vasculitis.

Primary IgAN

- May present at any age
- Organ involvement is restricted to the kidneys.
- Presents with diverse clinical patterns
  - Episodic macroscopic "gross" hematuria
    - More common in children
    - Associated with upper respiratory tract infection or gastroenteritis
      - Gross hematuria occurs concurrently (synpharyngitic) or within 3

days of onset of infection.
    - Typically resolves by 3 days (different than postinfectious glomerulonephritis [PIGN])
    - Hematuria may be accompanied by flank or loin pain.
- Asymptomatic hematuria and proteinuria (incidental finding):
    - More common in adults
    - Prolonged remission of clinical signs is common.
- HTN and impaired kidney function
- Gross hematuria with concurrent AKI
- Nephrotic-range proteinuria
    - Occasionally with concomitant kidney biopsy findings consistent with MCD
    - May have concomitant FSGS and present with or without NS
- Slowly progressive chronic kidney injury
- Rapidly progressive (crescentic) glomerulonephritis (RPGN)

Secondary IgAN

- Generally, secondary IgAN presents in association with conditions involving organs that produce or clear IgA, conditions that stimulate IgA production, or autoimmune diseases.
- Conditions associated with IgAN:
    - Skin: dermatitis herpetiformis, psoriasis, psoriatic arthritis
    - Liver: alcoholism, primary biliary cirrhosis, cirrhosis; hepatitis B, chronic schistosomiasis. Cirrhotic liver has reduced capacity to metabolize/clear IgA.
    - Gastrointestinal (GI) tract: inflammatory bowel disease, celiac disease, ulcerative colitis, Crohn
    - Pulmonary: sarcoidosis, idiopathic hemosiderosis, cystic fibrosis, bronchiolitis obliterans, antineutrophil cytoplasmic antibody (ANCA) disease involving upper respiratory tract
    - Neoplasia: lung, larynx, pancreas, mycosis fungoides
    - Infection: HIV, leprosy

- Systemic or immunologic disorders: systemic lupus erythematosus (SLE), rheumatoid arthritis, cryoglobulinemia, ankylosing spondylitis, Sjögren, Behçet, Reiter, familial immune-mediated thrombocytopenia, autoantibody IgA-mediated Goodpasture
- Infectious: IgA-dominant infection-related GN (IgADIRGN)

Systemic IgA Vasculitis (i.e., Henoch–Schönlein Purpura)

- IgA vasculitis (IgAV) usually occurs in the first decade of life but may occur at any age.
- Children: Ankara 2008 composite IgAV classification requires:
  - Purpura or petechiae with lower limb predominance, and
  - At least one of the following four criteria: (1) abdominal pain, (2) histopathology, (3) arthritis or arthralgia, (4) renal involvement
  - 100% sensitivity and 87% specificity for IgAV
- Adults: American College of Rheumatology (1990) published criteria for IgAV
  - Requires at least two of the following: (1) age ≤20 years at disease onset, (2) palpable purpura, (3) acute abdominal pain, (4) skin or bowel wall biopsy showing granulocytes in the walls of small arterioles/venules
  - 87.1% sensitive and 87.7% specific for IgAV
- Patients with IgAV should be screened for malignancy and other secondary causes.

Diagnosis of IgAN

- Diagnosis is by kidney biopsy.
- Currently, there are no validated surrogate diagnostic or prognostic markers.

Histopathology (Fig. 7.3)

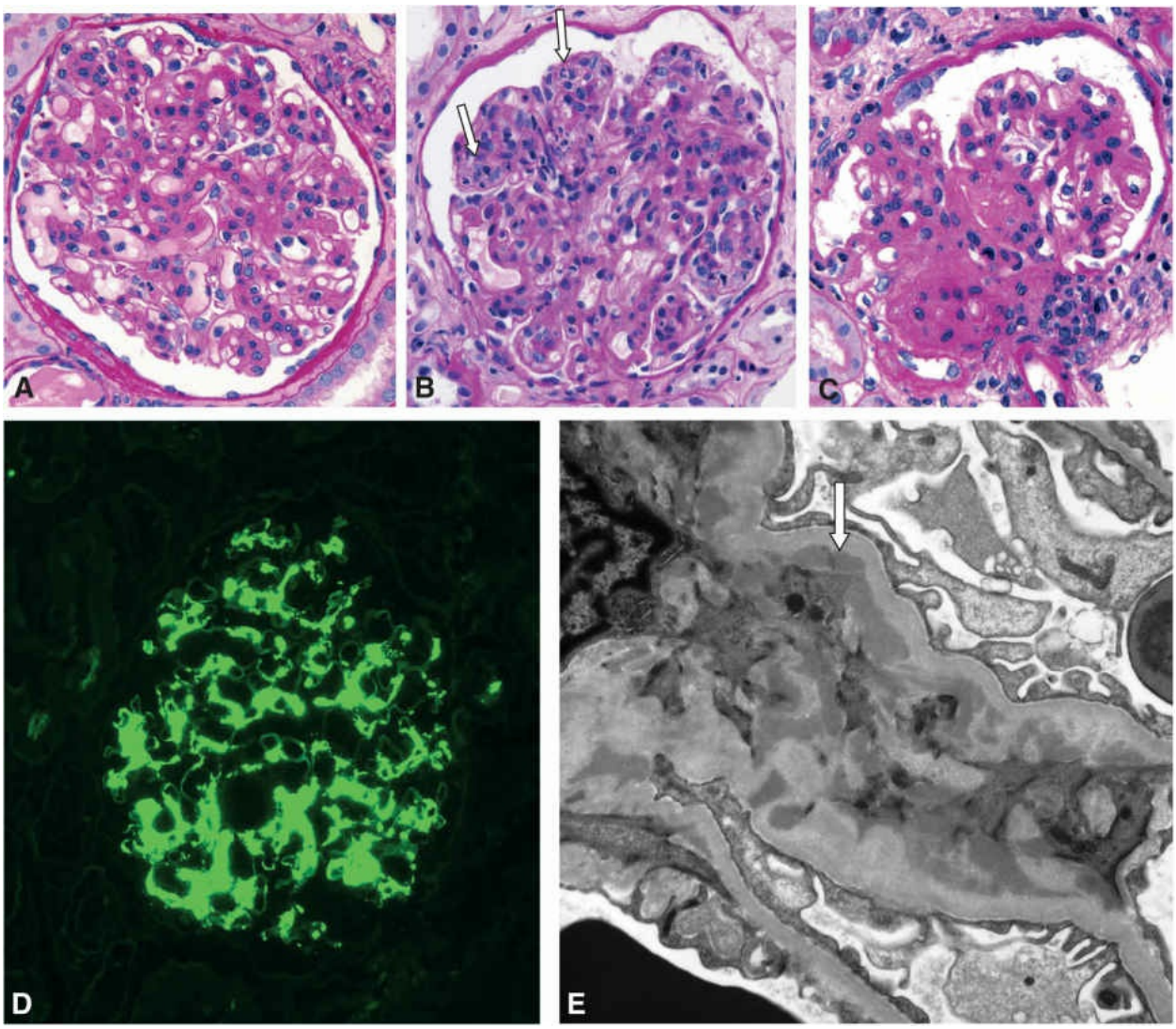

FIGURE 7.3 Immunoglobulin A (IgA) nephropathy. **A.** Global mesangial hypercellularity (M1 lesion) (periodic acid–Schiff ×400). **B.** Endocapillary hypercellularity with luminal occlusion (*arrows*) (E1 lesion) (periodic acid–Schiff ×400). **C.** Mesangial hypercellularity and segmental glomerulosclerosis (M1 and S1 lesions) (periodic acid–Schiff ×400). **D.** Global mesangial IgA (×275). **E.** Mesangial electron-dense deposits, prominent in the paramesangial region (*arrow*) with a single subepithelial deposit (×14,000).

- Light microscopy (LM): mesangial expansion and hypercellularity, may be segmental and/or global glomerulosclerosis, endocapillary hypercellularity, crescents
- Immunofluorescence (IF): dominant or co-dominant mesangial IgA deposits
  - IgG, IgM, *and/or* C3
  - Staining for λ is typically greater than κ.

"MEST-C" OXFORD Classification for primary IgAN

- Definition:
  - **M**esangial hypercellularity: >50% glomeruli = M1, otherwise M0
  - **E**ndocapillary hypercellularity: ≥one occluded glomerular capillary = E1, otherwise E0
  - **S**egmental sclerosis: ≥one segment of sclerosis or adhesion = S1, otherwise S0
  - **T**ubular atrophy and interstitial fibrosis: T0 = 0% to 25%, T1 = 26% to 50%, T2 >50%
  - **C**rescents**:** C0 = no crescent
    - C1 = active (cellular/fibrocellular) crescent in at least one glomerulus but <25% of glomeruli
    - C2 = active crescents in ≥25% of glomeruli
- MEST-C scoring predicts renal outcome.
  - M1, S1, ≥T1, and ≥C1 are associated with worse prognosis.
  - M1, S1, and T1 are additive.
  - E1 and C1 may be improved with immunosuppression.
- There are insufficient data to support the use of MEST-C scoring to guide treatment or predict response in patients with IgAN.

Management

- Table 7.1 summarizes management strategies for patients with IgAN.

Table 7.1 Management strategies for primary IgAN and variants

All patients with any form of IgAN	• BP control with goal systolic pressure 120 mm hg using standardized office bp as safely tolerated • ACEI or ARB is recommended if proteinuria > 1 g/d, otherwise ACEI/ARB is suggested. • Aldosterone blockers may also be considered for antiproteinuric and antifibrotic effects. • Healthy lifestyle modifications per routine ACA/AHA hypertension guidelines • IST is not recommended if eGFR 30 mL/min/1.73 m^2 (not reflecting AKI) and/or kidney biopsy evidence of chronic disease.
Primary IgAN	• Consider IST for persistent proteinuria > 1g/d despite maximal routine care above for 6 mo

	• Suggested IST (data on optimal therapy are still lacking):
	  • Oral prednisone at 0.8–1.0 mg/kg/d × 2 mo, then reduce by 0.2 mg/kg/d per month for the next 4 mo, *or*
	  • Intravenous bolus of 1 g methylprednisolone × 3 d at months 1, 3, and 5, followed by oral prednisone at 0.5 mg/kg/d on alternate days × 6 mo
	• Alternative:
	  • Low-dose corticosteroid + MMF (Chinese study)
	  • MMF was not beneficial in a study involving Caucasians.
	• Other considerations:
	  • Tonsillectomy: only consider in patients with recurrent tonsillitis
	  • Not recommended due to lack of evidence: anticoagulants, antiplatelets, AZA, CYC, fish oil

Secondary IgAN	• Treat underlying etiology if possible
Nephrotic IgAN with MCD	• Treat as MCD
Rapidly progressive/crescentic IgAN	• Rule out and treat secondary causes (e.g., acute inflammatory disorders or ongoing infections) • Treat with CYC and corticosteroids analogous to ANCA-associated vasculitis if clinical safe
IgA vasculitis (HSP)	• Consider corticosteroids course above
Pregnancy	• Consider 6-mo course of IST prior to conception if high progression risk
Children	• Most pediatric nephrologists treat children with proteinuria > 1g/d and mesangial hypercellularity (Oxford M1) with RAASi + corticosteroids. • Children with rapidly progressive IgAN have a poor outcome, corticosteroids and oral CYC may be considered.

Abbreviations: ACA/AHA, American Cardiology Association/American Heart Association; ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ANCA, antineutrophil cytoplasmic antibody; ARB, angiotensin-receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; IgAN, IgA nephropathy; MCD, minimal change disease; MMF, mycophenolate mofetil; RAASi, renin–angiotensin–aldosterone system inhibitor.

Supportive care

- Provide supportive care as tolerated for all patients with any variant of IgAN
- ACEI or ARB, but not both, is *recommended* in all patients with proteinuria > 0.5 g/d with or without HTN.
- Aldosterone blockers may also be considered for antiproteinuric and antifibrotic effects.
- Healthy lifestyle modifications per routine American College of

Cardiology/American Heart Association (ACA/AHA) HTN guidelines
- Consider tonsillectomy only if recurrent tonsillitis

Immunosuppressive therapy for primary IgAN

- Consider treatment for patients with high risk of chronic kidney disease (CKD) progression, for example, persistent proteinuria > 1 g/d despite maximal supportive care for 6 months.
- Consider enrollment in clinical trial if applicable.
- Otherwise, consider a 6-month course of corticosteroid (weak evidence). Mycophenolate mofetil (MMF) may be considered as a steroid-sparing agent in Chinese patients. Data for non-Chinese are insufficient.
- Agents not recommended at this time: azathioprine (AZA), cyclophosphamide (CYC) (unless rapidly progressive IgAN [RP IgAN]), calcineurin inhibitor (CNI), rituximab (RTX), fish oil; data on Acthar gel remain scant.

Considerations for IgAN variants

- Nephrotic IgAN with minimal change on biopsy: treat as minimal change
- IgAN with AKI in the absence of common reversible causes: Repeat kidney biopsy if AKI persists for ≥ 2 weeks to rule out rapidly progressive (RP) IgAN.
- RP IgAN: treat with CYC and corticosteroids similar to the treatment of ANCA-associated vasculitis (AAV). RTX has not been shown to be effective in this IgAN subset. (RP IgAN is defined as a kidney biopsy with mesangial and endocapillary hypercellularity, many crescentic glomeruli, often with segmental focal necrosis. Clinically, RP IgAN is defined as ≥50% decline in eGFR over 3 months or less after excluding reversible causes [e.g., pre- and post-kidney causes]. Having crescents without a concomitant decline in kidney function does not define RP IgAN.)
- Secondary IgAN: evaluate and treat secondary causes
- IgAV: for patients at high risk for CKD progression despite maximal supportive care: treat with corticosteroids as described above for primary IgAN.
- IgAN in pregnancy planning: For patients with high CKD progression risk,

consider a 6-month course of immunosuppression to optimize proteinuria prior to conception.

- IgAN in children:
  - Most pediatric nephrologists treat children with proteinuria > 1 g/d and mesangial hypercellularity (Oxford M1) with RAASi + corticosteroids.
  - Children with RP IgAN have a poor outcome. Treatment with corticosteroids and oral CYC may be considered (limited data).

Caveats regarding immunosuppressive therapy for patients with IgAN

- For patients with non-nephrotic proteinuria, the benefits of corticosteroids have not been proven. Corticosteroids should be avoided in patients with relative contraindications, including diabetes mellitus (DM), obesity, latent infections (e.g., viral hepatitis, TB), secondary IgAN, uncontrolled psychiatric illness, and a history of upper GI bleeding.
- Immunosuppressive therapy is not recommended for patients with eGFR <30 ml/min/1.73 m^2 that does not reflect aki and/or those with a high-quality (good sampling) kidney biopsy consistent with chronic disease.
- Risks and benefits of using immunosuppression must be discussed in patients with eGFR < 50 ml/min/1.73 m^2 due to the increased likelihood of adverse effects.
- The presence of crescents in a kidney biopsy is not an automatic indication for starting immunosuppression in the absence of concomitant functional change.

Prognostic indicators

- Patients with IgAN who have persistent *proteinuria* ≥1 g/d despite ≥ 90 days of optimal supportive care are at high risk for progressive CKD.
- Risk stratification for disease progression based on the IgAN International Prediction Tool:
  - https://qxmd.com/calculate/calculator_499/international-igan-prediction-tool
  - This risk-stratification tool does not predict responses to any particular treatment.

RENAL AND SYSTEMIC VASCULITIDES

Classification of Vasculitis

Large-sized vessels: aorta ã renal artery

- Granulomatous arteritis: giant cell or Takayasu arteritis (Table 7.2)

Table 7.2 Large-sized vasculitis: Giant cell versus Takayasu arteritis

	Giant Cell Arteritis	Takayasu Arteritis
Age of onset	Typically > 50 y old	10–20 y old; very rare after age 50
Gender	Female:Male: 4:1	Female:Male: 9:1
Pathogenesis	Unclear: thought to involve genetics, sex, and age-related alterations of the immune and arterial systems	Unclear: presumed autoimmune disease triggered by bacteria, viruses, or tuberculosis followed by an autoimmune process driven by molecular mimicry
Clinical manifestations	Headaches, temporal artery tenderness, blindness, deafness, jaw claudication, tongue dysfunction, reduced pulses, extremity claudication; >50% have polymyalgia rheumatica (stiffness and aching of the neck, hips, shoulders); renal involvement is rare compared with Takayasu; hypertension possible	Reduced pulses, vascular bruits, claudication, renal ischemia due to renal artery stenosis or aortic coarctation; hypertension possible
Pathology	Renal arteries may be involved, but significant disease is rare.	Ischemic renal disease relatively common; glomerular lesion possible; nodular mesangial matrix expansion, mesangiolysis
Treatment	Same for both conditions: corticosteroid (prednisolone 1 mg/kg/d for 1 mo, followed by slow taper over several months. Persistent disease requires prolonged corticosteroid and/or cytotoxic agents (e.g., cyclophosphamide); patients with giant cell arteritis should also be on low-dose aspirin to reduce thrombotic risks. Surgical bypass or angioplasty may be required when disease is quiescent.	

- Patients >50 years of age: giant cell arteritis
- Patients <50 years of age: takayasu arteritis

Medium-sized vessels: renal artery ã interlobar artery ã arcuate artery

- Necrotizing arteritis: polyarteritis nodosa (PAN) or Kawasaki disease (Table 7.3)

Table 7.3 Medium-sized vasculitis: Polyarteritis nodosa versus Kawasaki arteritis

	Polyarteritis Nodosa (PAN)	Kawasaki
Age of onset	• Age 40–60 y old	• Young children, peaks at age 1, typically 5 y old
Epidemiology	• No gender preference	• Asians and Polynesians > Caucasians and blacks • Sporadic; occasional endemic or endemic pattern
Pathogenesis	• Unknown; immune-complex trigger (e.g., HBV, other infections) suggested, but not confirmed • Absence of ANCA	• Not clear • Possible precipitating factors: agent or environmental toxin • Both cell- and antibody-mediated mechanisms possible
Clinical manifestations	• ACR criteria: having a radiographic or pathologic diagnosis of vasculitis and ≥three of the following: (1) weight loss ≥ 4 kg, (2) livedo reticularis, (3) testicular tenderness, (4) myalgia or leg weakness/tenderness, (5) mononeuropathy or polyneuropathy, (6) DBP > 90 mm Hg, (7) elevated BUN or SCr unrelated to dehydration or obstruction, (8) HBsAg or HBsAb, (9) arteriogram with aneurysms or occlusions of visceral arteries, (10) positive polymorphonuclear neutrophils in biopsy of small- or medium-sized artery • **No mucocutaneous lymph node involvement**	• **Mucocutaneous lymph node syndrome:** fevers, mucosal inflammation, swollen red (strawberry) tongue, polymorphous erythematous rash, indurative edema of extremities, erythema of palms/soles, desquamation from tips of digits, conjunctival injection, lymphadenopathy, coronary arteritis (possible myocardial infarction). • Renal arteritis is uncommon. • Disease is typically self-limited.
Histopathology	• Renal artery, interlobar, arcuate, interlobular arteries; involvement of capillaries, arterioles venous beds *exclude PAN* • Nodular inflammatory lesions and aneurysms in arteries • Acute arterial lesion: segmental transmural fibrinoid necrosis and/or leukocyte infiltration; chronic changes: arterial wall erosions from necrotizing inflammation into surrounding	• Small and medium arteritis with necrotizing inflammation, frequently involving coronaries and renal arteritis (interlobar > arcuate > interlobular arteries) • Pseudoaneurysm formation and thrombosis may occur.

	perivascular tissue leading to appearance of enlarged lumen, hence "pseudoaneurysm" and propensity for thrombosis and rupture • **Note:** Light microscopy changes of involved vessels are indistinguishable from ANCA-associated GN.	
Treatment	• Corticosteroid alone may be adequate if benign (younger age, no cardiac, gut, or renal involvement). • If no hepatitis B: corticosteroid and/or cytotoxic agent (e.g., cyclophosphamide) • If hepatitis B+ and severe disease: consider a short course of corticosteroid + plasma exchange pending response to antiviral therapy.	• Aspirin and intravenous Ig therapy and/or corticosteroids • Recurrence is rare if promptly treated.

Abbreviations: ACR, American College of Rheumatology; ANCA, antineutrophil cytoplasmic antibody; BUN, blood urea nitrogen; DBP, diastolic blood pressure; GN, glomerulonephritis; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B; SCr, serum creatinine.

- Polyarteritis nodosa
  - Usually occurs in adults and without mucocutaneous lymph node (MCLN)
  - Microaneurysms may resemble "beads on a chain" on angiogram (**Fig. 5.3**).
- Kawasaki disease
  - Typically occurs in children in association with MCLN syndrome

Small-sized vessels: interlobar artery ã arcuate artery ã interlobular artery ã arterioles ã glomerular capillaries

- Immune complexes in vessel walls:
  - Cryoglobulins: cryoglobulin deposits often affecting both skin and glomeruli
  - IgA-dominant deposits (IgAV): vasculitis involving skin, gut, and glomeruli, with associated arthritis/arthralgias
  - SLE or rheumatoid arthritis
  - Others: postinfectious, hypocomplementemic urticarial (anti-C1q) vasculitis
- Circulating ANCAs with paucity of vascular or glomerular Ig staining:

- Lung granulomas and no asthma: granulomatous polyangiitis (GPA)
- Eosinophilia, asthma, and lung granulomas: eosinophilic granulomatosis with polyangiitis (EGPA)
- No asthma or lung granulomas: microscopic polyangiitis (MPA)

ANCA Vasculitis

Definition of ANCA

- ANCA are antineutrophil cytoplasmic auto**antibodies** directed against various lysosomal enzymes that "serve" as **antigens.**
  - Some ANCA are directed *against* proteinase 3 (anti-PR3).
  - Some ANCA are directed *against* myeloperoxidase (anti-MPO).
  - Other (atypical) ANCA are directed *against other* antigens/proteinases (e.g., human neutrophil elastase [HNE], lysozyme).
    - The pathogenic roles of atypical ANCAs are unclear.
    - Cystic fibrosis: ANCA directed against bactericidal/permeability-increasing protein
    - Cocaine adulterated with levamisole:
      - Most if not all patients appear to have MPO-ANCA, 50% also with PR3-ANCA.
      - ANCA may also be directed against HNE.
      - Affected patients may present with purpuric to necrotic skin lesions, often earlobes and nose
      - Renal manifestations may include crescentic GN or renal infarction
    - Inflammatory bowel disease: atypical ANCA directed at high mobility groups (HMG) 1 and/or 2

c-ANCA and p-ANCA

- Cytoplasmic (c-ANCA) and perinuclear (p-ANCA) refer to the ANCA staining pattern in ethanol-permeabilized neutrophils exposed to patient serum.
  - All antigens (including MPO) are cytoplasmic in vivo.
  - c-ANCA is typically directed against PR3.

- p-ANCA is typically directed against MPO.
- Atypical ANCAs are directed at antigens other than MPO or PR3.
- c-ANCA and p-ANCA can bind to proteinases other than PR3 and MPO that are not necessarily pathogenic.
- Initial testing for ANCA should include indirect immunofluorescence microscopic assay (IFA) for c-ANCA or p-ANCA pattern followed by enzyme immunoassay (EIA) for specificity against PR3, MPO, or other antigens.

Notes regarding ANCA

- Classic PAN is usually ANCA negative.
- 30% of patients with anti–glomerular basement membrane (anti-GBM)–positive sera, 25% of patients with SLE, and 25% of patients with idiopathic IC crescentic GN have concurrent ANCA.
- 5% of patients with ANCA-positive sera also have anti-GBM antibodies.
- Patients with concurrent anti-GBM and ANCA antibodies:
  - Rare occurrence
  - May be fortuitous coexistence of anti-GBM and ANCA
  - Anti-GBM may develop following GBM injury from ANCA-associated GN.
  - Disease course is similar to anti-GBM GN in early disease, but relapse pattern is similar to ANCA disease.

Proposed pathogenesis of AAV

1. Priming of neutrophils by cytokines (e.g., from a viral infection) *leads to*:
2. Increased neutrophil expression/trafficking of cytoplasmic ***ANCA antigens*** (e.g., PR3 or MPO) onto cell surfaces, where they are accessible to ANCA.
3. The **ANCA–ANCA antigen** interaction in cytokine-primed neutrophils *leads to*:

   a. Neutrophil release of enzymes from granules, toxic oxygen metabolites, inflammatory mediators into surroundings *and*

   b. Adherence of activated neutrophils to endothelial cells, *both leading to*:
4. Endothelial cell injury, vascular thrombosis, and downstream ischemia

Clinical manifestations

- See Table 7.4 for well-characterized ANCA syndrome specific clinical manifestations.

Table 7.4 Clinical manifestations of ANCA-associated vasculitis syndromes

ANCA-associated vasculitis syndromes	MPA 30%–40% PR3, 50%–60% MPO, 10%–30% negative ANCA	GPA 75%–90% PR3, 10%–20% MPO, 5%–10% negative ANCA	EGPA 5%–10% PR3, 40%–60% MPO, 30%–50% negative ANCA	Renal limited vasculitis[a] 10%–20% PR3,70%–90% MPO, 10% negative ANCA
Patient characteristics	Fifth to eighth decade of life with MPO-ANCA in the older age range; slight male predominance; more common in white than black.			
Lungs	Necrotizing vasculitis *without* granulomatous inflammation	Necrotizing **G**ranulomatous inflammation; sinusitis, rhinitis, otitis media, lung nodules/cavitation, saddle nose, ocular lesions more specific with PR3-ANCA; MPO-ANCA may present with chronic lung fibrosis	Asthma; **E**osinophil-rich and **G**ranulomatous inflammation	
Kidneys	Often rapidly progressive disease but can be indolent or chronic, PR3-ANCA tends to be more acute in presentation compared to the more indolent chronic presentation seen with MPO-ANCA.		Kidney disease is less frequent and less severe than MPA or GPA.	ANCA-positive glomerulonephritis without any classic systemic symptomology for MPA, GPA, or EGPA
Gastrointestinal	50% of patients with MPA, GPA, or EGPA may have abdominal pain, bloody stool with mesenteric ischemia/intestinal infraction/perforation, pancreatitis, hepatitis.			
Skin	Nodular cutaneous lesions are rare	Skin nodules due to dermal or subcutaneous arteritis and necrotizing granulomatous infiltration		
Neurological	Peripheral neuropathy, usually mononeuritis multiplex pattern; up to 70% in EGPA, 50% GPA, 30% MPA Central nervous system involvement less common, may present as vasculitis within meninges			
Other organ involvement	20% cardiac involvement (e.g., heart blocks, ventricular hypokinesis)	20% cardiac involvement	Eosinophilia: systemic infiltration 50% cardiac involvement	

[a]Drug-induced AAV may also more commonly present with MPO-ANCA. Additionally, positivity for both PR3 and MPO-ANCA is not uncommon with drug-induced AAV.

Abbreviations: AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatous polyangiitis; GPA, granulomatous polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3.

- ANCA-associated GN may present with non-nephrotic proteinuria and hematuria, acute nephritis with necrosis and new crescents, rapidly progressive nephritis with crescentic GN, or slowly progressive nephritis.
- Nonspecific signs and symptoms of necrotizing vasculitis: cutaneous purpura, papular/ulcerated lesions, peripheral neuropathy (mononeuritis multiplex), nonspecific muscular/joint pain, evidence of GI bleed, tendency for venous thrombosis

Histopathology

- ANCA-associated (pauci-immune) crescentic GN often has crescents in different stages simultaneously (acute, subacute, and chronic lesions) due to the relapsing nature of the disease (**Fig. 7.4**).

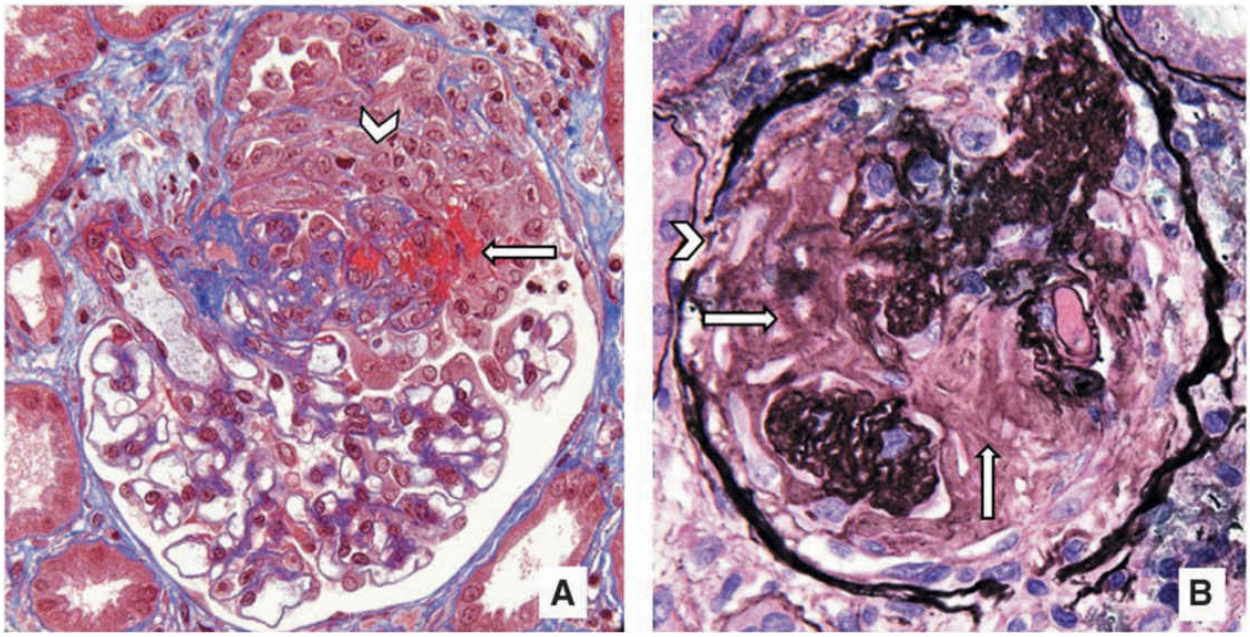

FIGURE 7.4 Glomerular crescents in antineutrophil cytoplasmic antibody–associated vasculitis. **A.** Necrotizing and cellular (active) crescent. There are segmental necrosis with capillary disruption and urinary space fibrin (*arrow*), and inflammatory and epithelial cells in the urinary space (*arrowhead*) (Masson trichrome ×400). **B.** Fibrotic (chronic) crescent. There is collagen in the urinary space (*arrows*) separating the obliterated glomerular tufts with a break in Bowman capsule (*arrowhead*) (Jones silver ×400).

Management

- Table 7.5 summarizes management strategies for AAV.

Table 7.5 Management strategies for ANCA-associated vasculitis

Induction	New Diagnosis or Relapse AAV Non-rapidly Progressive	Rapidly Progressive AAV[a]
Induction regimen depends on the severity of initial presentation.	1. CYC[b] or RTX[c] **plus** 2. Corticosteroids[d]	1. CYC or (CYC + RTX)[e] **plus** 2. Corticosteroids
	No PLEX	Consider PLEX,[f] particularly if diffuse pulmonary hemorrhage is present (see text regarding PLEXIVAS trial results published in 2020)
Maintenance	Options for maintenance therapy	
• Maintenance therapy may be started at 3–6 mo once remission is achieved. • There is no consensus on duration of maintenance (range of 18–48 mo per published studies). • 48-mo duration appears to confer lower relapse rates than 24-mo.	• AZA 1–2 mg/kg/d × > 18 mo *or* • RTX (On demand *OR fixed* schedule for > 18 mo[g]); fixed schedule; RTX 500 mg IV q 6 mo for up to 18 mo, tailored dosing based on CD19 counts, *or* • MMF may be prescribed, up to 1 g bid for ~2 y, if intolerant of AZA, *or* • Methotrexate (initially 0.3 mg/kg/wk, maximum of 25 mg/wk) in patients intolerant of both AZA and MMF, but not if GFR 60 mL/min/1.73 m^2	
Relapse		
• Rituximab and corticosteroid are the preferred agents for SCr 4 mg/dl. • CYC and corticosteroid are preferred if SCr is >4 mg/dL. • In non–life-threatening relapse, reinstitute or increase current corticosteroid dose, with or without AZA or MMF.		
Refractory Disease[h]		

• Change therapy
  • Switch to RTX if previously treated with CYC (especially if PR3-ANCA AAV) or vice versa
  • Oral CYC if previously treated with IV CYC and RTX is not available.
• Consider PLEX.		

Note: Treatment outline is based on Rovin BH, Caster DJ, Cattran DC, et al. Management and treatment of glomerular diseases (part 2): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2019;95:281–295.

[a]Rapidly progressive AAV is defined as serum creatinine > 4 mg/dL, crescentic glomerulonephritis, or diffuse pulmonary hemorrhage.

[b]CYC (0.5–0.75 g/m^2 IV q 3 to 4 weeks or 1.5 to 2.0 mg/kg/d orally); reduce dose if age > 60 years or eGFR < 20 ml/min/1.73 m^2. induction therapy with cyc should be discontinued after 3 months if patient remains dialysis dependent and free of extrarenal disease manifestations.

[c]Rituximab (375 mg/m^2 weekly × 4 *or* 750 mg/m^2 [maximum dose 1,000 mg] biweekly × 2). Rituximab may be used as alternative initial treatment in combination with corticosteroids in patients

without severe disease or in whom CYC is contraindicated.
[d]Corticosteroids (methylprednisolone 500 to 1,000 mg IV pulse daily × 1 to 3 days for a maximum of 1 to 3 g, followed by 1 mg/kg/d of prednisone with taper over 16 weeks to 5 mg po daily). See PLEXIVAS trial in list of **Suggested Readings**.
[e]Rituximab-based regimen per the international, randomized, open-label trial comparing a rituximab-based regimen with a standard cyclophosphamide/azathioprine-based regimen in the treatment of active, generalized ANCA-associated vasculitis (RITUXVAS) trial.
[f]PLEX regimen: 60 mL/kg ideal body weight; replacement fluid is typically 5% albumin. Fresh-frozen plasma and/or cryoglobulins may be used at the end of apheresis session to replace coagulant factors, especially for patients with a recent renal biopsy and/or diffuse alveolar hemorrhage. Number of treatments: For vasculitis: seven treatments over 14 days if diffuse pulmonary hemorrhage (start with daily treatment until bleeding stops, then every other day, up to total of 7 to 10 treatments). For vasculitis in association with anti-GBM antibodies: Daily treatment for 14 days or until anti-GBM antibodies are undetectable. *Must* monitor daily prothrombin time and fibrinogen and replace volume with fresh-frozen plasma and 10 units of cryoprecipitate, respectively, as needed to correct coagulopathy associated with removal of coagulant factors with apheresis. Monitor electrolytes daily.
[g]On-demand rituximab therapy is based on peripheral B-cell repopulation plus ANCA reappearance. Benefit of one over the other approach remains to be defined by the Comparison Study of Two Rituximab Regimens in the Remission of ANCA-associated Vasculitis (MAINRITSAN 2).
[h]Refractory disease is defined as no improvement by 4 weeks, improvement of <50% in 6 weeks of treatments as measured by bvas/wg, or chronic persistent disease after more than 12 weeks.
Abbreviations: AAV, antineutrophil cytoplasmic antibody–associated vasculitis; AZA, azathioprine; CYC, cyclophosphamide; Ig, immunoglobulin; IV, intravenous; MMF, mycophenolate mofetil; PLEX, plasma exchange; PR3-ANCA, antineutrophil cytoplasmic antibody directed against proteinase-3; RTX, rituximab; q, every.

Induction therapy

- Corticosteroids *plus* either CYC or RTX is recommended for new-onset AAV with renal involvement.
- Considerations to select CYC versus RTX:
  - CYC is the preferred agent for the following:
    - Patients with SCr ≥ 4 mg/dL because data for other agents are limited in patients with severe kidney injury.
    - For patients with SCr < 4 mg/dl and one or more of the following:
      - Baseline serum total IgG is low.
      - Patient is hepatitis B surface antigen (HBsAg) positive.
      - RTX is not available.
  - RTX may be preferred in the following cases:
    - Patients with SCr < 4 mg/dl
    - Fertility concerns for children, men, or women

    - Frail elderly patients
    - Patients for whom leukopenia avoidance and/or a steroid-sparing protocol is a high priority
    - Relapsing disease
    - PR3 disease
- Corticosteroids:
    - 2020 PLEXIVAS trial, total *n* = 704, reported that reduced-dose regimen of corticosteroids was noninferior to standard-dose regimen with respect to death or ESKD. *Reduced-dose regimen consisted of: week 1: identical steroid dose to standard regimen; week 2: dose reduced by approximately 50% from standard dose while dose in standard group was gradually reduced starting in week 3; at 6 months, the cumulative dose of oral corticosteroids in the reduced-dose group was less than 60% of that in the standard-dose group; after 22 weeks, both groups received 5 mg daily of prednisone or prednisolone until week 52.*
    - Recommendation for prednisone dosing: start at 1 mg/kg/d, for example, 60 mg/d (maximum 75 to 80 mg/d); taper to half dose by week 2, quarter dose by week 8, then 2.5 mg/d step decrease to reach 5 mg/d (or 7.5 mg/d in patients who start out at 75 to 80 mg/d) by week 16. Continue low dose for 52 weeks, then discontinue at the discretion of the treating physician.

Plasma exchange (PLEX)

- Add PLEX in patients with concurrent anti-GBM disease and AAV
- Consider PLEX in patients with rapid rise in SCr, requirement for dialysis at presentation, or diffuse alveolar hemorrhage
- **Note:** Despite current practice/guideline in using PLEX as outlined above, the PLEXIVAS trial reported no reduction in the incidence of death or ESKD with PLEX in patients with severe AAV (defined as an eGFR < 50 ml/min/1.73 m^2 or diffuse pulmonary hemorrhage). future recommendations may change.

Maintenance therapy

- For patients not on dialysis, maintenance therapy with RTX alone or AZA plus corticosteroids is recommended. There is no role for the addition of oral corticosteroid or other immunosuppressive agents with RTX maintenance.
- The optimal duration of maintenance therapy remains undefined:
  - 18 to 48 months has been suggested.
  - 48-month duration appears to confer lower relapse rates compared with 24-month.
  - The optimal duration of RTX maintenance is undefined (18 months may be considered).
- Choice of maintenance therapy (*preferred):
  - *AZA, * RTX, MMF, or methotrexate
  - The following should be considered in selecting AZA versus RTX as maintenance therapy:
    - AZA plus corticosteroids may be preferred if:
      - Total IgG is <300 mg/dl.
      - HBsAg is positive.
      - RTX is not available.
    - RTX alone may be preferred if:
      - PR3 disease
      - Treating a relapse
      - Patient is a slow metabolizer of AZA (i.e., patients with thiopurine methyltransferase [TPMT] deficiency—the diagnosis may be made with measuring TPMT activity or genetic testing).
      - Steroid avoidance is important.
    - Methotrexate may be considered if:
      - Methotrexate is used as induction therapy.
      - Intolerance of all other immunosuppressive agents
- Duration of maintenance therapy may be prolonged if any of the following characteristics is present because they are associated with higher risk of relapse:
  - Diagnosis of GPA

- Anti-PR3 positivity
- Multiple organ involvement, particularly upper respiratory tract
- History of relapse
- Persistence of ANCA titer following induction

Other treatment considerations for AAV

- Relapse:
  - RTX and corticosteroids are preferred if SCr < 4 mg/dl.
  - CYC and corticosteroids are preferred if SCr is ≥4 mg/dL.
  - In non–life-threatening relapse, reinstitute or increase corticosteroid dose, with or without AZA or MMF.
- Resistant disease:
  - Increase in corticosteroid dose or addition of RTX or CYC is recommended, whichever is not already being used.
  - Suggested alternatives: IV Ig or PLEX may be considered.
- Disease monitoring: Although changes in ANCA titers may be modestly predictive of future disease relapse, modification of immunosuppressive therapy (i.e., intensifying or reinitiating therapy) based on increasing ANCA titer alone is *not* recommended.
- Avoid over-immunosuppression, provide *P. jirovecii* prophylaxis, and be vigilant with infectious complications in all patients receiving immunosuppressive therapy.
- Discontinue immunosuppressive therapy in dialysis-dependent patients without extrarenal manifestations who show no kidney response after 3 months of treatment.
- Future direction: Studies evaluating the efficacy of complement-targeted therapy involving the C5a-receptor inhibition with CCX168 avacopan to replace corticosteroid are ongoing.

Natural history/prognosis

- 5-year kidney and patient survival are approximately 65% to 75%.
- Poor prognostic risks: older age, higher presenting SCr or dialysis need at presentation, pulmonary hemorrhage

NOTE Risks for higher relapse rates of AAV include respiratory tract involvement and PR3-ANCA positivity.

- Others:
  - MPO-ANCA patients tend to present with worse kidney function and more chronic changes. However, if MPO-ANCA is diagnosed early, it may be associated with better renal outcome compared with PR3-ANCA.
  - Patients with EGPA more often have cardiac compared with kidney involvement.

Kidney transplantation

- Delay transplantation for at least 6 months after complete clinical remission
- It is not necessary to delay transplantation in patients with persistently positive ANCA.

Lupus Nephritis

Epidemiology

- 20% to 60% of patients with SLE will develop clinically significant LN in the course of the disease.
- Age:
  - Most patients who develop LN are younger than 55 years.
  - Severe nephritis is more common in children than elderly patients.
- Gender difference (female-to-male ratio) is noted for female predominance and varies with age:
  - 2:1 in prepubertal children
  - 4:1 in adolescents
  - 8 to 12:1 in adults
  - 2:1 in adults age greater than 60 years
  - Renal outcome portends worse prognosis in males than females.
- Race-related demographics:
  - SLE is more common in African Americans and Hispanics than whites.
  - Severe LN is more common in African Americans and Asians than in

other ethnic groups.
  - Patients of African ancestry with APOL1 risk alleles are at increased risk for worse renal outcomes.

Pathogenesis

- The pathogenesis likely involves multiple components including genetic susceptibility, epigenetic phenomena, immunoregulatory dysfunction, hormonal imbalances, and various environmental factors, among others.
- For interested readers, see **Appendix A** for more details regarding pathogenesis.

Diagnosis

- Routine laboratory findings:
  - Microscopic hematuria and/or red blood cell (RBC) casts, proteinuria and/or NS
  - Serologies:
    - Antinuclear antibody (ANA): sensitive, not specific for SLE
    - Anti-Smith: specific for the diagnosis of SLE
    - Anti–double-stranded DNA (anti-dsDNA), hypocomplementemia, and anti-C1q autoantibody levels are strongly associated with kidney involvement in patients with SLE and should be monitored in those at risk for LN or LN flare.
- Kidney biopsy is the gold standard.

Histopathology (Fig. 7.5)

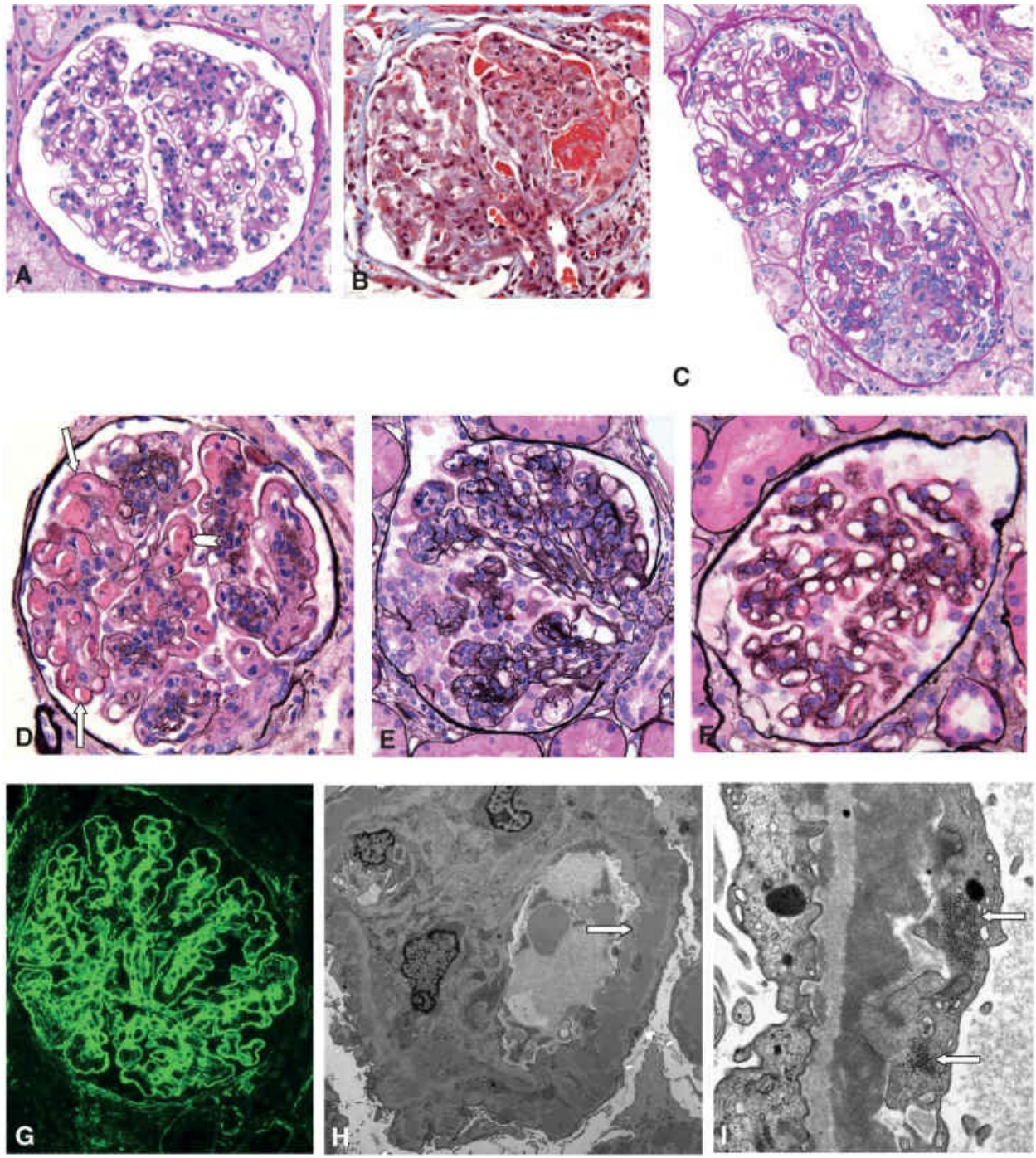

FIGURE 7.5 Lupus nephritis. **A.** Mesangial proliferative (class II) (periodic acid–Schiff ×400). **B.** Segmental proliferation with leukocytes and a necrotizing/crescentic lesion (Masson trichrome ×400). **C.** Active focal lupus nephritis (class III). There is segmental involvement of <50% glomeruli with proliferative features. in chronic focal lupus nephritis, there is focal scarring/sclerosis (periodic acid–schiff ×200). **D, E.** Active diffuse lupus nephritis (class IV). In **(D)**, there are large subendothelial deposits forming wire-loop lesions (*arrows*) and hyaline thrombi (*arrowhead*). In **(E)**, there is more leukocytic infiltration with a segmental cellular crescent. **F.** Membranous lupus nephritis (class V). Capillary walls are thickened with subepithelial deposits and spikes, with mild segmental mesangial hypercellularity (**D–F** Jones silver ×200). **G.** Global mesangial and capillary wall staining for

immunoglobulin G in mixed active diffuse and membranous lupus nephritis (class IV + V) (×400). **H.** Electron microscopy showing large subendothelial (wire loop) (*arrow*), mesangial, and segmental subepithelial electron-dense deposits (×6,000). **I.** Tubuloreticular inclusions (*arrows*) in endothelial cell cytoplasm beneath subendothelial deposits. Small subepithelial deposits are also present (×29,000).

International Society of Nephrology/Renal Pathology Society classification of LN

- LM:
  - Class I: minimal mesangial LN: normal glomeruli by LM; mesangial immune deposits by IF and electron microscopy (EM) only
  - Class II: mesangial proliferative LN: mesangial hypercellularity on LM; mesangial immune deposits by IF and EM
  - Class III: focal LN (<50% of glomeruli involved)
    - Class III(A): active lesions (leukocytes, karyorrhexis, necrosis, cellular or fibrocellular crescents, large subendothelial deposits forming “wire loops” or “hyaline thrombi”)
    - Class III(A/C): active and chronic lesions
    - Class III (C): chronic lesions (segmental or global glomerulosclerosis, fibrotic crescents)
  - Class IV: diffuse LN (≥50% glomeruli involved)
    - Class IV(A): active lesions
    - Class IV(A/C): active and chronic lesions
    - Class IV(C): chronic lesions
  - Class V: membranous LN (>50% subepithelial deposits with or without mesangial hypercellularity)
    - Class V may occur with Class III or Class IV.
  - Class VI: advanced sclerosing LN (≥90% globally sclerosed glomeruli without residual activity)
- IF: “Full-house” staining for IgG (strong), IgA, IgM, C1q (strong), and C3. Location depends on the LN class.
- EM: mesangial, subendothelial, and/or subepithelial depending on disease class
  - Usually deposits in at least two glomerular locations, may have a “fingerprint” substructure

- Endothelial cell tubuloreticular inclusions are usually present

Management

- Table 7.6 summarizes current management strategies for LN.

Table 7.6 Management strategies for LN

All patients with LN	• Antimalarials (hydroxychloroquine): yearly monitoring for retinopathy is advised with hydroxychloroquine. • Manage and treat complications: prevent/treat edema, hypertension, dyslipidemia, proteinuria, thrombosis whenever indicated • Use prophylaxis therapy against *Pneumocystis jirovecii* if receiving high-dose immunosuppressive therapy

Class I/II	• Disease-specific therapy is not generally necessary due to relatively benign course.
	• If nephrotic-range proteinuria:
	  • Evaluate for lupus podocytopathy (e.g., podocyte effacement) and, if present, treat as minimal change disease.
	  • Otherwise, consider low-dose corticosteroids and one additional agent (e.g., MMF).

Classes III/IV[a]	Induction therapy: corticosteroids plus either intravenous CYC or MMF. Aim to taper and discontinue corticosteroids by 12 mo if complete response. Maintenance: MMF or AZA. MMF is the first choice for maintenance therapy since it decrease the risk of LN relapse compared to AZA.
Class V	For subnephrotic proteinuria: initiate immunosuppression based on extrarenal indications For nephrotic-range proteinuria: initiate glucocorticoids and one additional agent (MMF, CYC, AZA, CNI, RTX)

[a]See **Table 7.7** for more detailed management of LN classes III/IV.
Abbreviations: AZA, azathioprine; CNI, calcineurin inhibitor; CYC, cyclophosphamide; LN, lupus nephritis; MMF, mycophenolate mofetil; RTX, rituximab.

For all LN classes

- Antimalarials (hydroxychloroquine):
  - All patients with LN should be treated with antimalarial unless contraindicated. Yearly monitoring for retinopathy is advised with hydroxychloroquine. Other adverse effects: cardiotoxicity (congestive heart failure, prolonged QT/arrhythmias), drug accumulation in podocyte lysosomes with formation of multilamellar zebra bodies mimicking Fabry disease, and hemolysis associated with G6PD deficiency.
  - Observational and cohort studies suggest that the use of antimalarial is associated with a reduction in the odds of developing LN in patients

with SLE and improved likelihood of complete renal response to treatment and lower ESKD risk in those with LN.

- Manage and treat complications: Prevent/treat edema, HTN, dyslipidemia, proteinuria, thrombosis whenever indicated.
- Monitoring of LN:
  - Serial proteinuria and SCr
  - Hematuria may persist for months even with improved proteinuria and SCr.
  - Anti-dsDNA, complement, and anti-C1q autoantibody levels
- Definitions of response to therapy:
  - Complete response:
    - Return of SCr to baseline (±10% to 15% of baseline), *and*
    - A decline in urine protein-to-creatinine ratio (uPCR) < 500 mg/g within 6 to 12 months
  - Partial response:
    - Stabilization (±10% to 15% of baseline) or improvement of SCr, *and*
    - ≥50% decrease in uPCR where final uPCR is <3,000 mg/g within 6 to 12 months

Class I/II LN-specific therapy

- Benign, no long-term adverse effect on kidney function
- Disease-specific therapy is not necessary.
- If nephrotic-range proteinuria, evaluate for lupus podocytopathy, and if present, treat as MCD. Otherwise, consider treatment with a low dose of corticosteroids in combination with another immunosuppressive agent (e.g., MMF).

Class III/IV LN-specific therapy (Table 7.7)

Table 7.7 Management strategies for lupus nephritis classes III and IV

Induction[a]	Dosage	Comments
Cyclophosphamide (CYC) NIH regimen	IV CYC: 0.5–1.0 g/m^2 given monthly for 6 mo	• IV therapy should be considered for patients who cannot comply with oral therapy for whatever reason.
CYC Euro-Lupus	IV CYC: 500 mg every	

regimen	2 wk for 3 mo	Study was limited to less severe patients and predominantly Caucasians.[b] • Unknown if efficacy of Euro-Lupus regimen is similar to that of NIH for LM class III/IV or in non-Caucasians.
CYC oral regimens	PO CYC: 1.0–1.5 mg/kg/d (maximum 150 mg/d) for up to 6 mo	• PO CYC provides similar efficacy to IV CYC in prospective observational studies. • Some, but not all, investigators suggested more adverse effects with PO CYC compared with IV CYC.
Mycophenolate mofetil (MMF)	1,000–1,500 mg twice daily for 6 mo	• MMF is preferred for fertility preservation, known history of high CYC exposure, and Hispanic, African American, or Asian ancestry. • ALMS trial: MMF had an equivalent response rate and similar incidence of adverse effects for induction compared with IV CYC at 6 mo.
Maintenance	**Maintenance therapy should be continued for at least 36 mo.**	

- First-line: MMF (1-3 g/d in divided doses) is the first choice for maintenance therapy since it decreases the risk of LN relapse compared to AZA (1.5–2.5 mg/kg/d). Maintenance therapy with AZA or MMF has been suggested to be superior to CYC based on the risk of death and development of CKD.
- Alternative: Use if CNIs or mizoribine is suggested for patients who cannot tolerate MMF or AZA.
- Unless corticosteroids are required for extrarenal lupus manifestations, gradual tapering of corticosteroids to aim for eventual discontinuation should be considered after patients have maintained a complete clinical kidney response for at least 12 mo.
- If disease relapses during tapering period, go back to previous level of immunosuppression that controlled the disease or an alternative recommended first-line therapy.

If disease worsens as evidenced by increasing SCr or proteinuria during the first 3 mo of therapy with either CYC or MMF

- Assess for compliance
- Switch therapy (e.g., from CYC to MMF or vice versa), or
- Consider prolonged IV CYC course or alternative therapies listed below below (e.g., CNI [cyclosporine or tacrolimus], rituximab, AZA)
- Consider IV Ig *or* plasmapheresis (in the setting of concomitant TTP or refractory APS)
- Consider repeating biopsy

Cyclosporine (CSA)	CSA: 4–5 mg/kg/d	• Nephrotoxicity limits use in patients with elevated SCr.
Tacrolimus (TAC)	Combination TAC (4 mg/d) + MMF (1 g/d)	• Comparable remission rates between combination TAC (4 mg/d) + MMF (1 g/d) and IV CYC (0.75 g/m^2) for 6 mo (Chinese RCT).

Rituximab (RTX)	RTX: doses vary among trials RTX: 1,000 mg on days 1, 15, 168, and 182 (dose used in LUNAR trial)	• LUNAR trial: Although RTX therapy led to more responders and greater reductions in anti-dsDNA and C3/C4 levels, it did not improve clinical outcomes after 1 y of treatment.
Azathioprine (AZA)	AZA: 1.5–2.5 mg/kg/d	• AZA had similar induction response rate compared with that for IV CYC at 2 y. AZA had fewer adverse effects, but higher late relapse rate, risk of doubling of SCr, and more chronic changes on late follow-up biopsies.
IV Ig or plasmapheresis		• May be considered in the setting of concomitant TTP or refractory APS

[a]Induction therapy should be used in combination with corticosteroids: oral prednisone 1 mg/kg (maximum 80 mg/d), to be tapered over 6 to 12 months per clinical response. Initial intravenous methylprednisolone (e.g., 5 to 10 mg/kg × 1 to 3 days) may be considered at induction for aggressive disease. Optimal dosing and duration of corticosteroid therapy remain to be defined.

[b]Severe disease was defined as >50% segmental glomerular necrosis or crescents and rapidly progressive kidney failure.

Abbreviations: ALMS, Aspreva Lupus Management Study (RCT involving patients with classes III, IV, and V LN); APS, antiphospholipid syndrome; CNI, calcineurin inhibitor; IV, intravenous; IV Ig, intravenous immunoglobulin; LN III/IV, lupus nephritis classes III and IV; LUNAR, Lupus Nephritis Assessment with Rituximab trial involving patients with LN III/IV randomized to receive either MMF + steroids or MMF + steroids + rituximab; MMF, mycophenolate mofetil; NIH, National Institute of Health; PO, per oral; RCT, randomized controlled trial; SCr, serum creatinine; TTP, thrombocytopenic thrombotic purpura.

- Induction therapy:
  - Corticosteroids plus either IV CYC or MMF. MMF should be the preferred agent in patients who wish to preserve fertility or who have Asian, Hispanic, or African ancestry or prior CYC exposure approaching maximum cumulative lifetime dose (see Safety Notes regarding CYC below).
  - Alternative options for induction therapy to be used in combination with corticosteroids may be considered in the case of drug intolerability, lack of response to standard therapy, or lack of availability and/or high cost of standard drugs. These may include CNI, RTX, AZA, or leflunomide, among others.
  - Antibiotic prophylaxis should be used to prevent infections with *P. jirovecii* during induction therapy.
- Maintenance therapy:

- MMF is the first choice for maintenance therapy since it decreases the risk of LN relapse compared to AZA. AZA is an alternative to MMF.
  - Maintenance therapy should be continued for a minimum duration of 36 months.
  - AZA or MMF maintenance therapy has been suggested to be superior to CYC in terms of risk of death and development of CKD.
  - Other alternatives: CNI, mizoribine (Japanese data)
  - Corticosteroids: aim to taper and discontinue by 12 months if complete response
- Safety notes regarding CYC:
  - Maximum lifetime dose of 36 g of CYC is suggested to minimize risk of hematologic malignancies.
  - Maximum cumulative dose for those who wish to conceive should not exceed 10 g.
  - Dose reduction with reduced kidney function (20% and 30% reduction for creatinine clearance [CrCl] 25 to 50 and 10 to 25 mL/min, respectively)
  - Adjust CYC dose to keep nadir leukocyte count ≥ 3,000/μL (10 to 14 days for IV CYC and 1 week for PO CYC)
  - Use sodium-2-mercaptoethane (mesna) to minimize bladder toxicity
  - Fertility protection while on CYC treatment:
    - Women: leuprolide, ovarian tissue cryopreservation
    - Men: testosterone (efficacy poorly established), sperm banking

Class V LN-specific therapy

- For subnephrotic proteinuria: Initiate immunosuppression based on extrarenal indications.
- For nephrotic-range proteinuria: Initiate immunosuppression with corticosteroids and one additional agent (e.g., MMF, CYC, AZA, CNI, RTX).

Advances in SLE-targeted therapy

- Belimumab: human monoclonal antibody that selectively neutralizes soluble B-cell activating factor (BAFF)

    - Food and Drug Administration (FDA) approved for treatment of ANA/anti-dsDNA positive adults with high disease activity on standard therapy
    - Short-term clinical trials suggest reduced SLE activity, flare rates, and corticosteroid need.
- Obinutuzumab: a humanized anti-CD20 monoclonal antibody
    - Improved complete remission rates in patients with diffuse proliferative LN in a phase 2 clinical trial comparing standard therapy (MMF and steroids) versus standard therapy plus obinutuzumab (Nobility trial)
    - Obinutuzumab was awarded FDA “fast-track” approval based on Nobility. It is currently approved for B-cell lymphomas as Gazyva.
- Omalizumab: recombinant humanized monoclonal antibody that blocks the binding of IgE to the FcεRI receptor

Poor prognostic indicators

- Patient characteristics: African or Hispanic ancestry, male gender, pediatric onset, frequent relapses, incomplete remission, neuropsychiatric lupus, proteinuria > 4 g/d at diagnosis
- Serologies: antiphospholipid syndrome (APS) or the presence of antiphospholipid antibodies (aPLs), persistent hypocomplementemia, elevated anti-dsDNA or anti-C1q antibodies
- Histologic findings: crescentic GN, thrombotic microangiopathy (TMA), or extensive tubulointerstitial fibrosis

Lupus and pregnancy

- Measurable SLE disease activity is present in 40% to 50% of pregnancies among patients with SLE, with LN occurring in up to 75% of these cases.
- Active SLE during pregnancy is associated with:
    - Increased risk of preeclampsia to 30% compared to 5% in the general population
    - Increased risk of fetal death and preterm birth
- Active LN during pregnancy is associated with:
    - Increased maternal adverse outcomes including increased risk of gestational HTN, preeclampsia, and maternal death. There is evidence to

suggest that LN classes III/IV may be associated with higher risk for HTN/preeclampsia compared to other LN classes.
    - Possible increased risks of preterm birth, intrauterine growth restriction, stillbirth, and neonatal death (inconsistent findings in the literature)
- Risk factors for adverse outcomes in pregnancy:
    - Active disease at conception
    - Positive aPLs
    - HTN, proteinuria, reduced GFR in the first trimester
- Management of APS/NS during pregnancy:
    - Adverse outcomes of APS and positive aPLs include late fetal loss (after 10 weeks of gestation) and increased relative risk of preeclampsia
    - Women with APS and arterial thrombotic events are also at high risks for stroke and maternal morbidity and mortality.
    - Routine screening for aPLs is recommended.
- Anticoagulation:
    - For women with known APS receiving chronic anticoagulation, convert warfarin to unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) during pregnancy.
    - For women with no known history of thrombotic events, but with obstetric criteria for APS of having either ≥ three pregnancy losses or late pregnancy loss, prophylactic anticoagulation consisting of a low-dose aspirin with either UFH or LMWH should be initiated.
    - For women with aPLs, but not meeting clinical criteria for APS, clinical surveillance with either antepartum aspirin or prophylactic UFH or LMWH is suggested.
    - For patients with NS, prophylactic anticoagulation should be considered.
- Differentiating between lupus flare and preeclampsia in a woman with AKI:
    - Lupus flare: AKI may occur any time including prior to 20 weeks of gestation and postpartum, presence of hypocomplementemia, RBC casts, and leukopenia.
    - Preeclampsia: AKI only occurs after 20 weeks of gestation with absence of findings seen with lupus flare above.

- Management of SLE/LN in pregnancy:
  - Delay pregnancy until at least 6 months after complete remission
  - Use of CYC, MMF, ACEI, and ARB is contraindicated due to potential teratogenicity.
  - Corticosteroids, hydroxychloroquine, AZA, and CNI are considered safe during pregnancy. LN patients who become pregnant while being treated with MMF should be switched to AZA.
  - Methotrexate is teratogenic and is contraindicated in pregnancy. Methotrexate should be discontinued ≥ 3 months prior to conception.
  - Hydroxychloroquine maintenance therapy should be continued during pregnancy. Discontinuation of hydroxychloroquine may lead to lupus flares including LN.
  - Low-dose aspirin should be started prior to 16 weeks of gestation to reduce risks of preeclampsia, intrauterine growth retardation, and fetal loss.
  - Patients with LN relapse during pregnancy should be treated with corticosteroids and, if necessary, AZA.
  - Patients receiving corticosteroids or AZA during pregnancy should not be tapered until at least 3 months postpartum.

ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE (ANTI-GBM)

Goodpasture's syndrome

This is an autoimmune disease that predominantly affects both the kidneys and lungs. When only kidneys are involved, the condition is referred to as anti-GBM disease.

Epidemiology

- Incidence: 0.5 to 1.0/million/y
- Predominantly Caucasians, recognized in Asians, rare in other ethnicities
- Peak age 20 to 30 years with slight male predominance; This group of patients more commonly present with pulmonary hemorrhage.
- Smaller peak at age 60 to 70 years with female predominance; This group

of patients more likely presents with isolated glomerular disease.

- Predisposing factors: HLA-DR15 and DR4 at increased risk

Pathogenesis

- Autoantibody formation against the GBM antigens:
  - Typical antigen involves the non-collagenous (NC1) domain of type IV collagen α3 chain [α3(IV)NC1], known as, the “Goodpasture antigen.”
  - Any other GBM constituents may also serve as antigens including the α3 to α5 type IV collagen chains of type IV collagen.
- Type IV collagen chains are also present in alveolus, cochlea, parts of eye (corneal basement membrane and Bruch membrane), choroid plexus of brain, and some endocrine organs.
- Presenting symptoms may be related to injury of these organs.

Clinical manifestations

- Disease develops over weeks to months.
- May have mild respiratory symptoms or incidental microscopic hematuria with disease progressing over months to years
- Precipitating factors:
  - Exposures to hydrocarbons, cigarette smoking, pulmonary infection, and fluid overload may lead to:
    - Alveolar injury that allows anti-GBM antibodies to access and injure alveolar membranes resulting in pulmonary hemorrhage
    - Pulmonary hemorrhage appears as “fluffy, fleeting infiltrates of rapid onset and clearing on chest radiographs.
  - Prior kidney injury/inflammation may predispose to development of anti-GBM disease. GBM injury allows anti-GBM antibodies access to their antigenic site.

Histopathology (Fig. 7.6)

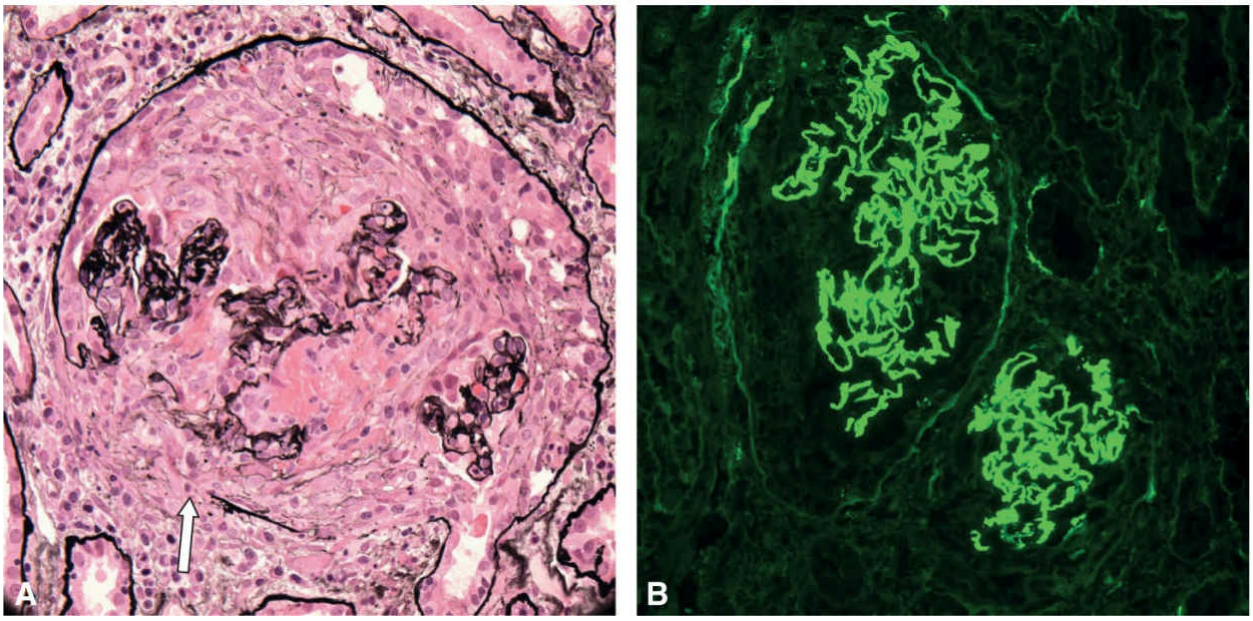

FIGURE 7.6 Anti-glomerular basement membrane antibody nephritis. **A.** Cellular crescent causing destruction of Bowman capsule segmentally (*arrow*) (Jones silver ×400). **B.** Linear capillary wall staining for immunoglobulin G (×200).

- LM: glomerular crescents without mesangial hypercellularity. Crescents are in the same stage (all active, subacute, or chronic) due to "one-shot" anti-GBM antibody production.
- IF: glomerular capillary wall IgG in a linear pattern
- EM: no deposits

Differential diagnoses

- Specific binding to GBM
  - Anti-GBM disease with kidney involvement only
  - Alport syndrome after kidney transplantation
- Nonspecific binding to GBM: DM, light-chain disease

Prognostic indicators

- Higher presenting SCr and higher percentage of crescents portend worse prognosis. Renal recovery is rare if SCr is >6 mg/dL.
- Need for dialysis, particularly if in association with 100% crescents

Management

Immunosuppressive therapy

Methylprednisolone 500 to 1,000 mg/d IV for 3 days, followed by
- prednisone, 1 mg/kg/d based on ideal body weight (maximum 80 mg/d) with slow taper to off by 6 months, *plus*
- CYC: 3 mg/kg/d orally for 2 to 3 months. For patients older than 55 years, reduce dose to 2.5 mg/kg/d × 2 to 3 months
- Corticosteroids should be started prior to tissue diagnosis if high suspicion due to rapidly progressive disease. Following diagnosis confirmation, add CYC and PLEX.
- RTX may be considered in refractory anti-GBM disease.
- *Exception* to immunosuppressive therapy initiation: patients who are dialysis dependent at presentation, have 100% crescents in an adequate biopsy sample, and do not have pulmonary hemorrhage

Plasmapheresis

- Daily or alternate-day 4 L exchange with 5% albumin
- Add 150 to 300 mL fresh-frozen plasma (FFP) at the end of each session or use FFP as replacement fluid if patients have pulmonary hemorrhage or have had recent surgery including kidney biopsy.
- Coagulation labs and fibrinogen levels must be obtained daily for FFP and/or cryoglobulins replacement as needed to correct any plasmapheresis-induced coagulopathy due to removal of coagulant factors.
- Plasmapheresis should be performed for 2 to 3 weeks until anti-GBM antibodies become undetectable.

Maintenance therapy

- Maintenance immunosuppressive therapy for anti-GBM GN is *not* recommended. This disease is not characterized by frequently relapsing course. Antibodies tend to disappear spontaneously after 12 to 18 months. Recurrence, if it occurs, presents at a mean time of ~4 years, ranges 1 to 10 years. Recurrence may manifest as kidney involvement or pulmonary hemorrhage. Relapses are thought to occur in patients who continue to smoke or have exposure to lung irritants. Treatment of recurrent disease is similar to initial regimen.
- Patients with GN who are positive for both anti-GBM and ANCA should

be treated with maintenance therapy as for patients with AAV.

Kidney transplantation

- Defer transplantation until anti-GBM antibodies are undetectable for at least 6 months.
- Recurrent disease is very unusual unless the kidney transplant is performed during anti-GBM positivity.
- New-onset anti-GBM disease following kidney transplantation should raise the suspicion of Alport syndrome in the native kidneys.

GLOMERULAR INJURY ASSOCIATED WITH INFECTIONS

- Bacterial infection–related GN may occur:
  - After a 1- to 3-week latent period following a bacterial infection (PIGN), or
  - With an ongoing, acute, or chronic bacterial infection (peri-infectious GN)
- Somewhat distinct clinical/morphologic entities have been described:
  - Post-infectious glomerulonephritis (PIGN) (i.e., poststreptococcal GN [PSGN])
  - Shunt nephritis
  - Infective endocarditis–related GN
  - IgADIRGN

Postinfectious GN

Definition

- PIGN has replaced the term PSGN since streptococcal infections account for only 28% to 47% of *postinfectious acute glomerular injury*. *S. aureus* or *Staphylococcus epidermidis* is isolated in 12% to 24% of cases and gram-negative bacteria in up to 22% of cases.

Epidemiology

- Decreased incidence in industrialized countries
- Traditionally a disease in children, now seen in debilitated elderly, patients

with chronic alcoholism, DM, IV drug abuse, poor communities due to lack of early medical care, antibiotics, and/or fluorinated water. Fluorinated water reduces expression of virulence factors in *Streptococcus pyogenes*.

Pathogenesis

- *Streptococcus-related PIGN:* putative nephritogenic streptococcal antigens causing immune-mediated glomerular damage: glyceraldehyde-3-phosphate dehydrogenase (GAPDH), streptococcal pyrogenic exotoxin B (SPEB), and its more immunogenic precursor zymogen
- Incubation is ~1 to 2 weeks after throat infection (pharyngitis) versus 4 to 6 weeks post-skin infections (impetigo)

Clinical manifestations

- HTN, edema, hematuria "coca-cola urine," azotemia common in adults, less commonly, NS
- Laboratory findings for PIGN:
  - Low serum C3 is more common than low C4; serum IgG and IgM are elevated in 80%.
  - Cryoglobulins and rheumatoid factor are elevated in up to one-third of cases.
  - Anti-DNA and ANCA may be positive in rare cases.
- Laboratory findings specific for PSGN:
  - Positive *Streptococcus* culture in up to 70% during epidemics; 20% to 25% of sporadic cases
  - Antistreptolysin O (ASO) titers are increased in > two-thirds with PSGN post-throat infection.
  - Anti-DNAse B titers are increased in 73% of post-impetigo cases (>two times normal).
  - Others: Streptozyme panel (ASO, anti-DNAse B, antihyaluronidase, antistreptokinase) is more sensitive and is positive in >80%.
  - Anti–complement factor B (anti-CFB) antibodies have been shown to be more frequently observed at the onset of illness in children with acute PSGN than in children with C3G.

Diagnosis

- Kidney biopsy is not required to diagnose PIGN, especially during epidemics. Diagnosis is often made based on history, physical findings, and laboratory data.
- Kidney biopsy should be considered when the clinical presentation is atypical and cultures are negative (e.g., persistent hypocomplementemia, microscopic hematuria, and proteinuria).

Histopathology (Fig. 7.7)

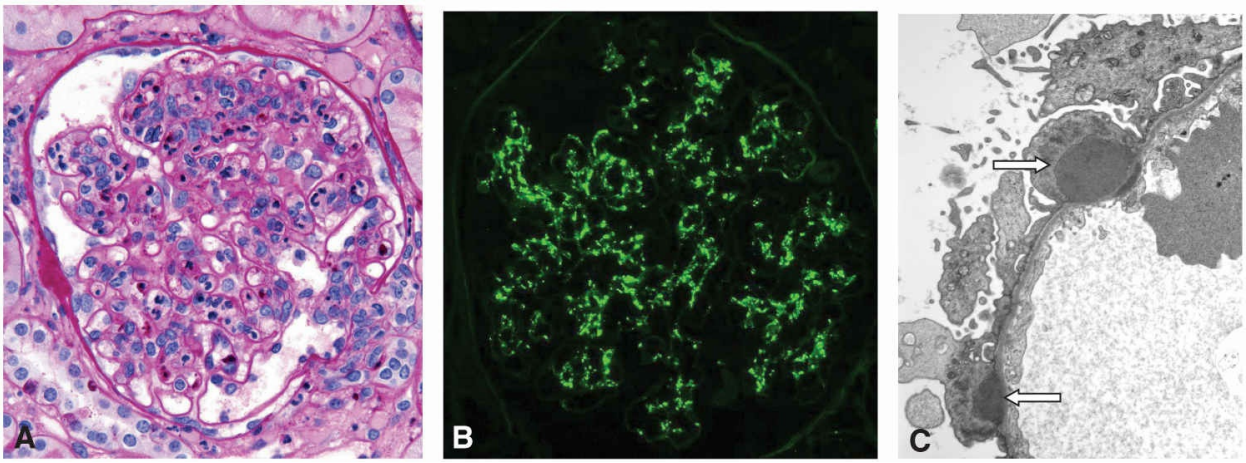

FIGURE 7.7 Postinfectious (infection-related) glomerulonephritis. **A.** Endocapillary hypercellularity with many leukocytes, including neutrophils, occluding glomerular capillary lumens (periodic acid–Schiff ×400). **B.** Irregular granular C3 in glomerulus (×400). **C.** Individual "hump"-shaped subepithelial deposits (*arrows*) (×19,000).

- LM: leukocytes, often neutrophils, in and occluding glomerular capillaries (large "bloodless" glomeruli) with or without crescents
- IF: irregular granular capillary and mesangial strong staining for C3 usually with small amounts of IgG and/or IgM. Has been described as "starry-sky," "garland," and "mesangial" patterns likely related to timing of biopsy
- EM: large single subepithelial "hump" or "gumdrop" shaped deposits often at the mesangial waist or notch area where the capillary meets the mesangium

Management

- Treat underlying infection if it is still present at the time of diagnosis.

- Consider treatment (for PSGN: penicillin [PCN] or erythromycin for 7 to 10 days if PCN allergic) even if no persistent infection to prevent epidemics.
- Antibiotic therapy in the absence of active infection does not alter the course of GN.
- Steroids/immunosuppression for crescentic PIGN carry serious potential risks and are of unproven benefit.
- Preventive antimicrobial therapy considerations:
  - At-risk populations during epidemics
  - Siblings of affected individuals with *Streptococcal* infection within 2 to 3 weeks
- Other supportive therapies: dialysis, treatment of HTN, edema, and heart failure

Natural history/prognosis

- Typically resolves within a few weeks
- Prognosis is excellent in children.
- Elderly: acutely azotemia (60% to 70%), congestive heart failure (40%), early mortality (25%); some adults experience persistently low GFR
- Mild proteinuria < 500 mg/d may persist for several months.
- Microscopic hematuria may persist up to a year.

NOTE In PIGN, complement levels should normalize within 3 months; otherwise, consider LN or C3 glomerulopathy.

Shunt Nephritis

Background

- Shunt nephritis is an IC-mediated GN that may rarely develop as a complication of chronic infection of ventriculoatrial or ventriculojugular and, less commonly, ventriculoperitoneal shunts inserted for the treatment of hydrocephalus.
- Infections occur in ~30% of shunts. GN may develop in 0.7% to 2% of infected ventriculovascular shunts ranging from months to many years after insertion.

- This entity is becoming rare with earlier recognition and treatment of infection.

Pathogenesis

- Infecting organisms are typically *S. epidermidis*, *Staphylococcus albus*, or *S. aureus*.

Clinical presentation/diagnosis

- Diagnosis is based on kidney biopsy findings below and clinical findings of microscopic hematuria and proteinuria (often nephrotic range), occasionally elevated SCr, HTN, and prolonged fevers or signs of chronic infection in a patient with an implanted shunt.
- ANCA titers may be positive.

Histopathology

- LM: usually a membranoproliferative pattern of injury
- IF: granular deposits of IgG, IgM, and C3
- EM: electron-dense mesangial and subendothelial deposits

Treatment/Prognosis

- Early recognition and antibiotic therapy confer good renal outcome.

Infective Endocarditis–Related Glomerulonephritis

Definition/epidemiology

- Occurs in approximately 40 cases/million/y
- Frequently seen in the elderly even without underlying heart disease and in patients with IV drug usage, HIV, hepatitis C, diabetes, prosthetic heart valves, and structural heart disease
- *S. aureus* has replaced *Streptococcus viridans* as the leading cause, with the highest risk in IV drug users.

Clinical presentation/diagnosis

- Presentation with acute kidney failure (79%), acute nephritis (9%), RPGN (6%), and NS (6%)
- Low serum complement C3 occurs more frequently than low C4 (50% vs. 20% respectively).

- ANCA and ANAs are present in ~20% to 30%

Histopathology

- LM: crescentic GN in >50% of patients, with fewer showing diffuse proliferative GN and mesangial proliferative GN
- IF: Glomeruli show C3 dominance with IgG in in about 25% and IgA in up to 50% of those with staphylococcal infections.
  - IgG is present in only 15% of those with crescents.
  - C3 predominance without C1q or C4 suggests alternative rather than classic complement pathway activation.
- EM: mesangial and capillary wall deposits; subepithelial "hump" deposits are rare.
- Findings most consistent with infection-related GN rather than IC or pauci-immune GN

Treatment/prognosis

- Immediate prognosis is good if there is prompt infection eradication with antibiotics for 4 to 6 weeks.

IgA-Dominant Infection-Related GN

Clinical manifestations/diagnosis

- Acute GN with declining kidney function, microscopic or gross hematuria, and either nephrotic or nephritic proteinuria in the presence of active blood or tissue infection
- Risk factors: DM, HTN, heart disease, malignancy, alcohol or substance abuse, or kidney transplantation
- Laboratory findings: Low complement C3 and C4 levels; serum IgA may be elevated.
- Definitive diagnosis: kidney biopsy
- Prognosis:
  - Recovery of kidney function is possible with recovery from inciting infection, but <20% returns to baseline.
  - Dialysis support may be needed during AKI.

Histopathology

- LM: Biopsy often shows endocapillary hypercellularity with prominent neutrophil infiltration; A minority of cases may have isolated mesangial proliferative or infrequently crescentic GN.
- IF: dominant IgA or co-dominant IgA and C3 mesangial and capillary wall staining, often with κ light-chain exceeding λ. Weaker staining for IgG or IgM may be present.
- EM:
  - Electron-dense deposits in mesangial and capillary wall, the latter often with subepithelial "humps," and less frequent subendothelial locations
  - Cryoglobulins, when present, often lack the usual substructure.

Management

- Antibiotics for underlying infection and antihypertensive therapy as needed for HTN
- Consideration for immunosuppressive therapy may be given for severe active kidney injury weighing risks and benefits.
- Routine supportive therapy and use of RAASi as safely tolerated
- Monitor kidney function, serum C3, C4, uPCR, and urinary albumin-to-creatinine ratio (uACR)
- C3 glomerulonephritis (C3GN) must be ruled out in patients with low C3 levels persisting beyond 12 weeks.

GLOMERULONEPHRITIS WITH MEMBRANOPROLIFERATIVE PATTERN OF INJURY

- The membranoproliferative pattern of injury (MPGN) injury pattern may arise from a number of conditions via (1) Ig-mediated or (2) complement-mediated activation of the complement system, or (3) endothelial injury and thrombotic microangiopathy (TMA) (**Fig. 7.8**).

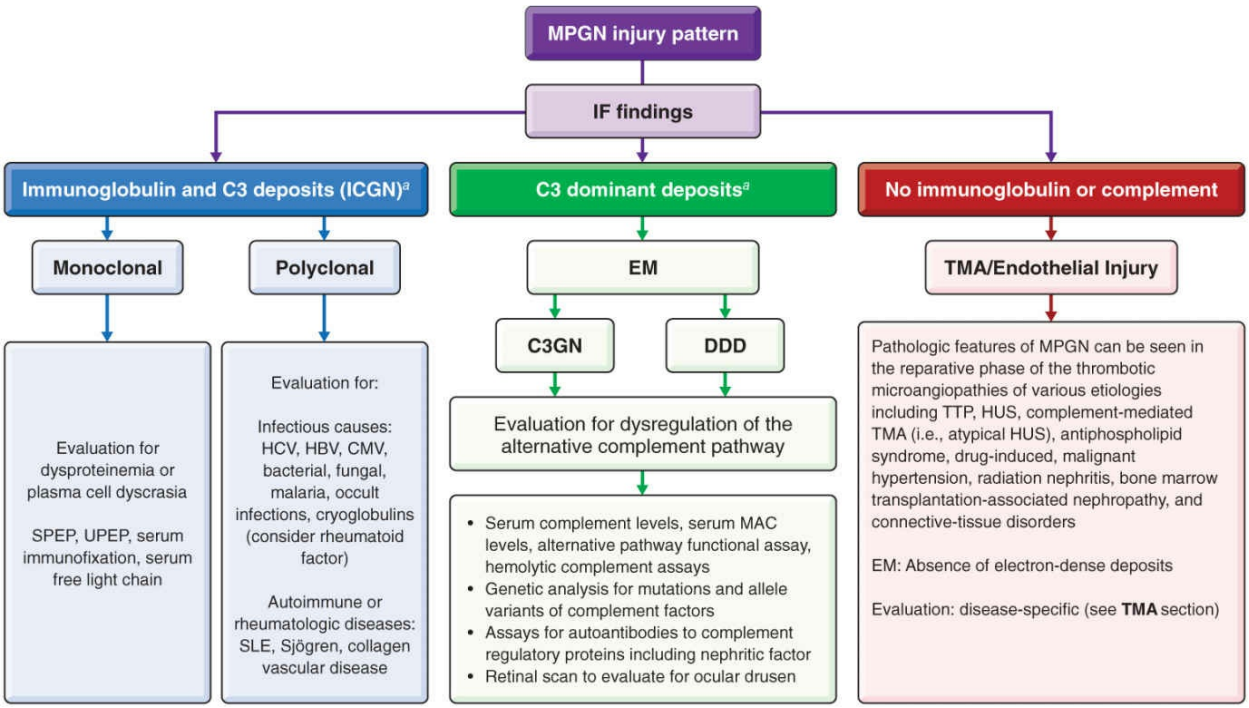

FIGURE 7.8 Classification of membranoproliferative glomerulopathy based on immunofluorescence findings.

[a]Immune complex–mediated MPGN: typically low C3 *and* C4. Complement-mediated MPGN: typically low (but may be normal) C3 and normal C4.

Abbreviations: C3GN, C3 glomerulopathy; CMV, cytomegalovirus; DDD, dense-deposit disease; EM, electron microscopy; HBV, hepatitis B virus; HCV, hepatitis C virus; HUS, hemolytic–uremic syndrome; ICGN, immune complex–mediated glomerulonephritis; IF, immunofluorescence; MAC, membrane-attack complex; MPGN, membranoproliferative glomerulonephritis; SLE, systemic lupus erythematosus; SPEP, serum protein electrophoresis; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; UPEP, urine protein electrophoresis.

- Clinical manifestations associated with MPGN injury pattern range from asymptomatic hematuria and proteinuria to acute glomerulonephritis with hypertension and AKI.

Histopathology of MPGN Injury Pattern (Fig. 7.9)

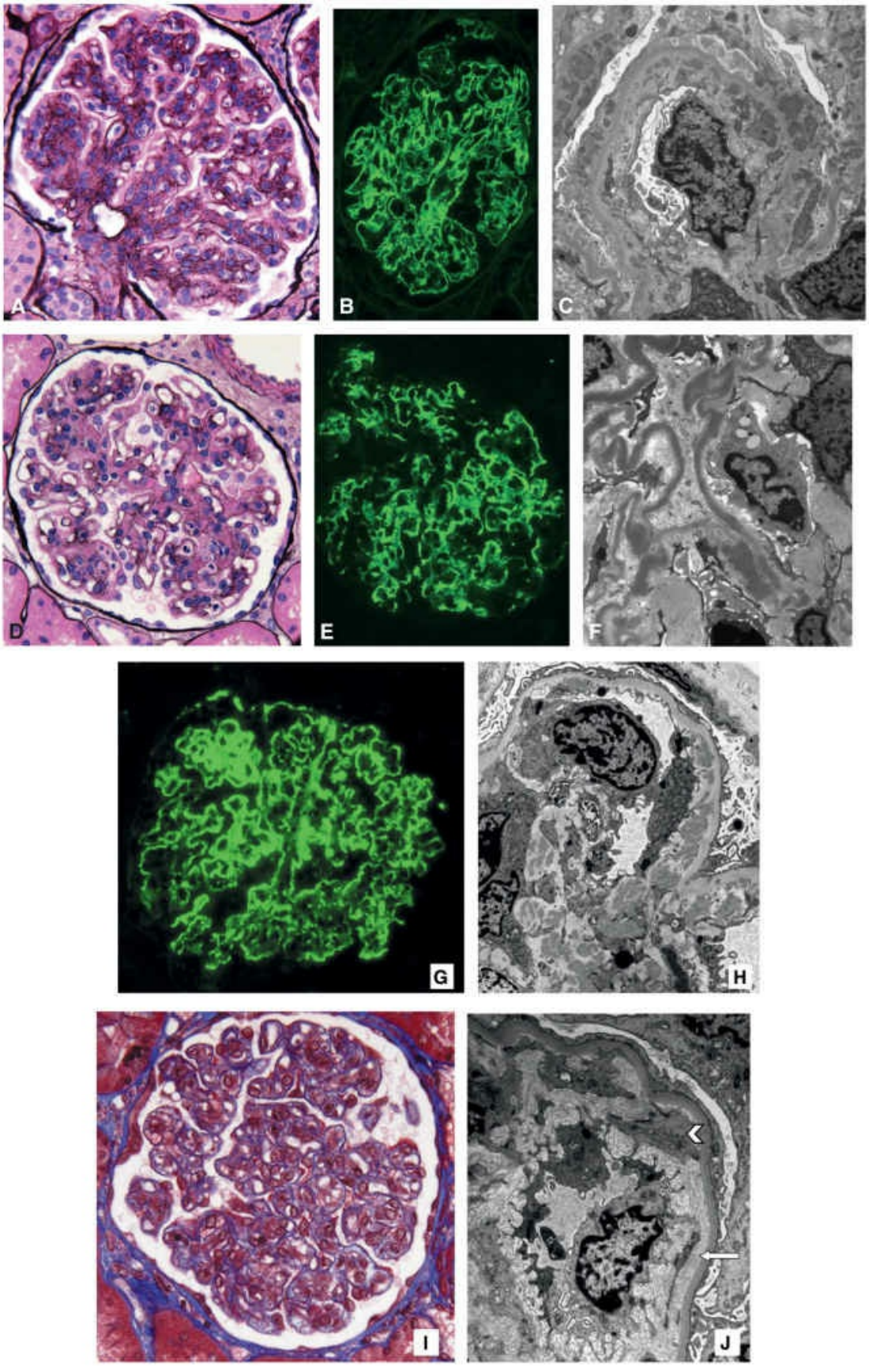
A
B
C
D
E
F
G
H
I
J

FIGURE 7.9 Membranoproliferative glomerulonephritis (MPGN) pattern of injury. **A.** Lobular hypercellular glomerulus (Jones silver ×400). **B, C.** Immune complex–mediated MPGN: **B.** Immunoglobulin G in a peripheral granular and mesangial pattern in immune complex–mediated MPGN (×250). **C.** Subendothelial deposits with new basement membrane deposition forming a double contour in immune complex–mediated MPGN. There also are scattered subepithelial deposits (×10,000). **D–H.** C3 glomerulopathy. **D.** Silver-negative material in widened mesangial regions and capillary walls. This may be seen with dense-deposit disease or C3 glomerulonephritis (Jones silver ×400). **E.** Coarse linear and segmental coarse granular C3 deposition in dense-deposit disease (×400). **F.** Electron-dense transformation of capillary basement membranes and segmentally in mesangial matrix in dense-deposit disease (×10,000). **G.** Granular to confluent granular mesangial and segmental capillary wall staining for C3 (×400). **H.** Electron-dense deposits in subendothelial and mesangial locations (×10,000). **I, J.** Nonimmune complex, noncomplement MPGN: **I.** Prominent capillary double contours and lobular appearance (×400). **J.** Subendothelial lucencies (*arrow*) and mesangial interposition (*arrowhead*) with new basement membrane deposition (*arrow*) forming double contours (×10,000).

- LM: Lobular appearance with mesangial and endocapillary hypercellularity and capillary wall double contours. There may or may not be crescents.
- IF: Three different staining patterns may be seen, which reflect the underlying pathogenesis.
  - **IC-mediated MPGN**: C3 plus other Igs and C1q or C4
  - **Complement-mediated MPGN**: Capillary wall and mesangial staining for C3 alone or C3 dominant by two orders of staining stronger compared to other immunoreactant (i.e., 1+ IgG and 3+ C3)
  - **Endothelial injury or TMA**: Negative staining for either C3 or Ig
- EM: When the IF is positive, there may be subendothelial deposits with mesangial migration and interposition with duplication of basement membrane forming capillary double contours, and variable mesangial and capillary wall deposits depending on the disease process. See below for more detailed descriptions of electron-dense deposits in the two subtypes of C3 glomerulopathy, C3 glomerulonephritis (C3GN), and dense-deposit disease (DDD).

Pathogenesis of Conditions Associated With MPGN Injury Pattern

Ig/IC-mediated MPGN

- Involves activation of the classic complement pathway
- IF microscopy typically shows *both* Ig and complement deposits.

Pathogenesis of Ig/IC-mediated MPGN

1. Chronic increase in Ig production due to infections, autoimmune disease, malignancies, or monoclonal gammopathies leads to:
2. Binding of the Igs to the GBM with subsequent activation of the complement cascade and induction of inflammatory changes (cellular or proliferative), followed by:
3. A reparative phase where new mesangial matrix is formed (mesangial expansion). Mesangial cells extend along the subendothelial area and, along with endothelial cells, produce new subendothelial GBM, forming capillary wall "tram tracks or double contours." The new GBM may entrap subendothelial capillary wall deposits and mesangial cell cytoplasm, with or without inflammatory cells.

Conditions with increased Ig production that may result in MPGN injury pattern

- Infections: chronic viral infections (e.g., hepatitis C >> B and/or cryoglobulins); bacterial infections (endocarditis, shunt/indwelling catheter nephritis, abscesses; common organisms: *Staphylococcus, Mycobacterium tuberculosis, Streptococci, Propionibacterium acnes, Mycoplasma pneumoniae, Brucella, Coxiella burnetii, Nocardia, Meningococcus),* fungal infections, parasitic infections (schistosomiasis, filariasis, malaria)
- Autoimmune diseases: SLE, Sjögren syndrome, rheumatoid arthritis, mixed connective tissue diseases
- Malignancies: lymphomas, chronic lymphocytic leukemia, and carcinomas
- Paraproteinemias: monoclonal gammopathies with or without cryoglobulins, immunotactoid glomerulopathy, proliferative GN with monoclonal immunoglobulin deposits (PGNMID); detection of a paraprotein in the deposits may require an antigen-retrieval technique on the LM specimen followed by routine IF.

Complement-mediated MPGN (C3 glomerulopathy)

C3 glomerulopathy may present as C3GN or DDD subtypes.

Pathogenesis of complement-mediated MPGN

C3 glomerulopathy involves C3 or C5 convertase dysregulation in the fluid

phase and glomerular microenvironment with resultant progressive glomerular inflammation and scarring. Complement dysregulation may occur via:

- **Autoantibody production against various complement pathway components or complexes** (e.g., C3, C4, or C5 nephritic factors, factor H or B, C3b)
  - C3 nephritic factors are autoantibodies that stabilize C3 convertase, thereby increasing its half-life and its consumption of C3.
  - Monoclonal Igs and/or light-chain fragments in monoclonal gammopathy may interfere with the alternative pathway and give rise to C3 glomerulopathy.
- **Genetic variants of complement or regulatory proteins of the alternative complement pathway** (e.g., genes encoding complement factor 3, complement factor B, and complement regulatory factors H and I, complement factor H–related proteins FHRP1-5)

Diagnosis of complement-mediated MPGN

The diagnosis of C3 glomerulopathy requires IF and EM studies:

- LM: may range from no glomerular hypercellularity to MPGN with or without crescentic and sclerosing patterns.
- IF: The staining intensity for C3 is of at least two orders of magnitude greater than that for any other immunoreactant (e.g., IgA, IgM, IgG).
- EM is required to distinguish C3GN from DDD.
  - DDD: EM shows highly electron-dense, osmiophilic deposits with a sausage-shaped appearance within the GBM.
  - C3GN: Electron-dense deposits are of lower density than those seen in DDD and approach that of glomerular matrix components. These deposits are ill-defined with cloudy appearance and may localize within the mesangium and/or appear as inclusions in subendothelial (intramembranous and/or subepithelial) regions.
  - Subepithelial humps can occur in both C3GN and DDD.
- Laser microdissection and mass spectrometry show large amount of C3. The presence of terminal complements is more typical for C3GN than

DDD.

- Of interest, C4GN and C4 DDD have also been described, where bright C4d instead of C3 staining is seen on IF microscopy. The underlying etiology remains to be defined.

Non-IC, non–complement-mediated MPGN

May be seen with TMAs or other forms of endothelial injury

Pathologic characteristics of non-IC, non–complement-mediated MPGN

- IF: no Igs or complements, capillary wall or luminal fibrin is present.
- EM: no electron-dense deposits. Subendothelial lucencies with or without luminal thrombi and capillary double contours

Conditions associated with non-IC, non-complement-mediated MPGN

- Thrombotic thrombocytopenic purpura or hemolytic–uremic syndrome, atypical hemolytic–uremic syndrome, antiphospholipid antibody syndrome, drug-induced TMA, malignant hypertension, radiation nephritis, bone marrow transplant–associated nephropathy, connective tissue disorders

General Evaluation for Kidney Biopsies With MPGN Injury Pattern

Laboratory findings

- Hypocomplementemia is often, but not always, present in GN with MPGN injury pattern:
  - IC-mediated MPGN: typically low C3 *and* C4
  - Complement-mediated MPGN: typically low C3 and normal C4

Diagnostic studies

Studies to be obtained are based on **IF findings** on the kidney biopsy.

IF: Positive staining for both Ig and complement deposits

- Blood cultures, polymerase chain reaction, and serologic tests for viral (e.g., hepatitis B, hepatitis C, CMV, bacterial, occult infections, malaria, and fungal infections [per local prevalence and/or symptoms])
- Cryoglobulins (consider rheumatoid factor: 70% cross-reactivity with

cryoglobulins)

- Serum and urine protein electrophoresis and immunofixation, serum κ/λ light chains
- Rheumatologic serologies for autoimmune disorders, particularly SLE
- Malignancy screen appropriate for age, gender, and personal risks

IF: Positive staining for complement deposits alone (with or without dense deposits on EM)

- Rule out secondary forms of C3 deposition, including postinfectious glomerulonephritis (PIGN) and paraproteinemia. Low C3 level should normalize within 12 weeks with PIGN. Prolonged hypocomplementemia C3 should prompt the evaluation for C3GN/DDD. Evaluate for paraproteinemia for patients >50 years old or per clinical suspicion for younger individuals.
- Measure complement levels and activities to determine the extent of complement dysregulation and response to therapy (C3, C3c, Bb, C4, nephritic factors, soluble C5b-9, properdin, factor H, CH50, APH50); genetic analysis may be considered at specialized laboratories.
- Retinal scan to evaluate for ocular drusen (may be seen in patients with C3 glomerulopathy)

IF: Negative staining for Ig or complement deposits

- ADAMST13, blood smear for schistocytes, LDH, indirect bilirubin, platelet count and volume

Management

- Table 7.8 summarizes management strategies for MPGN arising from various etiologies.

Table 7.8 Management Strategies for Immunoglobulin or Complement-Mediated GN (ICGN) with MPGN Pattern of Injury

Routine for all patients	• Use ACEI or ARB for proteinuria as safely tolerated • Anticoagulation therapy: unclear long-term benefit • *All* patients must be

	evaluated for secondary causes.
Idiopathic ICGN with *proteinuria 3.5 g/d, absence of nephrotic syndrome, normal eGFR*	• Supportive therapy alone
Idiopathic ICGN with *nephrotic syndrome* and relatively normal eGFR	• Glucocorticoid therapy limited to ~6 mo
Idiopathic ICGN with *active urinary sediment and declining kidney function* but without crescents	• Oral CYC or MMF *and* corticosteroids, with initial therapy limited to 6 mo
Rapidly progressive disease or crescentic idiopathic ICGN	• High-dose corticosteroids and CYC
ICGN with presenting *eGFR 30 mL/min/1.73 m^2 due to chronic disease*	• Supportive therapy alone
ICGN with *known underlying causes*	• Treat underlying disease (i.e., infections, monoclonal gammopathy, autoimmune disease) if applicable. • Rituximab may be beneficial if monoclonal gammopathy without overt hematologic malignancy • Consider plasmapheresis if symptomatic cryoglobulinemia
C3 glomerulopathy with proteinuria > 1g/d and active urinary sediment or declining kidney function for ≥ 6 mo and without associated monoclonal gammopathy **Note:** Rule out infection-related glomerulonephritis and paraproteinemia prior to making the diagnosis of C3GN	• MMF • If no response to MMF, consider eculizumab (eculizumab is an anti-C5 monoclonal antibody that inhibits C5 activation.) • Consider plasmapheresis in severe cases

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CNI, calcineurin inhibitor; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; HUS, hemolytic–uremic syndrome; MMF, mycophenolate mofetil; MPGN, membranoproliferative glomerulonephritis.

- Use RAAS inhibitors in all patients with MPGN as safely tolerated.
- For C3GN and DDD:
  - Immunosuppressive therapy: Consider MMF and prednisone for

proteinuria 0.5 to 2.0 g/d; if progression of proteinuria or disease, consider pulse methylprednisolone and anti-C5 therapy (eculizumab)

- Targeted therapies in ongoing clinical trials include anti-C3 (APL2, AMY-101), anti-C5aR1 (avacopan), and inhibitors of other complement factors.

Kidney Transplant Involving C3 Glomerulopathy

- Histologic recurrence may occur almost immediately posttransplant. The median time to graft survival following biopsy diagnosis of recurrence has been reported to be 18 months.
- Graft loss due to recurrence may occur in 50% of patients within 10 years of transplantation.
- Low serum C3 level at the time of transplantation may portend higher recurrence risk.

NEPHROTIC/HEAVY-PROTEINURIC GLOMERULAR DISORDERS

Minimal Change Disease (MCD)

Background

- Most common cause of NS in children (70% to 90% of NS in children <10 years of age); 50% in older children; 10% to 15% of primary ns in adults

Pathogenic mechanisms implicated in MCD

- T-cell dysfunction (likely immature and relatively undifferentiated T cells [CD34+], not in mature T cells [CD34−], have been implicated in the pathogenesis of MCD):
  - MCD improves with measles, a condition that modulates cell-mediated immunity
  - MCD is seen more commonly with Hodgkin disease
  - Atopic individuals are at higher risk for MCD
- B-cell dysfunction:
  - RTX (chimeric monoclonal antibody that depletes B cells expressing CD20 antigen) may improve steroid-sensitive disease.

    - Suggests a role for a glomerular permeability factor produced by B or T cells through pathways regulated or stimulated by B cells
  - Glomerular permeability factor possible, likely Th2-derived cytokines, for example, interleukin IL-13. IL-13 induces expression of podocyte CD80, which
    - Induces podocyte foot process effacement and proteinuria
    - IL-13 is associated with allergic states, conditions associated with MCD.
- Alterations in GBM such as, loss of negative charges induced by circulating factor
- Defect/alterations of key proteins in slit diaphragm, for example, mutation of *NPHS2* gene (podocin)

Clinical manifestations

- Classic presentation of MCD is sudden onset edema (i.e., days to weeks). Tip variant of FSGS may also present with sudden onset edema as MCD. Membranous nephropathy and most other forms of FSGS generally present with slowly progressive edema.
- Nephrotic syndrome
- Microscopic hematuria is seen in 20% to 25% in children, but more commonly in adults.
- AKI at presentation is common and often improves with diuresis, treatment of anasarca. Renal vein thrombosis should also be considered.

Clinical conditions associated with MCD

- Malignancies: Hodgkin, non–Hodgkin lymphoma, leukemia, rarely solid organ tumors
- Allergy, atopy, insect/bee stings, pollens, house dust
- Immunizations
- Drugs: nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors (long-term use), pamidronate, alendronate (bisphosphonates are also associated with collapsing FSGS), lithium, D-penicillamine, tiopronin, γ-interferon, sulfasalazine and 5-aminosalicylic acid derivatives, antimicrobials (rifampin, PCN derivatives)

Histopathology (Fig. 7.10)

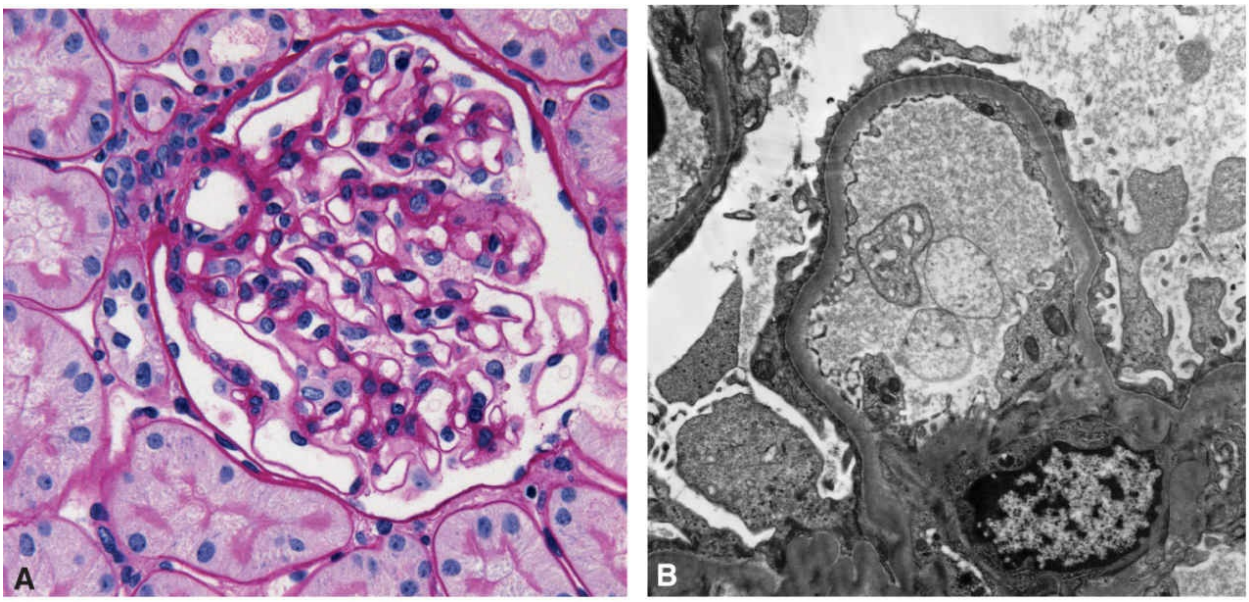

FIGURE 7.10 Minimal change disease. **A.** Normal glomerulus (periodic acid–Schiff ×400). **B.** Extensive podocyte foot process effacement over normal capillary basement membrane (×14,000).

- LM: normal glomeruli; tubules may have acute injury and luminal proteinaceous material due to heavy proteinuria.
- IF: generally no Ig or complement deposition or minimal C3 and/or IgM staining
- EM: podocyte foot process effacement (>75%)
- Glomerulonephropathies that may present as MCD on light microscopy:
  - IgMN is an idiopathic glomerulopathy.
    - Histopathology: mesangial deposition of IgM with/without mesangial hypercellularity and electron-dense deposits
    - IgMN prevalence estimated to be 2% to 5%.
    - Clinically, IgMN spans the spectrum of MCD and FSGS. Treatment is similar to MCD/FSGS due to lack of data.
  - C1qN is a rare idiopathic glomerulopathy.
    - Histopathology: dominant or co-dominant C1q mesangial deposits in the absence of clinical or immunologic features of SLE
    - LM and EM features may appear as MCD, FSGS, mesangial proliferative GN, or have minimal changes other than mesangial

deposits.

- Clinical manifestations, management, and prognosis generally reflect the histopathologic features.

NOTE Glomerulopathies that may have present as MCD on LM include IgM nephropathy (IgMN), C1q nephropathy (C1qN), and minimal mesangial LN. Early recurrence of primary FSGS in the transplant setting may also mimic MCD findings on allograft kidney biopsy.

Management of MCD

- Table 7.9 summarizes management strategies for patients with MCD.

Table 7.9 Management strategies for minimal change disease

Initial episode	• Prednisone or prednisolone at 1 mg/kg/d (maximum 80 mg/d) or alternate-day dose of 2 mg/kg (maximum 120 mg) for ≥ 4–16 wk as dictated by remission. • May use CYC, CNI, or MMF if corticosteroid intolerant or contraindicated
Steroid taper	• Begin tapering 2 wk after complete remission is achieved, usually by 10 mg every 2–4 wk

Relapses	• For infrequent relapses, restart corticosteroid as above.
	• For frequent relapses (i.e., ≥ 2 relapses within 6 mo or ≥ 4 within 12 mo) or steroid dependence (relapse occurring during or within 2 wk of completing corticosteroids therapy), consider one of the following:
	  • Oral CYC 2–2.5 g/kg/d for 8–12 wk, not to exceed 12 wk
	  • CNI, i.e., cyclosporine 3–5 mg/kg/d in 2 divided doses (target trough 5–10 ng/mL) for 1–2 y for those who relapse despite CYC or those who wish to preserve fertility.
	  • MMF 500–1,000 mg bid for 1–2 y for those intolerant to corticosteroid, CYC, CNI.
	  • Rituximab 1 g on days 1 and 15 for those who fail to achieve durable remission with CYC or CNI.

Supportive therapy	• For severe AKI, RRT may be necessary • Statins should not be used to treat hyperlipidemia as risk of coronary artery disease is not increased with MCD. • ACEI or ARB use is *not* suggested in normotensive individuals for the sole purpose of lowering proteinuria in MCD unless proteinuria is anticipated to be protracted.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin-receptor blocker; CNI, calcineurin inhibitor; CYC, cyclophosphamide; MCD, minimal change disease; MMF, mycophenolate mofetil; RRT, renal replacement therapy.

Initial episode

- Initial therapy should start with high-dose corticosteroids for a maximum of 16 weeks.
- Consider CYC, CNI, or MMF in patients with corticosteroid intolerance or contraindication. MMF + reduced-dose corticosteroid may also be considered.
- Steroid taper: Begin tapering 2 weeks after complete remission is achieved; Consider prednisone reduction by 10 mg every 2 to 4 weeks.

Relapses

- Relapse is defined as proteinuria > 3.5 g/d after complete remission has been achieved.
- For patients with infrequent relapses, restart corticosteroids.
- For patients with frequent relapses (i.e., ≥ two relapses within 6 months or ≥ four within 12 months) or steroid dependence (relapse occurring during steroid tapering or within 2 weeks of completing corticosteroid therapy), consider CYC, CNI, MMF, or RTX. A single course of CYC (2.0 to 2.5 mg/kg/d as safely tolerated) over 8 to 12 weeks may lead to remission in the majority of patients. A prolonged course of CYC for >12 weeks is not recommended due to cumulative toxicities.

Supportive therapy

- For severe AKI, renal replacement therapy may be necessary in combination with immunosuppressive therapy.
- Statins should not be used to treat hyperlipidemia as the risk of coronary artery disease is not increased with MCD. Benefit of statin's anti-inflammatory property has not been proven.
- ACEI or ARBs use is not suggested in normotensive individuals for the *sole purpose* of lowering proteinuria in MCD unless proteinuria is anticipated to be protracted.

NOTE In case of steroid-resistant or frequent relapsing MCD, consider erroneous diagnosis due to poor tissue sampling with initial kidney biopsy. Rebiopsy of kidney to evaluate for FSGS should be considered.

Focal Segmental Glomerulosclerosis

Background

- FSGS is a morphologic pattern of glomerular injury that may arise from:
  - A *primary* podocytopathy
  - A *secondary* adaptive process involving nephron mass reduction, reflux nephropathy, viral or drug toxicity, or other underlying glomerular disease
  - A genetic mutation
  - Undetermined cause

Clinical manifestations

Primary FSGS

- Refers to primary podocytopathy (i.e., primary alterations of glomerular epithelial cells with diffuse foot process effacement)
- May present with sudden- or gradual-onset edema and proteinuria
- Typical presentation: proteinuria > 3.5 g/d and serum albumin < 3.0 g/dl with or without edema or dyslipidemia

Secondary FSGS

- Refers to focal and segmental glomerulosclerotic changes due to an independent glomerular injury process or disease
- Development of edema and proteinuria is usually slowly progressive.
- Does not typically present with NS

Genetic inheritance/predisposition to FSGS

- A large number of autosomal dominant and recessive genes inherited with variable penetrance can cause FSGS. Clinical manifestations are variable.
- Genetic testing may be beneficial for some individuals, predominantly to avoid corticosteroids, as most are steroid resistant. Mutations in phospholipase C epsilon 1 (PLCε1) may be an exception.
- Apolipoprotein I (APOL1) variant
  - Inheritance of two polymorphic risk alleles of the apolipoprotein 1 (*APOL1*) gene increases the risk of FSGS and of progressive functional decline in patients with non–diabetic kidney diseases. These polymorphisms are more common in individuals of more recent African ancestry.

- Missense APOL1 polymorphisms predispose patients to an excess risk of ESKD.
- The presence of APOL1 risk polymorphisms is not a contraindication for a trial of corticosteroids.
- APOL1 polymorphisms protect against *Trypanosoma brucei*, a parasite spread by tsetse flies in Africa.

Pathogenesis

Primary (idiopathic) FSGS (1° FSGS)

- Evidence for the role of a circulating permeability factor:
  - Recurrence of proteinuria and 1° FSGS following kidney transplantation
  - Transient proteinuria in an infant born to a mother with 1° FSGS
  - Resolution of proteinuria in a retransplanted kidney from a recipient with 1° FSGS into a recipient without the condition
- Circulating permeability factor candidates including soluble urokinase-type plasminogen activator receptor, cardiotrophin-like cytokine-1, angiopoietin- like-4, CD80, and others remain to be independently validated.

Secondary FSGS

- Virus: HIV type 1, parvovirus B19, simian virus 40, CMV, Epstein–Barr virus
- Drugs: heroin, interferons (α, β, and γ), lithium, pamidronate, alendronate, sirolimus, anabolic steroids, CNIs, NSAIDs, heroin (adulterants), anthracyclines
- Adaptive structural–functional responses
  - Reduced renal mass: low birth weight, oligomeganephronia, premature birth, unilateral kidney agenesis, reflux uropathy, chronic allograft nephropathy, advanced renal disease with reductions in functioning nephrons
  - Initially normal renal mass: HTN, DM, atheroemboli/acute vasoocclusive process, obesity, increased lean body mass, anabolic steroids (body builders), cyanotic congenital heart disease, sickle cell anemia

- Malignancy (in particular lymphoma)
- Scarring due to underlying glomerular diseases: (IgAN, LN, pauci-immune focal necrotizing and crescentic GN), hereditary nephritis (Alport syndrome), membranous glomerulopathy, TMA

Genetic FSGS

- Familial/genetic: There are >50 known mutations, including nephrin (NPHS1), podocin (NPHS2), α-actinin 4, transient receptor potential cation 6 (TRPC6), WT1, informin-2, SCARB2 (LIMP2), formin (INF2), CD2-associated protein (CD2AP), PLCε1, mitochondrial cytopathies

Histopathology: General findings and considerations

- LM: segmental increase in mesangial matrix with obliteration of capillaries, sclerosis, hyalinosis, foam cells, podocyte hypertrophy with or without epithelial cell hyperplasia, and adhesions between glomerular tuft and Bowman capsule
  - The *deep* inner juxtamedullary glomeruli are preferentially affected in early primary FSGS.
  - Renal biopsies containing <15 glomeruli or only superficial cortical glomeruli may be insufficient to exclude fsgs.
- IF: usually negative staining, except for IgM and complement in insudates
- EM: podocyte foot process effacement varies
  - Primary and some genetic forms of FSGS with severe/diffuse foot process effacement
  - Most secondary and some genetic forms of FSGS may have partial effacement.
  - Secondary collapsing FSGS may have extensive foot process effacement.
  - Foot process effacement may be impacted by prior treatment.

Histopathology of FSGS variants (Fig. 7.11)

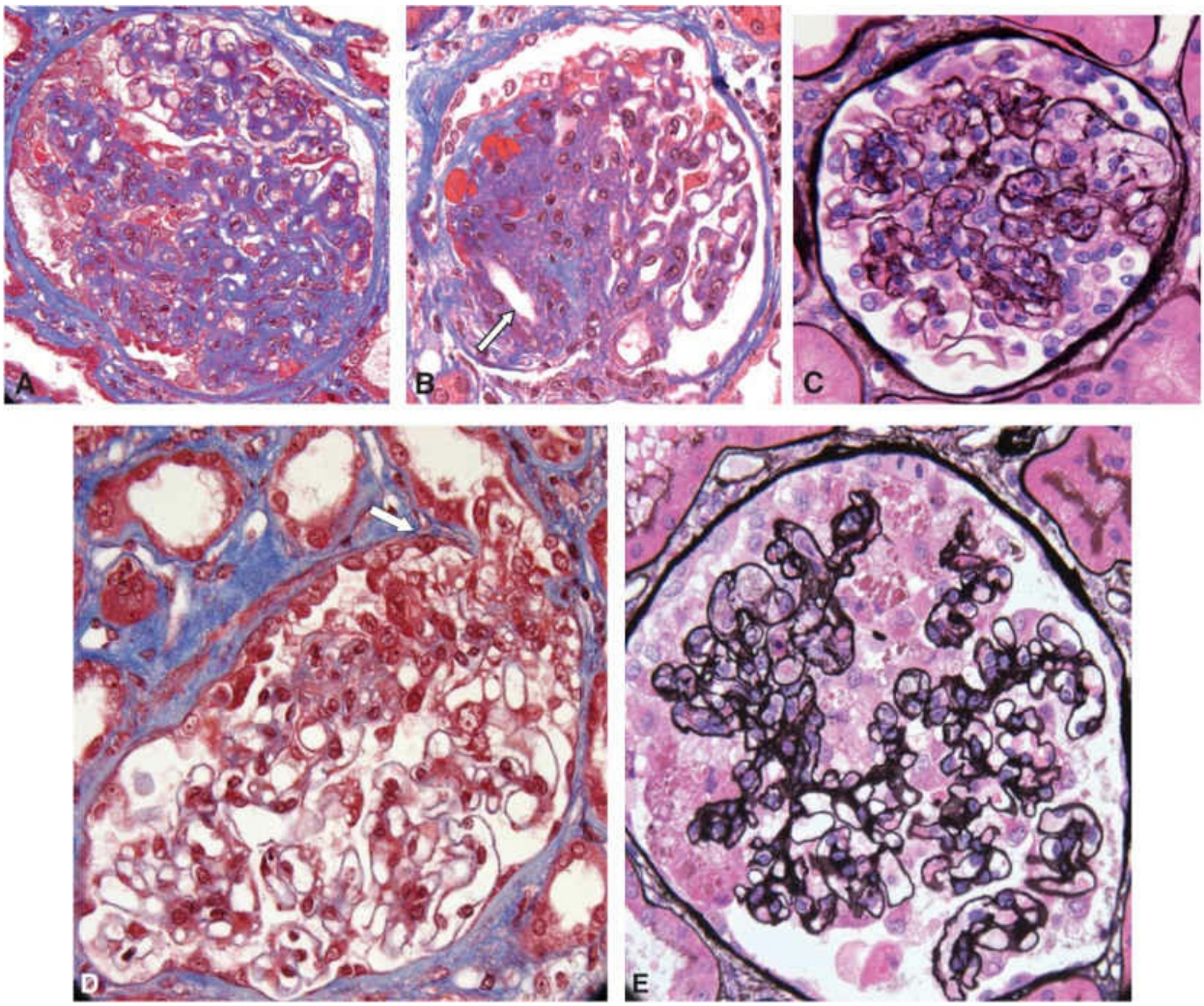

FIGURE 7.11 Focal and segmental glomerulosclerosis. **A.** Not otherwise specified variant. Segmental capillary obliteration, podocyte hypertrophy, adhesions to Bowman capsule, and insudative lesions not at the tip or perihilar region (Masson trichrome ×400). **B.** Perihilar variant. Segment of sclerosis is adjacent to the arteriolar pole (*arrow*) and characterized by capillary obliteration, insudative lesions (*orange*), and overlying halo formation (podocyte detachment with deposition of new light blue basement membrane material) (Masson trichrome ×400). **C.** Cellular variant. Segmentally, capillaries contain foam cells and leukocytes in association with podocyte hypertrophy (Jones silver ×400). **D.** Tip lesion variant. Podocyte hypertrophy and capillary obliteration are adjacent to the tubular pole (*arrow*). Note the sclerotic segment protruding into the proximal tubular lumen (Mason trichrome ×400). **E.** Collapsing variant. Capillary wall collapse and luminal obliteration with podocyte hypertrophy, hyperplasia, and cytoplasmic vacuoles and protein droplets (Jones silver ×400).

Perihilar FSGS

- Segments of sclerosis at glomerular vascular pole
  - LM: insudates, adhesions, foam cells
    - Podocyte hypertrophy may not be present.

        - May be associated with glomerular hypertrophy (glomerulomegaly)
    - EM: foot process effacement typically segmental and not severe
- Associations: adaptive FSGS
    - Thought to reflect increased filtration pressures at the afferent arterioles associated with compensatory demand
- Clinical features: typically subnephrotic proteinuria and normal serum albumin

Cellular FSGS

- Least common variant
- No specific glomerular location
    - LM: expansile segmental lesion with endocapillary hypercellularity, often including foam cells and leukocytes
        - May be glomerular epithelial cell hypertrophy
        - Variable glomerular epithelial cell hyperplasia
        - May be early/evolving FSGS or tip lesion without proper glomerular orientation
    - EM: usually severe foot process effacement
- Associations: usually primary, but may be seen with secondary causes
- Clinical features: typically NS

Tip lesion FSGS

- Segmental lesion involving tubular pole
    - LM: podocyte hypertrophy with or without confluence with tubular epithelial cells
        - May be adhesions to tubular outlet
        - Often endocapillary foam cells, may be insudates
        - Sclerotic segment may herniate into proximal tubular lumen.
    - EM: severe foot process effacement
- Compared with other variants, tip lesion has the least tubular atrophy and interstitial fibrosis.
- More common in white race
- Associations: usually primary; thought to be mediated by physical stresses

on paratubular segment due to convergence of protein-rich filtrate on tubular pole

- Clinical features: usually abrupt onset of NS; best prognosis, highest rate of response to corticosteroids compared to all other FSGS variants

Collapsing FSGS

- May be segmental or global
  - LM: implosive glomerular-tuft collapse with hypertrophy and hyperplasia of overlying epithelial cells
    - Hyperplastic glomerular visceral epithelial cells often with cytoplasmic protein droplets and vacuoles, which may fill urinary space resembling crescents
    - Severe tubular injury; tubular microcysts common
  - EM: often severe foot process effacement
- Associations: primary or secondary
- Clinical features: most aggressive variant of primary FSGS, African descent predominance and severe NS; worse prognosis, poor response to corticosteroids.

Not otherwise specified (NOS) FSGS

- Generic form of FSGS, not meeting any variant above
- Associations: most common subtype, can occur with primary or secondary including genetic forms; other forms can evolve into NOS over time
- Clinical features: variable

Management of FSGS

- Routine therapy for all FSGS variants: RAAS inhibition, blood pressure control, and dietary sodium restriction

Management of primary FSGS (Table 7.10)

Table 7.10 Management strategies for primary focal segmental glomerulosclerosis

Initial Therapy	
Routine management	RAAS inhibition, blood pressure control, and sodium restriction.

First-line therapy	Corticosteroid (CS)	Prednisone 1 mg/kg (maximum 80 mg) qd or 2 mg/kg (maximum 120 mg) qod for at least 4 wk, up to maximum of 16 wk
Alternative first-line therapy[a]	Calcineurin inhibitors (CNIs)[b]	CSA 3–5 mg/kg/d in divided doses (initial target levels 125–175 ng/mL) or TAC 0.1–0.2 mg/kg/d in 2 divided doses (initial targets 5–10 ng/mL) for at least 12 mo to minimize the risks of relapse.
Follow-Up Management	**8–16 wk**	
Steroid-induced CR[c]	Steroid-induced CR accomplished → slowly taper to complete a total course of 6 mo	
Steroid-induced PR[d]	Steroid-induced PR → continue CS for up to 16 wk → taper CS slowly if CR is achieved Steroid-induced PR and 24-h uP 1.5 g/d at 8–16 wk → Maximize nonimmunosuppressive treatment and observe Steroid-induced PR and 24-h uP > 1.5 g/d at 8–16 wk → consider adding a CNI	
No remission with steroids[e]	No remissions from steroids by 8–16 wk → add CNI	
CNI responders	Continue for at least 12 mo to prevent relapse on withdrawal	
Problematic Cases		
Frequent relapse or steroid dependent	Frequent relapse or steroid dependent (two relapses during or within 2 wk of completing steroid therapy) → treatment is similar to that for relapsing minimal change disease in adults	
No remission by 6 mo	No remission by 6 mo, discontinue therapy and consider referral for participation in clinical trial[f]	
Other therapeutic options that lack robust data include rituximab, mycophenolate mofetil, and repository corticotropin injection (Acthar gel)		

[a]Alternative therapy may be considered if there is intolerance or contraindications to corticosteroid use.
[b]Occasionally, patients will respond to either cyclosporine or tacrolimus, but not both (see text).
[c]Complete remission (CR, proteinuria <0.3 g/d, normal scr, and serum albumin > 3.5 g/dL).
[d]Partial remission (PR, proteinuria 0.3 to <3.5 g/d, stable scr or change in scr by <25%).
[e]No remission (i.e., proteinuria without response or declined but still > 3.5 g/d).
[f]Ongoing clinical trials at the time of this writing: NephCure Kidney International (https://kidneyhealthgateway.com), National Kidney Foundation (https://www.kidney.org/atoz/content/how-can-i-find-clinical-trial), Glomerular Disease Consortium (https://glomcon.org/category/clinical-trials).
Abbreviations: 24-h uP, 24-hour urine protein; CR, complete remission; CSA, cyclosporine; PR, partial remission; qd, everyday; qod, every other day; RAAS, renin–angiotensin–aldosterone system; TAC, tacrolimus.

- First-line therapy: high-dose corticosteroids until remission or as safely tolerated up to a maximum of 16 weeks (prednisone 1 mg/kg, maximum 80 mg/d, or alternate-day dose of 2 mg/kg, maximum 120 mg every other day), followed by taper below

- Steroid taper:
  - If complete remission is achieved early, continue high-dose corticosteroids for a total of ≥ 4 weeks or for 2 weeks after resolution of proteinuria, whichever is longer, then reduce prednisone by 5 mg every 1 to 2 weeks to complete a total course of 6 months.
- Second-line therapy: CNIs
  - Consider CNI in patients with intolerance or contraindications to corticosteroid use (e.g., uncontrolled diabetes, psychiatric conditions, severe osteoporosis) or corticosteroid-resistant primary FSGS. Treatment duration should be at least 12 months to minimize risk of relapse.
  - Occasionally, patients will respond to either cyclosporine or tacrolimus (TAC), but not both. If there is no response to one, assess sensitivity to the other.
    - Cyclosporine A (CSA) is thought to exert an antiproteinuric effect on the podocyte cytoskeleton (synaptopodin), independent of its immunosuppressive effect.
    - TAC may act on the podocyte TRPC6 channel.
- If there are frequent relapses or steroid-dependent FSGS (two relapses or relapse during steroid tapering or within 2 weeks of completing steroid therapy), treatment is similar to that for relapsing MCD in adults. CNI and CYC remain second-line and third-line agents. Relapse is defined as proteinuria > 3.5 g/d after complete remission has been obtained. Treatment should be ≥12 months to minimize relapse.
- Other options lacking robust data include RTX, MMF, and Acthar gel.
- Trials with pending results: Efficacy of RTX in comparison to continued corticosteroid treatment in idiopathic NS and pilot study to evaluate the safety and efficacy of abatacept (CD80 inhibitor) in adults and children with excessive loss of protein in urine due to either FSGS or MCD.

Management of secondary FSGS

- Adaptive FSGS: no immunosuppressive therapy; encourage healthy living including weight loss if obese, smoking cessation; BP control; RAAS inhibition

- Other: treat underlying disease or removal of etiologic agents

Management of genetic FSGS

- Patients with APOL1 risk polymorphisms should be treated the same as patients with primary FSGS.
- Patients with FSGS due to genetic mutations should be treated with RAASi, sodium restriction, and BP control.
- Immunosuppression is generally not indicated in genetic FSGS, except for specific mutations where partial response has been reported. See **Suggested Readings** list pertaining to FSGS.
- Coenzyme Q-10 and vitamin B_{12} supplement may be considered in FSGS associated with specific mutations, for example, COQ6, prenyl diphosphate synthase subunit, or aarF domain-containing kinase 4 for the former and cubilin for the latter.

Management of FSGS of undetermined cause

- Avoid immunosuppression

Kidney transplantation

- Recurrence occurs in 17% to 50% of primary FSGS.
- Risks for recurrence:
  - Younger age (e.g., children)
  - Nonblack race
  - Rapid course of ESKD (<3 years in native kidneys)
  - Heavy proteinuria prior to transplantation
  - Loss of previous allografts to recurrence
- Little chance of recurrence for most genetic forms, as the defect is in the native kidney and not the allograft.
- Live renal donors who have two APOL1 risk polymorphisms may be at higher risk of subsequent HTN, proteinuria, and CKD. Renal survival from deceased donors with two APOL1 risk polymorphisms may also be reduced. Also see **Chapter 9 Kidney Transplantation**.

Membranous Nephropathy

Epidemiology

- Less than 5% in children and 15% to 50% in adults with NS
- Male-to-female ratio is 2:1.
- US Renal Data System: 0.5% of ESKD population
- HLA-associated inherited risks reported
- Familial forms reported but rare

Pathogenesis

- Deposition of circulating antibody-*antigen* (Ab-Ag) complex or formation of Ab-Ag complex in situ at podocytes leads to complement activation and formation of the membrane attack complex (MAC) C5b-9.
  - The Ab-Ag complexes are capped and shed to form subepithelial deposits. MACs are incorporated into multivesicular bodies and transported by podocyte into urinary space.
  - Increased intracellular sublytic levels of MAC activate podocytes, leading to release of oxidants and proteases and subsequent GBM injury.

Endogenous antigens that may give rise to the development of MN

- M-type phospholipase A2 receptor 1 (PLA2R) (primary MN):
  - PLA2R is a transmembrane podocyte protein.
  - Anti-PLA2R antibodies are present in 50% to 80% of patients with MN and are predominantly of the IgG4 subtype.
  - Anti-PLA2R titer correlates with disease activity.
  - Anti-PLA2R titer predicts outcome: Lower titer is associated with more spontaneous remissions and shorter time to remission following therapy.
  - Hepatitis B has been associated with PLA2R-positive MN, especially among Chinese patients.
  - The presence of anti-PLA2R antibodies does not exclude a concurrent infection or cancer.
- Thrombospondin type 1 domain-containing 7A antigen (THSD7A) (primary or cancer associated MN):
  - Present in 2% to 4% of MN
  - Approximately one-third of patients with THSD7A MN may have an associated neoplasm.
  - Few patients are dual positive for THSD7A and PLA2R.

- Neural epidermal growth factor 1 (NELL-1) antigen (primary MN):
  - Present in ~5% to 10% of MN
  - The association with underlying neoplasm is reportedly uncommon in the United States, but more frequent in Europe.
- Exostosin-1 and exostosin-2 antigens (secondary MN):
  - Exostosins are glycosyltransferases responsible for the synthesis of the heparin sulfate backbone that add glycosaminoglycan residues to the core protein, resulting in the generation of complex polysaccharides in the GBM.
  - Implicated as target antigens or biomarker proteins of secondary (autoimmune) MN in adults
- Rarely, transplacental passage of maternal antineutral endopeptidase (NEP) antibody causes MN in neonates. Father expresses NEP, but mother is null for NEP and develops anti-NEP antibodies.

Conditions associated with secondary MN

- Autoimmune diseases (dysregulated autoantibody formation against self-antigen): SLE, rheumatoid arthritis, mixed connective tissue disease, dermatomyositis, ankylosing spondylitis, Crohn disease, graft-versus-host disease, temporal arteritis, Sjögren, bullous pemphigoid, autoimmune thyroid disease
- Infectious antigens (e.g., chronic active infections): hepatitis B (presence of HBsAg, HBcAg, and usually HBeAg), hepatitis C, syphilis, TB, HIV, enterococcal endocarditis, leprosy, filariasis, malaria, schistosomiasis, hydatid disease
- Drugs/toxin antigens: captopril, gold penicillamine, NSAIDs, COX-2 inhibitors, hydrocarbons, mercury, formaldehyde, lithium, clopidogrel
- Malignancies (tumor antigen): solid organs (lungs, GI, breast, kidney, etc.)
- Antigen from foods: Antibody formation against the cationic bovine serum albumin (cSBA) (e.g. from cow milk) with resulting IC deposits and development of MN has been reported in children.

Clinical manifestations

- Gradual onset (as opposed to acute onset in MCD and often FSGS tip

variant)

- BP is normal to mildly elevated.
- NS (60% to 80%), benign urinary sediment, microscopic hematuria (25% to 50%)
- Complements are typically normal, but can be low in ~50% of hepatitis B virus (HBV)–associated MN.

Natural history of primary MN

- One-third rule: One-third achieves spontaneous remission, one-third remains the same, one-third slowly progresses to renal failure.
- Risks for worse kidney outcome: older age, male gender, HTN, severe hypoalbuminemia, reduced GFR, severe proteinuria (e.g., >8 g/d lasting >6 months), increased urinary IgG, β2-microglobulin, or C5b–9 excretion, presence of two APOL1 risk polymorphisms, biopsy with marked tubulointerstitial disease, FSGS, or extensive GBM damage (thickened GBM or intramembranous lucencies due to resorbed ICs)

Risk of progression categories (see Management section for immunosuppressive options)

- Classic strata associated with risk (proteinuria, eGFR, renal biopsy features)

  High PLA2R antibody titer is associated with diminished likelihood of
- complete remission.
- Low risk (<5% chance of progression):
  - Normal kidney function, proteinuria < 3.5 g/d, and/or serum albumin > 3 g/dL
- Moderate risk:
  - Normal kidney function, persistent proteinuria ≥ 4 g/d, and absence of kidney function decline by > 50% after 6 months of conservative therapy; low PLA2R antibody titer (<50 ru/ml suggested); mild low-molecular-weight proteinuria;

    *selectivity index (SI) < 0.15; urine igg < 250 mg/d
  - *In the urine protein selectivity test, the concentrations of a small (e.g., albumin or transferrin) and a large molecule (e.g., IgG) are measured in both the serum and urine and the ratio of the clearances calculated.

Selective proteinuria (highly selective, e.g., SI < 0.16) suggests a greater loss of the smaller molecules compared with the larger igg molecules and has been shown to have a high correlation with steroid responsiveness. the more selective the proteinuria, the greater the chance of response to steroid therapy.

  - The presence of serious complications of NS (e.g., AKI, infections, thromboembolic events) justifies increasing the risk profile of patients with 4 to 8 g/d proteinuria from medium to high risk.
- High risk:
  - eGFR < 60 ml/min/1.73 m^2; proteinuria > 8 g/d for > 6 months; high degree of low-molecular-weight proteinuria; urine IgG > 250 mg/d; SI > 0.20; high PLA2R antibody level (>150 RU/mL suggested)
- Very high risk:
  - Life-threatening NS
  - Rapid deterioration of kidney function
  - High degree of low-molecular-weight proteinuria in two urine samples collected within interval of 6 to 12 months

Progression/outcome of secondary MN

- Resolution may occur within 1 week (NSAIDs) to years (gold, penicillamine) following withdrawal of underlying agent/condition.

Complications/conditions associated with MN

- Dyslipidemia increases cardiovascular risk, particularly if remission cannot be achieved.
- Increased risk for thromboembolic disease including deep vein thrombosis, renal vein thrombosis, pulmonary embolism (40%)
- Neoplasms and MN
  - Up to five times increased incidence of associated malignancy, especially in those > 65 years old, most often in PLA2R-negative MN
  - Rarely associated with PLA2R-positive MN
  - More common in THSD7A-positive and secondary MN
  - The presence of PLA2R with THSD7A antibodies (dual-positive MN) does not exclude concurrent malignancy.

- Age-appropriate evaluation for neoplasms should be performed in most patients with primary MN, including PLA2R-positive MN and MN in adults associated with THSD7A, NELL-1, exostosin-1/2, cBSA.

Diagnosis

- A kidney biopsy is needed to diagnose MN in a few settings:
  - Cases with negative anti-PLA2R antibodies
  - NS with unexplained AKI/rapid progression, regardless of anti-PLA2R status.
  - Presence of at least one risk factor for disease progression (see **Risk Stratification** above) or serious complications of NS
- PLA2R-positive primary MN may be diagnosed without a kidney biopsy in some settings:
  - When there are significant contraindications necessitating biopsy deferral
  - Patient preference, especially if the eGFR is within normal range
- Without a kidney biopsy, important glomerular, tubulointerstitial, and vascular histopathologic or prognostic information may be missed.

Histopathology (Fig. 7.12)

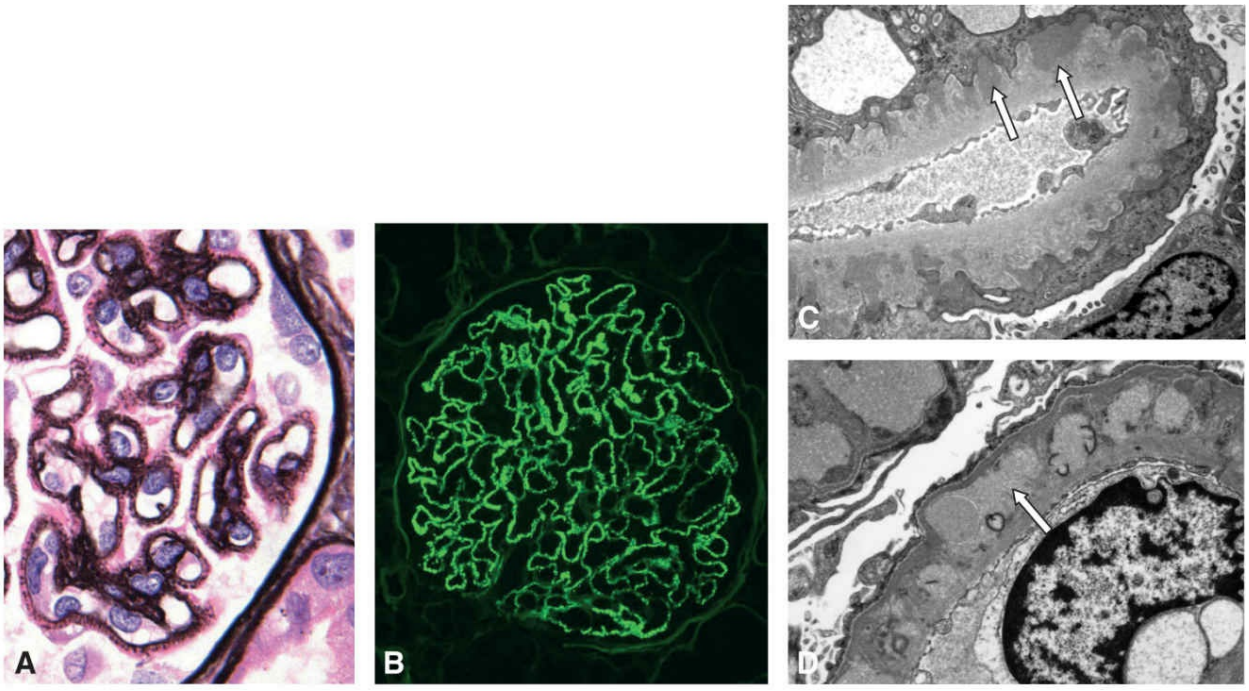

FIGURE 7.12 Primary membranous nephropathy. **A.** Global subepithelial deposits with intervening spikes of basement membrane material (Ehrenreich and Churg stage 2) (Jones silver ×600). **B.** Immunofluorescence for Immunoglobulin G showing granular capillary wall staining (×400). **C.** Subepithelial electron-dense deposits (*arrows*) with intervening spikes of basement membrane material (×14,000). **D.** Predominantly cleared intramembranous deposits (*arrow*) with new subepithelial layer of basement membrane material in stage 4 disease (×14,000).

- LM:
  - Variably thick capillary walls
    - Silver positive subepithelial projections of GBM between deposits giving a characteristic spike-like pattern (stage 2)
    - GBM thickening with lucencies or double contours due to resorption of subepithelial and intramembranous immune deposits (stages 3 to 4)
  - No mesangial hypercellularity in primary disease. Mesangial hypercellularity and inflammation may be seen in secondary MN.
  - Endocapillary leukocytes, including polymorphonuclear leukocytic infiltrates, with renal vein thrombosis
  - Concurrent FSGS is present in up to 30% and may portend worse prognosis, rapid progression and poor response to therapy.
  - Tubulointerstitial injury and fibrosis are common; may indicate advanced disease.
- IF:
  - IgG and often C3 deposits are seen in capilllary wall.
  - Primary MN: IgG4 is usually dominant or co-dominant; IgG1, IgG2, and/or IgG3 predominate in secondary MN. C1q and C4 are usually absent.
  - C3 is present in ~50% of patients, likely reflecting active immune deposit formation and complement activation. Minimal C3 staining suggests inactive or very early disease.
  - Mesangial and C1q staining are associated with secondary MN; “Full house” (C1q, C3, IgG, IgM, and IgA) staining suggests membranous LN.
- EM:
  - *Diffuse subepithelial granular electron-dense deposits that parallel IgG*

staining

- In primary MN, deposits are restricted to subepithelial and intramembranous sites.

- In secondary MN, there may be mesangial and/or subendothelial deposits.
- MN lesions with endothelial cell tubuloreticular inclusions are associated with lupus or underlying viral infection (e.g., hepatitis C). Tubuloreticular structures may also be seen in HIV-associated GN or interferon therapy.
- Severe foot process effacement

Management

- Table 7.11 summarizes management strategies for patients with primary MN.

Table 7.11 Management strategies for primary MN

Conservative management for all patients, regardless of risk of progression	• ACEI/ARB as tolerated • Statin (if LDL > 100 mg/dL) • BP control with goal systolic pressure 120 mm hg using standardized office bp measurement as safely tolerated • Evaluate for secondary causes (e.g., malignancy per personal risks, underlying infections) • Full anticoagulation (warfarin or heparin) is recommended for the duration of the nephrotic syndrome for patients with known thrombotic complications • Prophylactic anticoagulation therapy with oral warfarin (with heparin bridging) may be considered in high-risk patients.[a]

IST	• Choice of IST may be based on risk stratification (see text for risk stratifications):
	  • Low risk: conservative management; if disease deteriorates, initiate immunosuppressive therapy.
	  • Moderate risk: conservative management for 6 mo; if no improvement or there is deterioration of disease, initiate immunosuppressive therapy. Suggested IST: RTX or CNI
	  • High risk: RTX, CYC, or CNI + RTX
	  • Very high risk: CYC
	  • Note that although MMF may confer similar remission rates as CYC, relapses rates have been shown to be markedly higher for MMF compared with CYC.
	• Common dosages as IST used to treat MN:

	Rituximab (RTX) 1 g IV × 2 on day 1 and day 15. Solu-Medrol 1 g, then 100 mg, may be given IV on RTX infusion days to reduce infusion reactions and prevent anti-mouse, anti-human, and anti-chimera antibody formation
	• "Ponticelli" protocol:
	  • Months 1, 3, 5: IV methylprednisolone 1 g/d × 3 d, followed by oral methylprednisolone 0.5 mg/kg/d × 27 d
	  • Months 2, 4, 6: oral chlorambucil (0.15–0.2 mg/kg/d) or oral CYC (2.0 mg/kg/d) × 30 d

Comments	Monitor SCr, urinary protein excretion, serum albumin, and white blood cell (WBC) count every 2 wk × 2 mo, then every month × 6 mo. For chlorambucil, monitor transaminases for hepatotoxicity. IST may be less effective if SCr is persistently > 3.5 mg/dL or eGFR 30 ml/min/1.73 m^2 *and* reduction of kidney size on ultrasound *or* concomitant severe or potentially life-threatening infections.

[a]High risk is defined as serum albumin < 2.0 to 2.5 g/dl *and* ≥ one of the following: proteinuria >10 g/d, body mass index >35 kg/m^2, prior history of thromboembolism, family history of thromboembolism with documented genetic predisposition, New York Heart Association functional class III or IV congestive heart failure, recent abdominal or orthopedic surgery, or prolonged immobilization. It is reasonable to maintain anticoagulation over the duration of nephrotic syndrome.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BP, blood pressure; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; IST, immunosuppressive therapy; IV, intravenous; LDL, low-density lipoprotein; MN, membranous nephropathy; SCr, serum creatinine.

Conservative management for all patients regardless of progression risk

- ACEI/ARB as tolerated
- Statin (if low-density lipoprotein [LDL] >100 mg/dL)
- Systolic blood pressure control to <120 mm hg using standardized office bp measurement
- Evaluate for secondary causes (e.g., chronic infections, malignancy for older patients such as chest computed tomography [CT], kidney ultrasound, urine cytology, mammography, upper endoscopy, colonoscopy, prostate ultrasound and biopsy, colposcopy as clinically indicated). More sensitive positron emission tomography (PET) scan may be considered.
- Full anticoagulation with warfarin or heparin congeners is recommended for the duration of the NS for patients with known thrombotic complications.
- Prophylactic anticoagulation therapy with oral warfarin (with heparin bridging) may be considered for MN patients with NS and high thromboembolic risks (see **General Management Considerations for Glomerular Diseases** section). It is reasonable to maintain anticoagulation

over the duration of NS.

Immunosuppression for primary MN

- Immunosuppression is not necessary for patients with proteinuria <3.5 g/d and egfr > 60 mL/min/1.73 m^2.
- Immunosuppression should be considered in patients with NS *and* at least *one* of the following:
  - Proteinuria persistently > 4 g/d *and* remains >50% of baseline during an observation period of at least 6 months
  - Presence of severe, disabling, or life-threatening symptoms related to NS
  - SCr increases by ≥30% within 6 to 12 months from time of diagnosis, but baseline eGFR remains ≥ 30 mL/min/1.73 m^2.
  - Declining kidney function, disabling symptoms, or "full-blown" NS persisting for ≥6 months
- Choice of immunosuppressive therapy (IST) may be based on risk stratification:
  - Low risk: conservative management; if disease deteriorates, initiate immunosuppressive therapy.
  - Moderate risk: conservative management for 6 months; if no improvement or there is deterioration of disease, initiate immunosuppressive therapy. Suggested IST: RTX or CNI
  - High risk: RTX, CYC, or CNI + RTX
  - Very high risk: CYC
  - Note that although MMF may confer similar remission rates as CYC, relapse rates have been shown to be markedly higher for MMF compared with CYC.

Definitions of complete and partial remission of primary MN

- Complete remission: proteinuria <0.3 g/d (or upcr < 0.3 g/g creatinine), confirmed by two values at least 1 week apart, accompanied by a normal serum albumin concentration and normal scr
- Partial remission: proteinuria <3.5 g/d (or upcr <3.5 g/g creatinine), and a ≥50% reduction from peak values; confirmed by two values at least 1 week

apart, accompanied by an improvement of normalization of serum albumin concentration and stable scr

- Immunologic monitoring of PLA2R antibody level may also be used as an indication of response. A fall in >50% at 3-month follow-up has been suggested to indicate a good clinical response to therapy.

Transplant recurrence of primary MN based on anti-PLA2R antibody positivity

- Disappearance of anti-PLA2R antibody at the time of transplant confers a low risk of recurrence (10%).
- Persistent positivity of anti-PLA2R antibody at the time of transplantation is associated with a high risk of recurrence (50%).
- MN without ever having anti-PLA2R antibody in either serum or kidney biopsy is associated with a medium risk of recurrence (30%).
- Treatment of disease recurrence in the allograft with proteinuria > 1 g/d: Consider RTX 1 g at days 1 and 15.

MISCELLANEOUS

Paraprotein (Monoclonal Gammopathy)-Related Disorders

Epidemiology

- Kidney involvement is common.
- 40% of patients present with SCr > 1.5 mg/dL.
- May be associated with myeloma, monoclonal gammopathy of renal significance (MGRS), and lymphoproliferative disorders including chronic lymphocytic leukemia (CLL) and Waldenström macroglobulinemia
- Survival is associated with kidney function and renal recovery with treatment of multiple myeloma.

Renal manifestations (Table 7.12)

Table 7.12 Kidney injury patterns related to monoclonal gammopathy

Location	Disease	Histopathology	Pathogenesis
Tubulointerstitium and glomeruli	Cast nephropathy	PAS-negative cracked angulated casts and/or surrounding giant cells	Precipitation of filtered LC causing tubular obstruction
	Light-chain	Cell cytoplasm filled with	Reabsorption of

	proximal tubulopathy	crystalline (κ) or rounded protein inclusions	nondegradable filtered LC variable domain fragments; FS
	Malignant cell infiltrates	Clusters/sheets of atypical plasma cells/lymphocytes	Malignant cells travel from primary site
	Monoclonal immunoglobulin deposition disease	Linear staining for LC/HC, ATN, and/or nodular glomerulosclerosis	Paraprotein deposition in BM and extracellular material
	Amyloids	Silver negative, Congo red–positive material, 10 nm haphazardly arrange fibrils	Partially metabolized LC precipitate as β-pleated fibrils
Glomeruli	Proliferative glomerulonephritis with monoclonal immunoglobulin deposits	MPGN or endocapillary proliferative pattern, deposits with LC/HC-restriction and often C3	Paraprotein deposition without fibrils, abnormal clone often not identified
	C3GN	C3-dominant staining; need to check for masked deposits	Paraproteins or their fragments inhibit alternative complement regulatory proteins.
	Cryoglobulinemic GN	Luminal/subendothelial deposits of 20–30 nm curvilinear microtubules	The paraproteins precipitate as cryoglobulin.
	Fibrillary GN	Mesangial/capillary wall deposits of 16–24 nm fibrils	Paraprotein precipitation as fibrillary deposits
	Immunotactoid GN	Mostly capillary wall deposits of 30–40 nm microtubules in parallel arrays	Paraprotein precipitation as microtubules
	MCD/FSGS/ collapsing glomerulopathy	Foot process effacement/segmental sclerosis/epithelial cell hypertrophy/hyperplasia with capillary collapse	May be secondary to therapies such as bisphosphonates (MCD, collapsing FSGS) GVHD (MCD), or coincidental
	Waldenström macroglobulinemia	Large occlusive PAS-positive capillary luminal IgM “thrombi”	Likely related to abnormal IgM properties, not hyperviscosity
Vessels	TMA (atypical HUS [i.e., complement-mediated HUS])	Vascular wall fibrin, thrombi, intimal lucencies	Paraproteins or their fragments inhibit alternative complement regulatory proteins.
Systemic	Hypercalcemia, infection,	ATN with myoglobin deposition	Bone resorption; Ca^{2+} deposition in heart &

	multiorgan failure, hyperkalemia		muscle lead to CRS & rhabdomyolysis respectively

Note: “Proteinuria mismatch” is present in cast nephropathy but not with lesions with glomerular basement membrane injury due to the pathologic filtering of albumin that can be detected by routine urine dipstick testing.

Abbreviations: ATN, acute tubular necrosis; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; GVHD, graft-versus-host disease; HUS, hemolytic–uremic syndrome; IgM, immunoglobulin M; MCD, minimal change disease; TMA, thrombotic microangiopathy.

BM, basement membranes; CRS, cardiorenal syndrome; FS, Fanconi syndrome; LC/HC, light chain/heavy chain;

- A combination of the below lesions may be present in same patient.
- Renal manifestation (e.g., cast nephropathy, amyloidosis, deposition disease) depends on the properties of the monoclonal protein, not the host response.

Tubulointerstitial lesions

- Light-chain (Bence Jones protein) cast nephropathy, also known as “myeloma kidney”:
  - Most common renal presentation (40% to 60%)
  - Pathogenesis of cast nephropathy: Glomerular filtration of light chains leads to intratubular cast formation, obstruction, and tubular injury.
  - Histopathology (**Fig. 7.13**):

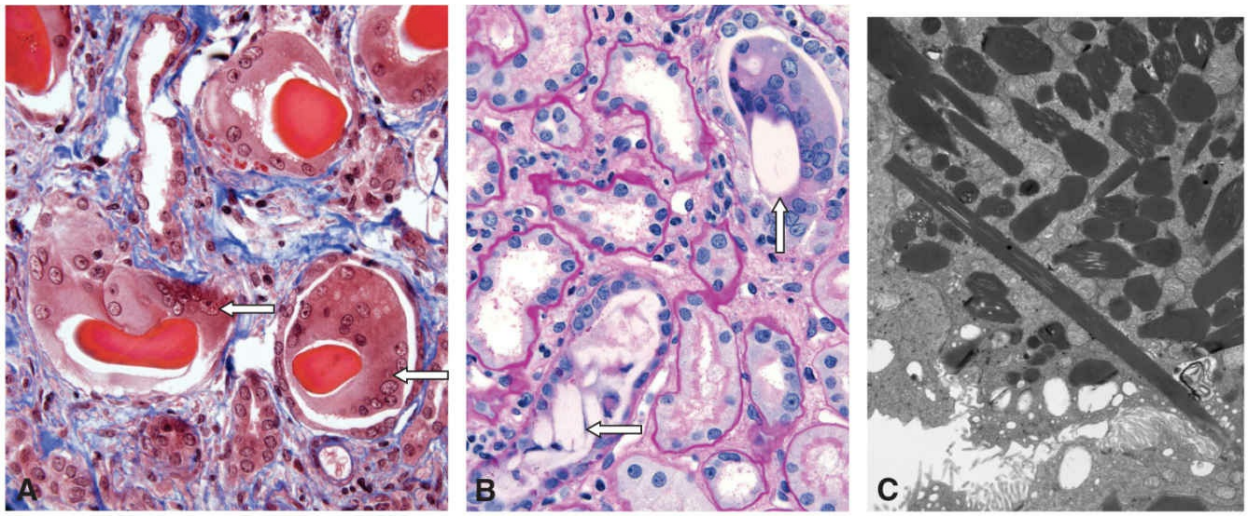

FIGURE 7.13 Light-chain tubulointerstitial lesions by light microscopy. **A, B.** Light-chain (Bence Jones) cast nephropathy. **A.** Orange light-chain casts with adjacent and engulfing multinucleated giant cells (*arrows*) (Masson trichrome ×400). **B.** Periodic acid–Schiff (PAS)–negative light-chain casts (*arrows*), the upper right cast surrounded by a giant cell (PAS ×400). **C.** Crystalline tubulopathy. Light chain depositing as electron-dense crystals in tubular cells (×7,500).

        - **LM:** Light-chain casts are periodic acid–Schiff (PAS) negative, orange on Masson trichrome, angulated, fractured or coarsely granular, and often surrounded by multinucleated giant cells; primarily in distal tubules.
        - **IF:** casts stain strongly for the abnormal light chain with minimal staining for other immune reactants.
    - Light chain nephropathy is associated with “proteinuria mismatch”
        - Urine dipsticks predominantly detect albumin, but not FLC, the protein comprising the “cast” nephropathy. However, total urine protein measured as uPCR or 24-hour urine collection does detect and measure all types of proteins. Thus, in the presence of FLC, uPCR and 24-hour urine protein may be >> routine dipstick protein.
        - Proteinuria mismatch may be unmasked by the addition of sulfosalicylic acid (SSA) to the urine sample because SSA precipitates all proteins, including all albumin and FLC.
- Light-chain proximal tubulopathy
    - Pathogenesis: Reabsorption and accumulation of crystallized nondegradable variable domain fragments of the filtered light chains cause proximal tubular injury.
    - Clinical manifestations:
        - Fanconi syndrome with various proximal tubular transport defects, including proximal renal tubular acidosis (RTA), phosphate wasting, uricosuria (hence hypouricemia), euglycemic glycosuria, and aminoaciduria
        - Distal tubular dysfunction is also possible.
        - Typically associated with κ light chains
    - Histopathology (**Fig. 7.13**)
        - LM shows tubular injury with expanded tubular cell cytoplasm containing inclusions of the reabsorbed abnormal light chain.
        - IF: tubular inclusions stain for the aberrant light chain
        - EM: Intracellular light chains may precipitate as electron-dense crystalline inclusions with needle, rod, rhomboid, or rectangular

shapes (κ), or as rounded protein inclusions without a substructure (λ)

- Interstitial infiltration of malignant plasma cells or lymphocytes

Combined glomerular and tubulointerstitial lesions

- Monoclonal immunoglobulin deposition disease (MIDD)
  - Pathogenesis: involves the deposition of monoclonal light chain (80%), and less commonly heavy chain (10%), or both (10%) in basement membranes, mesangial matrix, and extracellular material
  - Most often monoclonal κ light chain (two-thirds of cases)
  - Histopathology (**Fig. 7.14**):

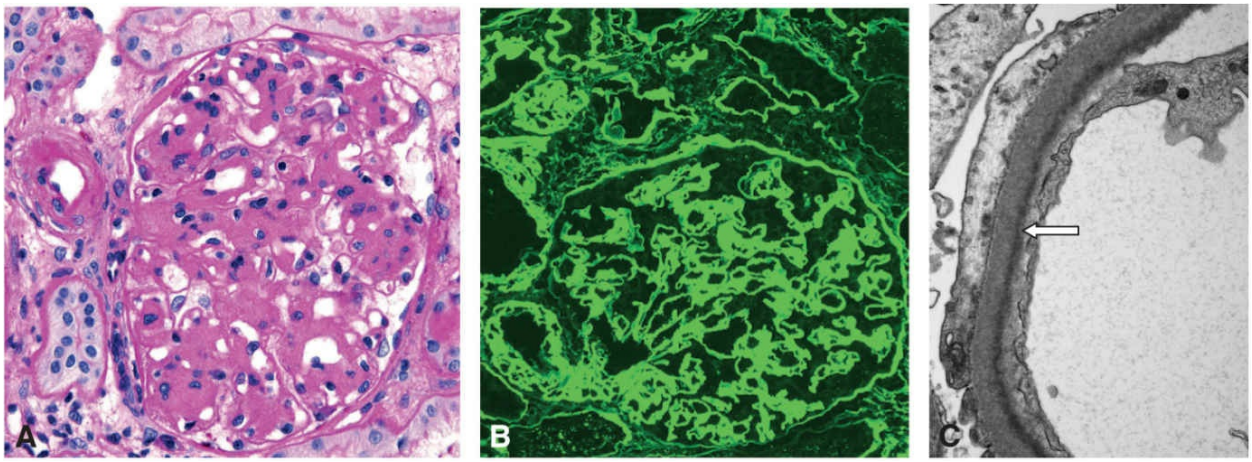

FIGURE 7.14 Monoclonal immunoglobulin deposition disease. **A.** Thickened and somewhat nodular mesangial regions; this may mimic nodular diabetic glomerulosclerosis (periodic acid–Schiff ×400). **B.** Strong linear κ light-chain staining of all basement membrane and extracellular material (×300). **C.** Arrow: Dark granular electron-dense material along the glomerular capillary basement membrane; it also involves tubular basement membranes (×19,000).

    - LM: typically expanded mesangial regions, sometimes lobular, with variable hypercellularity. May be crescents or normal glomerular appearance
    - IF: linear staining of all basement membranes and mesangial regions for the appropriate light and/or heavy chain
    - EM: finely granular to powdery electron-dense material in GBMs with similar material or small fibrils in mesangial regions
  - GBM is affected, which leads to significant albuminuria. Thus, MIDD does not present with proteinuria mismatch.

- Amyloidosis
  - 20% to 30% of glomerular involvement in myeloma
  - May be composed of light chain (AL), light and heavy chain (ALH), or rarely heavy chain only (AH)
  - Two-thirds of cases are λ light chain.
  - Pathogenesis: The abnormal proteins are partially metabolized in macrophages and mesangial cells, then secreted. The metabolized fragments may precipitate into granular deposits and/or β-pleated fibrils as "amyloid."
  - Histopathology (**Fig. 7.15**):

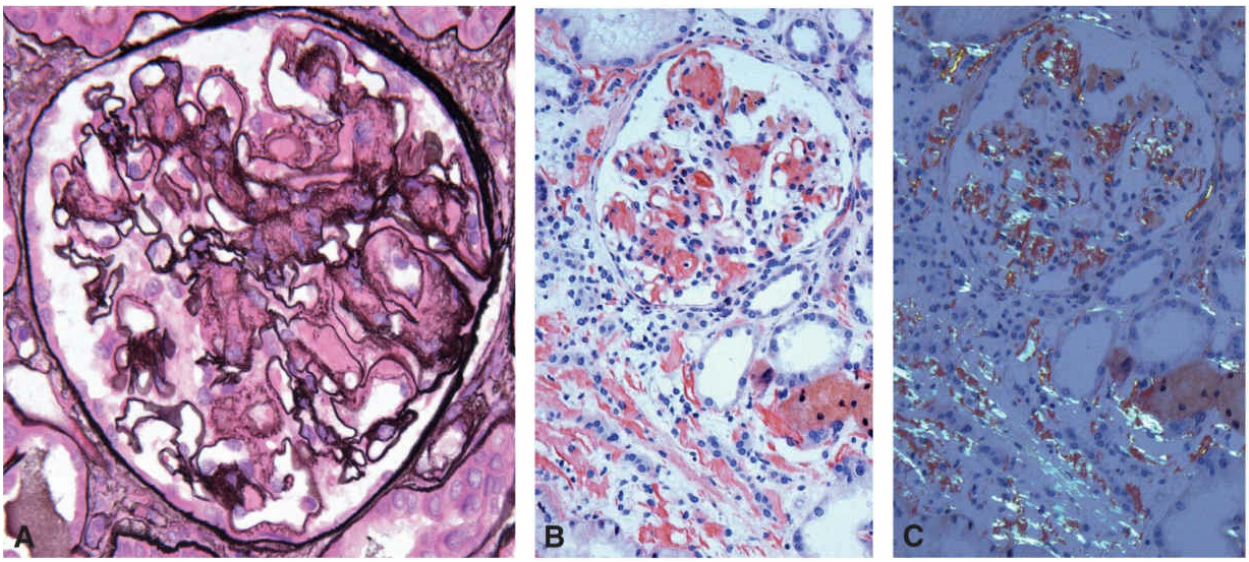

FIGURE 7.15 Amyloidosis. **A.** Silver-negative material in mesangial regions and capillary walls (Jones silver ×400). **B.** Positive Congo red stain in glomerular and interstitial amyloid (×200). **C.** Polarized Congo red stain showing apple green birefringence in the amyloid (×200).

    - LM: Amyloid is silver and PAS negative in mesangial regions and/or capillary walls. It is Congo red positive and displays apple green birefringence when viewed with polarized light.
    - IF: smudgy amorphous staining for the appropriate light and/or heavy chain
    - EM: 10 nm haphazardly arranged nonbranching fibrils
  - Techniques for amyloid identification include IF, immunohistochemistry, and mass spectrometry.

- Glomerular amyloid deposition can manifest as albuminuria and even nephrotic-range proteinuria. Albuminuria is present, so "proteinuria mismatch" is not characteristic.
- Treatment targets reducing amyloid protein synthesis. Approaches used include steroids, alkylating agents, proteasome inhibitors, and autologous stem cell transplantation (ASCT).
  - Measurements of FLC and κ/λ ratio are useful response markers.
  - Untreated patients with myeloma-associated AL amyloidosis have a median survival of less than a year, often due to cardiac involvement.
- Of note, there are other forms of amyloidosis *unrelated* to myeloma:
  - AA (secondary) amyloid
    - AA amyloid is associated with chronic infections (often TB outside North America) and chronic inflammatory diseases (familial Mediterranean fever, rheumatoid arthritis, etc.).
    - Treatment targets the underlying infectious or inflammatory disease process.
  - Leukocyte chemotactic factor 2 (ALECT2)
    - Commonly occurs in patients of Mexican or Egyptian origin
  - Less common intrarenal amyloid proteins include mutant transthyretin, fibrinogen Aα, gelsolin, lysozyme, and apolipoproteins I, II, IV, and CII.

Glomerular lesions with organized deposits (Fig. 7.16)

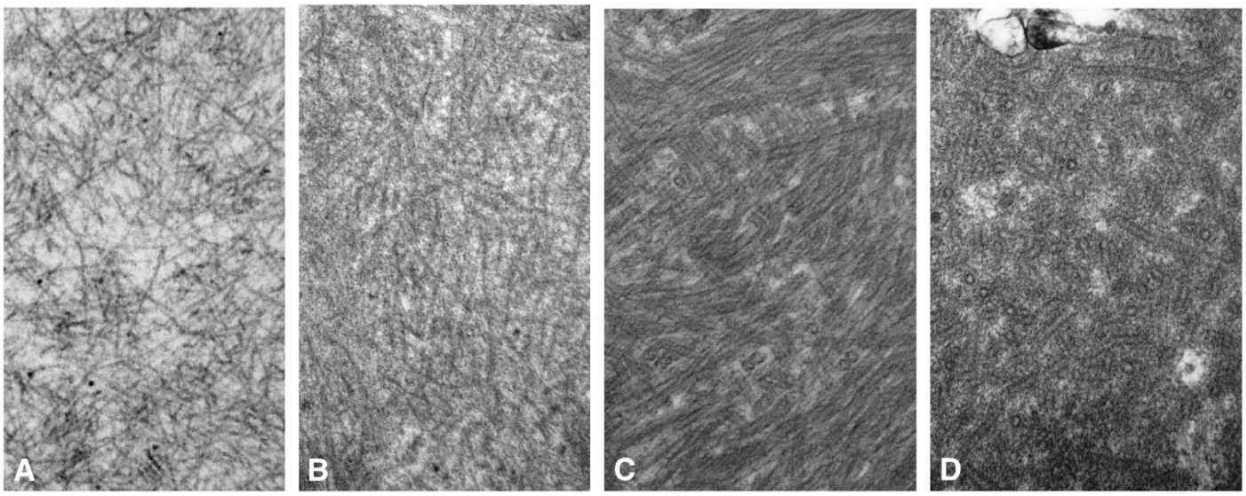

FIGURE 7.16 Organized deposits. **A.** Amyloid. Haphazardly arranged 10 nm fibrils. **B.** Fibrillary glomerulonephritis. Randomly arranged 15 to 25 nm fibrils. **C.** Immunotactoid glomerulonephritis. Parallel arrays of 35 to 50 nm microtubules, often monoclonal. **D.** Cryoglobulin. Randomly arranged to clusters of 20 to 30 nm curved microtubules (all ×72,000).

- Deposits stain for the abnormal light/heavy chains
- Monoclonal cryoglobulinemia (type I cryoglobulin)
  - Precipitation of the paraprotein as cryoglobulins
  - Histopathology
    - LM: MPGN pattern with endocapillary cryoglobulin PAS-positive thrombi and many monocytes
    - EM: Subendothelial and capillary luminal deposits may or may not have the typical 20 to 30 curvilinear microtubules.
- Fibrillary GN
  - Most cases are not associated with a monoclonal protein.
  - Histopathology EM: GBM and mesangial randomly oriented 16 to 24 nm fibrils
- Immunotactoid GN
  - Very rare
  - More often associated with a monoclonal gammopathy/lymphoproliferative disease compared with fibrillary GN
  - Histopathology EM: parallel arrays of 30 to 50 nm microtubules predominantly in the capillary wall
- Table 7.13 summarizes key clinical and morphologic features and management of amyloidosis, fibrillary glomerulopathy, and immunotactoid glomerulopathy.

Table 7.13 Summary of key clinical and morphologic features and management of amyloidosis, fibrillary glomerulopathy, and immunotactoid glomerulopathy

	Amyloidosis	Fibrillary GN	Immunotactoid GN
Clinical manifestations	Depends on type of amyloid; Typical: waxy skin, easy bruising, enlarged muscles, liver, tongue, heart failure, abnormal cardiac conductions neuropathy, coagulopathy	Mean age 50 y Hematuria, proteinuria, nephrotic syndrome, hypertension, elevated serum creatinine	Older population compared to fibrillary GN One-third of patients have *hypocomplementemia*.
Clinical associations	Primary (AL) predominantly due to monoclonal Ig light-chain fragments and secondary (AA) due to chronic inflammatory disease Periodic fever syndromes (e.g., familial Mediterranean fevers)	Idiopathic May be associated with malignancy, low association with monoclonal gammopathy (15%) Autoimmune diseases Hepatitis C	Idiopathic *Frequent* association with chronic lymphocytic leukemia and B-cell lymphomas, 60%–70% with monoclonal gammopathy Cryoglobulinemia and lupus Hepatitis C
Monoclonality	Yes—AL	Oligotypic (IgG1 + IgG4) much more common than monotypic deposits	Predominantly monoclonal
Light microscopy	Nodular or diffuse pink deposits of amorphous materials in mesangial matrix and basement membranes of capillary loops, arteriolar walls Nodular lesions resemble diabetic Kimmelstiel–Wilson nodules.	Focal mesangial or diffuse proliferative, or membranoproliferative or membranes GN	Same as fibrillary GN
Immunofluorescence microscopy	Smudgy amorphous staining for abnormal light and/or heavy chain in AL amyloid Immunohistochemistry or mass spectrometry for other amyloid protein	Mesangial or glomerular capillary wall deposits for IgG, C3, *Both* κ and λ light chains; and/or C1q deposits	Monoclonal Ig deposition with a restricted light chain, *either* κ *or* λ
Electron microscopy	10 nm fibrils	Randomly arranged fibrils 16–24 nm; more randomly arranged than immunotactoid	30–50 nm microtubules
Congo red stain	Positive May be negative in very early disease, heavy-chain amyloidosis	Negative	Negative
Management	Serum free light chains: treat underlying disease. Dialysis support Kidney transplant in dialysis-related amyloidosis Liver transplant in certain hereditary amyloidosis **Note:** Fat pad biopsy is recommended over biopsies of liver or kidneys due to lowest bleeding complications.	*Annual screening* for associated diseases: complete blood count with differential, serum immunofixation and free light chains, hepatitis C *Treat underlying disease*; use of *ACEI or ARB*; use of *immunosuppressive* therapy per findings on light microscopy *Dialysis support* *Renal transplant* is an option. Hematology/oncology service should be consulted.	

Abbreviations: AA, amyloid A; ACEI, angiotensin-converting enzyme inhibitor; AL, amyloid light chain; ARB, angiotensin-receptor blocker; GN, glomerulonephritis.

- Other fibrillary glomerular diseases *not related* to paraproteins
  - Fibronectin glomerulopathy: autosomal dominant disorder associated with massive deposition of subendothelial and mesangial fibronectin, fibrils measure 10 to 16 nm
  - Collagenofibrotic (collagen III) glomerulopathy: massive accumulation of subendothelial and mesangial atypical type III collagen fibrils measuring 35 nm
  - Nail-patella syndrome and hereditary multiple exostoses syndrome (or hereditary multiple osteochondromas syndrome): autosomal dominant with NS and deposition of type III collagen fibril bundles in the GBM and less often mesangium

Glomerular lesions without organized deposits

- Deposits stain for the abnormal light/heavy chains
- Proliferative GN with immunoglobulin deposit (PGNMID)
  - Most often IgG3 or IgG1 but can be any heavy chain, often has C3
  - <50% have a detectable systemic paraprotein identified.
  - Histopathology
    - LM: usually MPGN, may be endocapillary proliferative pattern
    - EM: deposits in mesangium and capillary wall
  - PGNMID and immunotactoid GN may have low C3 in one-third of cases.
- C3GN with or without masked monoclonal deposits
  - Pathogenesis: alternative complement pathway dysregulation due to monoclonal Ig proteins and/or their fragments inhibiting regulatory proteins (CFH or C3Bb)

NOTE Between 35% and 50% of adults with C3GN will have a circulating paraprotein requiring further biopsy evaluation for masked paraprotein deposition.

  - Histopathology LM: MPGN pattern similar to C3GN
    - IF: C3 staining > two orders of magnitude over other immune

reactants. In adults, IF microscopy should be reviewed from pronase-treated LM sections to unmask a potential paraprotein.
        - EM: Subendothelial and capillary luminal deposits may or may not have the typical 20 to 30 curvilinear microtubules.
- Waldenström macroglobulinemia
    - May be associated cryoglobulins
    - Histopathology LM: large PAS-positive plugs of IgM and the abnormal light-chain occluding capillary lumens without mesangial hypercellularity
- Rarely MCD or FSGS

Other clinical manifestations of monoclonal gammopathies

- Hypercalcemia (especially multiple myeloma): nephrocalcinosis, interstitial nephritis, reduced renal perfusion due to hypercalcemia-induced vasoconstriction, intratubular calcium salt precipitations
- Hyperuricemia: acute uric acid nephropathy, interstitial nephritis
- Light-chain deposition in muscle leading to rhabdomyolysis
- Hyperviscosity syndrome:
    - Associated with excessive formation of abnormal polymers of IgM (Waldenström), IgA or IgG3 or κ light chains
    - Clinical manifestations: blurred vision, neurologic symptoms, confusion, oral/nasal bleeding, heart failure, kidney injury/acute tubular necrosis (ATN)
    - Treatment:
        - Plasmapheresis if obvious symptoms, regardless of serum viscosity index
        - Serum viscosity index may not correlate well with symptoms.
- Volume depletion, poor renal perfusion:
    - Hypercalcemia-induced nephrogenic diabetes insipidus
    - Reduced oral intake
    - Cardiomyopathy (e.g., amyloid involvement)
- Treatment related:
    - Drugs (NSAIDs), antibiotics

- Use of IV contrast dye with CT
- Bisphosphonates (zolendronate: ATN; pamidronate, zolendronate: collapsing FSGS)

Diagnosis

- Nonspecific clues suggesting the possibility of paraproteinemia, multiple myeloma:
  - Urine studies:
    - Routine urinalysis is typically “bland.”
    - Urine FLCs >1,500 mg/L, proteinuria mismatch, and low percentage of albuminuria compared to total proteinuria indicate myeloma cast nephropathy.
    - Glucosuria in the absence of hyperglycemia, phosphaturia, RTA
  - Chemistries:
    - Low to positive serum anion gap
    - Hypercalcemia (especially multiple myeloma)
    - Hyperphosphatemia out of proportion to the degree of kidney failure if high levels of serum FLC as they may give falsely high phosphate levels by some automated analyzers
    - High serum total protein-to-albumin ratio
    - Low complements in PGNMID and immunotactoid GN
- Testing options for monoclonal gammopathy:
  - Evaluation of suspected monoclonal gammopathy (International Myeloma Working Group):
    - Serum protein electrophoresis with immunofixation
    - 24-hour urine protein electrophoresis
    - Serum FLC
  - For interested readers, see **Appendix A** for more details on monoclonal gammopathy testing.
- Techniques for amyloid identification include IF, immunohistochemistry, and mass spectrometry.

Management

- Replete volume with normal saline
- Management of hypercalcemia:
  - Administer normal saline as tolerated
  - Corticosteroids and/or bisphosphonates (first-line pamidronate; second-line zolendronate due to dosing concerns with low GFR for the latter; calcitonin if refractory to bisphosphonates or rapid calcium reduction is needed)
  - Hemodialysis for severe hypercalcemia, i.e., serum calcium level >18 mg/dL.
- Chemotherapy for underlying multiple myeloma: Common regimens include bortezomib (proteasome inhibitor) + CYC + dexamethasone; bortezomib + melphalan + prednisone; lenalidomide (Revlimid) + dexamethasone; melphalan + prednisone + thalidomide; thalidomide + dexamethasone; bortezomib + lenalidomide + dexamethasone
- Reduction of serum FLC with chemotherapy predicts renal response in multiple myeloma.
- Treatment of AL amyloidosis:
  - Nonmyeloablative chemotherapy coupled with ASCT
    - Preferred therapy, but high risk of serious complications
    - Criteria of eligibility for ASCT: NT-pro-B natriuretic peptide < 5,000 ng/ml, troponin t < 0.06 ng/ml, age <70 years, < three organs involved, scr < 1.7 mg/dl
  - Triple therapy if cannot tolerate ASCT:
    - CYC + thalidomide (or lenalidomide or bortezomib) + dexamethasone
    - Melphalan + lenalidomide + prednisone
  - Double therapy if cannot tolerate triple therapy: oral melphalan and dexamethasone
- Dialysis support as necessary
- Plasmapheresis in the presence of hyperviscosity

Alport Syndrome and Thin Basement Membrane Nephropathy

Epidemiology

- Alport syndrome is an inherited glomerular disease associated with mutation of the α3, α4, or α5 chains of collagen type IV.
- Thin basement membrane nephropathy (TBMN) involves mutations of the α3 or α4 chains of type IV collagen, which generally manifest a more benign renal outcome. In some families, individual family members may have either Alport disease or TBMN.
- Prevalence ~ 1/50,000 live births

Pathogenesis

Background

- There are six genetically distinct collagen type IV chains (α1, α2, α3, α4, α5, α6) that form three triple helical protomers [α1, α1, α2], [α3, α4, α5], and [α5, α5, α6], where
  - [α1, α1, α2] protomer is present in all basement membranes.
  - [**α3, α4, α5**] protomer is present in **kidney GBMs and some TBMs**, lung, testis, cochlea, and eye.
  - **[α5, α5**, α6] protomer is present in **skin**, smooth muscle, esophagus, and **kidney Bowman capsule and some TBMs**.
  - COL4A1 and COL4A2 at 13q34, encodes α1, α2, respectively.
  - COL4A3 and COL4A4 at 2q35–37, encodes α3, α4, respectively.
  - COL4A5 and COL4A6 on *chromosome X*, encodes α5, α6, respectively.
  - Mutations of α5 and α6 chains are transmitted as expected for X-linked genes.

Disease state

- Mutations of the α3(IV), α4(IV), or α5(IV) chains alter the type IV collagen triple helical complex, impair the GBM organizational structure, and cause glomerulosclerosis.
- In X-linked Alport syndrome, the α5(IV) mutations lead to proteasomal degradation of the α3(IV), α4(IV), and α5(IV) chains. All three chains are thus absent from the GBM and replaced by endothelial-derived α1(IV) and α2(IV) chains.
- In autosomal recessive Alport syndrome, the mutations are in the α3(IV) or α4(IV) chains, which prevent type IV collagen triple helix assembly and

incorporation into the GBM.

- Large deletion or nonsense mutations produce more severe disease compared with missense mutations.

Genetic inheritance of Alport syndrome and TBMN

- X-linked (80% to 85%) mutations of the *COL4A5* gene encoding the α5(IV) chain:
  - More women are affected than men because only women can get a mutated X chromosome from either the mother or father.
  - Female heterozygous carriers: have hematuria but with variable outcome
    - Less severe disease with a minority developing ESKD presumably due to "lyonization" (a process where one X chromosome/cell is inactivated so only half of the cells express the mutant gene)
    - Affected males have a more severe phenotype.
- Autosomal recessive (10% to 15%) mutations involving either *COL4A3* or *COL4A4* genes encoding the α3(IV) chain (which contains the Goodpasture antigen) and the α4(IV) chain, respectively:
  - Females are as severely affected as males.
  - Clinical manifestations in both sexes are identical to those of classic X-linked Alport in males.
- Autosomal dominant (<5%) with heterozygous mutations in either *COL4A3* or *COL4A4* gene:
  - Variable phenotypes
    - There may be clinical and pathologic features similar to X-linked disease but with slower kidney function decline.
    - Some patients develop TBMN, with microscopic hematuria without progression to ESKD.
    - Genetic factors other than mutations in these collagen genes have been suggested to affect phenotypes.
- Mutations of the α3(IV)-α5(IV) chains may also occur **de novo**.

Clinical manifestations

Renal manifestations of Alport syndrome

- Asymptomatic persistent microscopic or gross hematuria

- Boys without hematuria by age 10 are unlikely to have Alport syndrome.
- In X-linked females, recurrent gross hematuria, proteinuria, high-frequency hearing loss, and diffuse GBM thickening are associated with worse renal outcomes.
- ESKD:
  - X-linked or autosomal recessive disease: ESKD usually occurs by age 35 but may be later in life.
  - Autosomal dominant: ESKD occurs later in life, at age 45 to 60 years.

Extrarenal manifestations of Alport syndrome

- Sensorineural hearing loss:
  - Thought to be due to impaired adhesion of the auditory sensory cell containing Organ of Corti to the inner ear basilar membrane that lacks the normal α3-4-5(IV) collagen network
  - Initial hearing loss is in high-frequency range.
  - Rate of hearing loss is similar to the rate of kidney disease progression.
- Ocular abnormalities:
  - Anterior lenticonus due to abnormal [α3, α4, and α5(IV)] and associated with thinning of the lens capsule
  - Other ocular findings: spherophakia, anterior polar and posterior cortical cataract, corneal changes with recurrent corneal erosions
  - Retinal findings: drusen, perifoveal dot-and-fleck retinopathy, neovascularization
- Leiomyomas:
  - May be associated with X-linked Alport but is rare
  - Affected patients carry deletions that involve COL4A5 extending into the adjacent *COL4A6* gene. Deletions involving both the COL4A5 and COL4A6 are thought to cause misregulation of neighboring genes and resultant smooth muscle overgrowth.
  - In addition to leiomyomas, arterial aneurysms have been reported in young males and may involve thoracic, abdominal aorta, and even intracranial arteries.

Histopathology (Figs. 7.17 and 7.18)

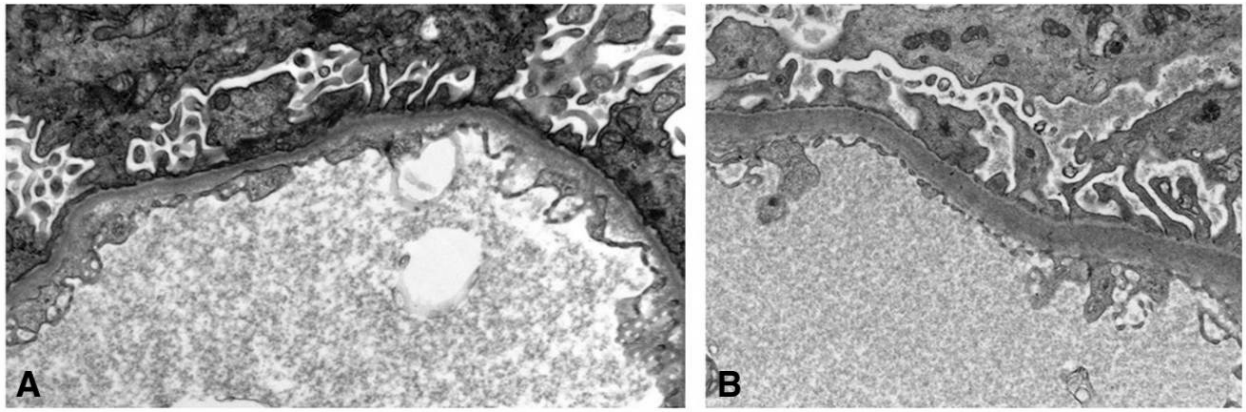

FIGURE 7.17 Thin basement membrane nephropathy. **A.** Thin glomerular capillary basement membrane, measuring 107 to 125 nm in width. Note that there is no subepithelial scalloping or layering/lamellation of the basement membrane, and the podocyte foot processes are partially effaced. **B.** Normal glomerular capillary basement membrane measuring 320 nm for comparison (original magnification ×12,000).

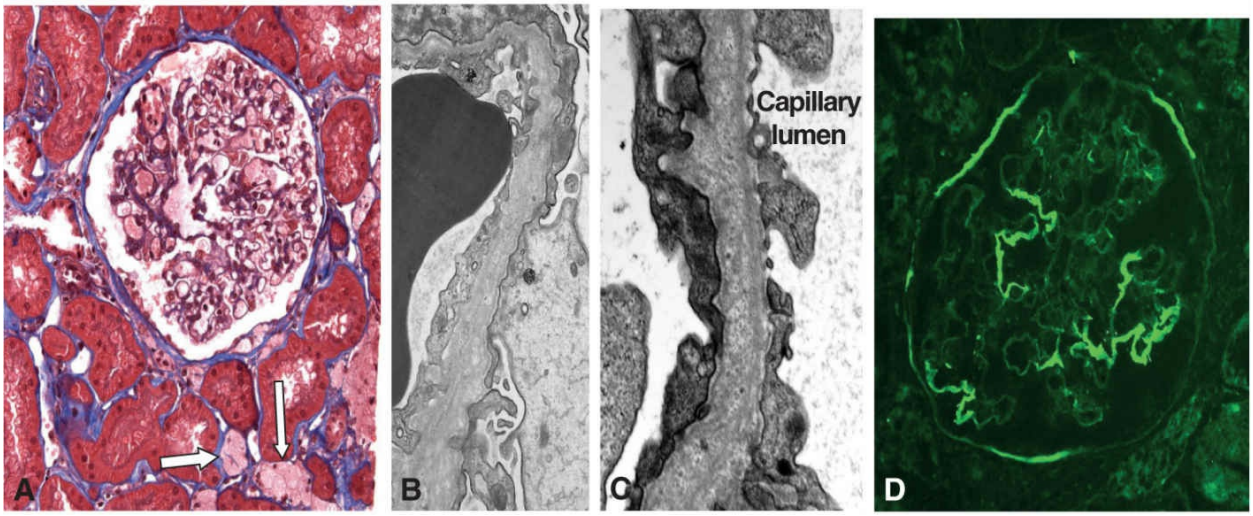

FIGURE 7.18 Alport syndrome. **A.** Normal glomerulus and interstitial foam cells (*arrows*) (Masson trichrome ×200). **B.** Irregular thick and thin layered glomerular capillary basement membrane (×19,000). **C.** Thick glomerular capillary basement membrane with "basket-woven" appearance and subepithelial scalloping (×25,000). **D.** Focal Bowman capsular and glomerular capillary basement membrane staining for α5(IV) collagen chain in a female heterozygote for Alport syndrome (×400).

- LM: interstitial foamy macrophages in the absence of significant proteinuria or NS. Global and/or segmental glomerulosclerosis may be present in more advanced disease.
- EM: abnormal GBMs
  - Classic Alport: GBMs show irregular thinning and thickening, layered or lamellated "basket-weave" appearance due to GBM injury and remodeling, and subepithelial scalloping. There are no electron-dense

deposits.

- TBMN: thin GBMs (<230 nm) without layering or subepithelial scalloping. may be irregularities if it is “progressive” tbmn due to a more pathogenic mutation

- IF: The staining pattern depends on the involved mutation and chain that is being stained.
  - Preserved (positive) α3(IV) or α5(IV) chain staining can be seen in normal GBMs, some TBMs and α5(IV) in Bowman capsule
  - Complete loss of α3(IV), α4(IV), and α5(IV) chains in GBMs, TBMs, and of α5(IV) in Bowman capsule in an X-linked Alport male
  - Segmental staining of α3(IV), α4(IV), and α5(IV) chains in GBM, TBMs, and of α5(IV) in Bowman capsule in an X-linked Alport female due to lyonization
  - Loss of α3(IV)-α5(IV) in GBMs and some TBMs but preserved α5(IV) in Bowman capsule and some TBMs in autosomal recessive Alport

NOTE Features of TBMN do not rule out Alport syndrome. Clinical correlation is required.

- TBMs on EM may reflect sampling variability or early Alport syndrome.
- Preservation of α3(IV) to α5(IV) staining may occur with compound heterozygote Alport syndrome.
- Patients with TBMN should be evaluated for hearing loss, abnormal optical lens, and family history, with follow-up visits to rule out Alport syndrome.

Diagnosis

- Clinical syndrome, particularly if known family history
- Kidney or skin biopsy:
  - Kidney biopsy: Note that classic lamellation of GBM may not be present in early disease.
  - Skin biopsy is stained for α5(IV) chain. Absent or segmental staining suggests X-linked Alport. Normal staining may signify:
    - Autosomal recessive Alport syndrome involving either α3(IV) or

α4(IV) chains
    - Mutation of α5(IV) that affects the function, but not structure, of the chain
    - Diseases other than Alport
- Genetic testing (www.genereviews.org)

Management

ACEI or ARB reduces proteinuria and rate of disease progression.

Kidney transplantation

- Recurrent disease does not occur in the transplanted allograft because the donor kidney has normal GBM.
- Anti-GBM disease occurs in 3% to 4% of affected males who receive transplants.
    - In males with X-linked disease, antibodies are typically directed against the α5(IV) chain, but may be against the α3(IV) chain.
    - In autosomal recessive Alport syndrome, anti-GBM antibodies are against the α3(IV) chain.
    - If a first allograft is lost to anti-GBM disease, there is a high risk of recurrence.

Diabetic Kidney Disease

Epidemiology

- DKD is the most common primary diagnosis for patients who start dialysis (~50%).
- Kidney diseases in diabetic patients who present with ESKD:
    - 60%: classic DKD (large kidneys, proteinuria > 1 g/d, and/or diabetic retinopathy [DR])
    - 25% to 30%: another primary kidney disease in addition to DKD
    - 10% to 15%: atypical presentation with ischemic nephropathy (low-level proteinuria)
- Cumulative prevalence of:
    - Proteinuria is ~50% to 60% at 25 years after diagnosis of diabetes.
    - Progression to ESKD is ~60% at 5 years *after the onset of proteinuria*.

Risks for the development of DKD and progression

- Unmodifiable risks:
  - Genetic susceptibility:
    - Family history of predisposition to abnormal sodium handling and HTN
    - Genotypes: ACE, angiotensin II type 2 receptor, aldose reductase
  - Ethnicity: African descents, Hispanics, Pima Indians with type 2 DM (T2DM)
  - Gender: Caucasian males and females of African descent
  - Age: possibly early onset
  - Duration of DM
- Modifiable risks: HTN, early glomerular hyperfiltration, prolonged uncontrolled hyperglycemia, obesity, tobacco smoking, use of oral contraceptives, high-protein diets

Pathogenesis

- Hyperglycemia:
  - Enhances matrix production, glycation of matrix proteins, formation of advanced glycation end (AGE) products, matrix accumulation
  - Stimulates vascular endothelial growth factor (VEGF), endothelial injury
  - Increases expression of both a profibrotic and a proinflammatory phenotype
- AGE products:
  - AGE cross-linking with collagen
  - AGE and AGE-receptor interaction (AGE:RAGE) leads to oxidative stress, activation of protein kinase C (PKC)
- Activation of PKC pathway leads to:
  - Endothelial dysfunction with decreased nitric oxide (NO) production
  - Increased expression of endothelin 1, VEGF, NFκB, and plasminogen activator inhibitor 1 (PAI-1), leading to tissue inflammatory response, TMA, vascular injury
- Polyol pathway (via aldose reductase): thought to contribute to diabetic

complications, such as diabetic cataracts, neuropathy, hyperfiltration, albuminuria. Use of aldose reductase inhibitors has been disappointing due to hypersensitivity reactions and liver abnormalities.

- Accumulation of N-acetylglucosamine via hexosamine pathway: N-acetylglucosamine may lead to increased synthesis of transforming growth factor β1 (TGF-β1), PAI-1.
- Prorenin activation of mitogen-activated protein kinases
- Reduction of nephrin expression presumably via angiotensin II
- Systemic HTN
- Metabolic stress leading to mitochondrial dysfunction (which may lead to type B lactic acidosis observed in patients with diabetic ketoacidosis)

Clinical manifestations

- Albuminuria:
  - Moderate increase in albuminuria may predict high risk for eventual DKD.
  - The American Diabetes Association recommends screening for microalbuminuria in:
    - All patients with T2DM at the time of diagnosis and annually thereafter
    - All patients with T1DM 5 years after the diagnosis and annually thereafter
- Of note, 10% to 25% of patients with T2DM and reduced kidney function have little or no proteinuria despite having biopsy-proven DKD.
- (Microscopic) Hematuria:
  - May occur with DKD
  - RBC casts may be present but other glomerular diseases *must* be ruled out.
- Morbidities and mortality:
  - Increasing albuminuria and decreasing GFR correlate with cardiovascular and renal events withT2DM.
  - Mortality among diabetics with ESKD is 1.5- to 2.0-fold greater compared to nondiabetics.

Natural history

Proposed scheme of DKD stages for T1DM (less reliable for DKD in T2DM)

- *Pre-DKD:* 0 to 5 years since disease onset: glomerular hyperfiltration, renal hypertrophy
- *Incipient DKD:* 5 to 15 years
  - Albuminuria (30 to 300 mg/24 hours or overnight albuminuria at 20 to 200 μg/min in at least two of three consecutive nonketotic sterile urine samples) in 20% to 30% of patients
    - <50% will progress to overt nephropathy, htn.
  - Structural changes: mesangial expansion, moderate GBM thickening, arteriolar hyalinosis
- *Overt DKD:* 15 to 25 years
  - Proteinuria (>300 mg albuminuria/24 hours or overnight albuminuria > 200 μg/min)
  - With severe albuminuria, most will progress to ESKD, NS, reduced glomerular filtration
- *ESKD* > 25 years: 4% to 17% at 20 years from the time of diagnosis

Structural changes and histopathology (Fig. 7.19)

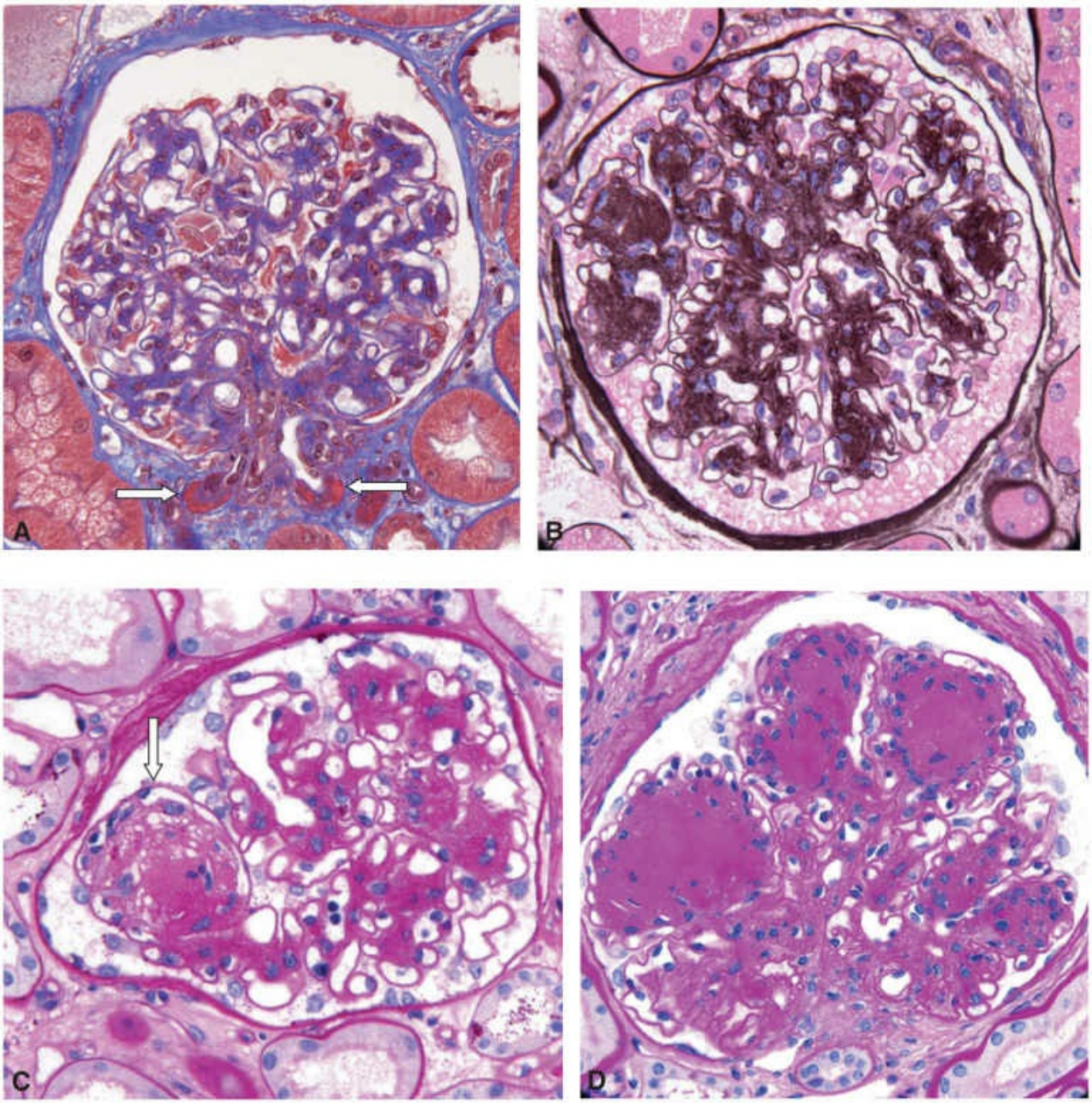

FIGURE 7.19 Diabetic kidney disease. **A.** Mild/early diffuse diabetic glomerulosclerosis with mild expansion of matrix. Note hyalinization of afferent and efferent arterioles (*arrows*) (Masson trichrome ×400). **B.** Moderate diffuse increase in mesangial matrix (Jones silver ×400). **C.** Diffuse and nodular matrix expansion with mesangiolysis and microaneurysm formation (*arrow*) (periodic acid–Schiff ×400). **D.** Global mesangial matrix nodules with peripheral nuclei (periodic acid–Schiff ×400).

- *Gross:* Kidney weight increases by ~15% due to glomerular hypertrophy and hyperfiltration.
- Glomerular changes
  - GBM thickening (up to three times normal)

- Mesangial matrix expansion
  - Mild-to-severe diffuse with/without mesangial nodules
- Matrix nodules (Kimmelstiel–Wilson lesion):
  - Associated with mesangiolysis and capillary microaneurysms
  - Differential diagnoses include dysproteinemias (e.g., amyloidosis and monoclonal Ig deposition diseases, and immunotactoid GN), smoking-related glomerulopathy, fibronectin glomerulopathy, collagen III glomerulopathy, chronic TMA, chronic MPGN, metabolic syndrome, or idiopathic.
  - Patients with matrix nodules more often have DR and worse kidney function.
- Often with associated segmental glomerulosclerosis and insudates

- Vascular lesions include hyalinization of afferent and efferent arterioles (pathognomonic for DKD), and arterial intimal fibrosis.
- Thickened tubular basement membranes
- Advanced diabetic sclerosis

Indications for kidney biopsy in patients with DM

- Absence of diabetic retinopathy (DR) (particularly in T1DM)
- DR is present in ~50% to 65% of patients with T2DM and DKD.
  - The absence of DR in T2DM does not exclude DKD but increases the likelihood of having a nondiabetic glomerular disease.
  - Patients with T1DM and DKD *almost always* have other evidence of diabetic microvascular disease (i.e., DR, neuropathy); however, not all patients with DR have DKD.
- Acute onset of proteinuria, particularly if less than 5 years from diagnosis in T1DM
- Presence of active urinary sediment (e.g., RBC casts) or significant hematuria (gross hematuria)
- Rapid decline in kidney function
- Presence of extrarenal manifestations and/or positive serologies suggestive of another glomerular disease (e.g., positive ANCA, hypocomplementemia)

Management

- DKD management should focus on healthy living (optimal weight, exercise, smoking cessation) and optimal BP, lipid, and glycemic control.

Glycemic control

- Individualize HbA1c range from <6.5% to <8.0% in patients with non-dialysis dependent ckd
- Lower HbA1c targets (e.g., <6.5% or <7.0%) may be considered with close self-blood glucose monitoring and the use of anti-hyperglycemic agents that are not associated with hypoglycemia.

NOTE In patients with long-standing DM and known cardiovascular disease, available data do not support strict glycemic control in reducing risk for further CVD events or mortality (see **Appendix A** for clinical data).

- Protective effects of intensive glycemic control:
  - Reduction in rates of development of microalbuminuria
  - Partial reversal of glomerular hypertrophy and hyperfiltration
  - Stabilization or decrease protein excretion in patients with albuminuria after apparent normoglycemia >2 years
  - Slowing of GFR decline
  - Successful pancreas transplantation has been suggested to stabilize glomerular structure at 5-year follow-up and significantly reverse of histopathologic changes at 10 years.

Specifics about noninsulin therapy in T2DM

- In patients with T2DM and established ASCVD, multiple ASCVD risk factors, or DKD, the use of an SGLT2 inhibitor with demonstrated cardiovascular benefit (empagliflozin > canagliflozin) is recommended to reduce the risk of major adverse CVEs and heart failure hospitalization.
- In patients with T2DM and established ASCVD or multiple risk factors for ASCVD, the use of a GLP-1–receptor agonist with demonstrated cardiovascular benefit (liraglutide > semaglutide > exenatide extended release) is recommended to reduce the risk of major CVE.
- For many patients, the use of either an SGLT2 inhibitor or a GLP-1–

receptor agonist to reduce cardiovascular risk is appropriate.

- Table 7.14 summarizes pharmacotherapeutic glycemic control in patients with T2DM.

Table 7.14 Pharmacotherapy for patients with type 2 diabetes mellitus

Class of Drugs: Mechanism of Action	Benefits	Adverse Effects	Considerations in CKD[a]
Biguanides (Metformin) • ↓Hepatic glucose production • ↓Intestinal glucose absorption • ↑Insulin sensitivity via increase in peripheral glucose uptake and utilization	• Low hypoglycemia risk • Modest weight loss • Cardioprotective effect	• Lactic acidosis • Vitamin B_{12} malabsorption with resulting anemia and peripheral neuropathy (treat with B_{12} supplement)	• Stable CKD with eGFR> 30: may continue • eGFR 45: do not start • eGFR 30: contraindicated
Glucagon-like peptide 1 receptor agonists (GLPI-RA: exenatide, lixisenatide, liraglutide, albiglutide, dulaglutide and semaglutide) • Stimulate glucose-dependent insulin secretion • Suppress glucagon secretion • Reduce gastric motility • Suppress appetite	• Low hypoglycemia risk • Reduce fluctuations and postprandial glucose levels • Weight loss • Improve lipid profile and BP • Improve CV outcomes[b]: Recommended in patients with established or high ASCVD risk	• Should not be used if personal or family history of medullary thyroid carcinoma or with MEN2[c] • Avoid use in patients with pancreatitis • Delayed gastric emptying possible, especially with initial use	• CrCl 30 ml/min: do not use exenatide • No dose adjustment for liraglutide, semaglutide, dulaglutide • Generally safe for eGFR > 45. The use of exenatide and lixisenatide is not recommended for eGFR 30 and 15 mL/min/1.73 m^2, respectively, due, in part, to limited clinical data
Sodium-glucose cotransporter 2 inhibitors (SGLT2i: cana-, dapa-, ertu-, empa-gliflozin) • Inhibits proximal tubular glucose reabsorption via SGLT2	• ↓Weight and BP • Improve CV outcomes[d]: Recommended in patients with established or high ASCVD risk	• ↑Risk of urinary tract/genital mycotic infections, Fournier gangrene • Volume depletion, falls, AKI	• eGFR 45: limited efficacy since SGLT2i inhibits tubular glucose reabsorption following glomerular filtration.

		• Possible ↑risk of DKA[e]	
Dipeptidyl peptidase 4 inhibitors (DPP4i: alo-, lina-, saxa-, sita-, vilda-gliptin) • Inhibit DPP4, thereby increasing GLP1 and other incretin hormones that stimulate glucose-dependent insulin synthesis and secretion and suppress glucagon secretion	• Low hypoglycemia risk	• May have increased risk of HF with saxagliptin and alogliptin • Use with caution in patients with a history of pancreatitis	Generally safe No dose adjustment for linagliptin • Dose adjustments are needed for sitagliptin and saxagliptin at eGFR 60 and 45, respectively.
Thiazolidinediones (TZD, pioglitazone) • Reduce insulin resistance	• Pioglitazone may confer ASCVD benefits.	• Fluid retention (edema, HF)[f] • ↑Risk of fractures in elderly males and postmenopausal females	• No dose adjustment in CKD • However if significant edema, reduce dose or consider combined use with SGLT2i
α-Glucosidase inhibitors (AGi, acarbose, miglitol, voglibose) • Inhibits the breakdown of complex carbohydrates, thereby delaying their absorption in the GI tract	• Low hypoglycemia risk • ASCVD benefits suggested	GI effects: bloating, flatulence, diarrhea	Use with caution in patients with CKD
Insulin secretagogues • Sulfonylureas (glipizide, glyburide) • Glinides (nateglinide, repaglinide)	• Potent A1C-lowering effect	• Hypoglycemia risk • Glinides have lower risk of hypoglycemia. • Weight gain	• Glipizide: dose conservatively • Glyburide: avoid use for eGFR 45 • Nateglinide, repaglinide: • eGFR 30 nondialysis: use with caution • eGFR 15 and on dialysis, avoid use
Colesevelam • Bile acid sequestrant	• Modestly lowers glucose • Does not cause	• ↑Triglyceride levels[g] • Not	• No dose adjustment necessary

	hypoglycemia • Decreases LDL-C	recommended in patients with gastroparesis, GI motility disorders, risk for bowel obstruction	
Bromocriptine-QR • ↑Hypothalamic dopamine levels and inhibits excessive CNS sympathetic tone, resulting in ↓hepatic glucose production	• Modest glucose lowering effect • Does not cause hypoglycemia • May reduces CV events	• Nausea • Orthostasis	• Renal excretion 10%; no adjustment necessary
Glycemic Control Per AACE/ACE 2020 (1) For patients with entry A1C 7.5%, start monotherapy with metformin, glpi-ra, slgit2i, dpp4i,*tzd, agi, or *su/gln in order of preference. (2) for entry a1c > 7.5% to 9.0% or >9% without symptoms (e.g., polydipsia, polyuria, weight loss), use dual therapy for 3 mo with metformin + one of the following: GLPi-RA, SGLT2i,*TZD,*SU/GLN, *basal insulin, DPP4i, colesevelam, bromocriptine-QR, or AGi in order of preference. (3) If goal A1C is not achieved after 3 mo of dual therapy, add a third agent from GLPI-RA, SGLT2i, *TZD, *SU/GLN, *basal insulin, DPP4i, colesevelam, bromocriptine-QR, or AGi in order of preference. (4) Add insulin if goal A1C is not achieved after 3 mo of triple therapy. (5) For entry A1C > 9% with symptom, initiate insulin with or without other agents. *Use these agents with caution.			

[a]Units for eGFR is mL/min/1.73 m^2.

[b]GLP1-RA: Strongest evidence for liraglutide > semaglutide > exenatide extended release.

[c]Liraglutide has been shown to stimulate calcitonin release and led to hyperplasia of thyroid gland C cells and tumors in rodent model.

[d]SGLT2i: Evidence is modestly stronger for empagliflozin > canagliflozin.

[e]Contraindicated in New York Heart Association functional classes III and IV or hepatic impairment.

[f]Contraindicated for patients with triglyceride levels > 500 mg/dL.

Abbreviations: AACE/ACE, American Association of Clinical Endocrinologists/American College of Endocrinology; AKI, acute kidney injury; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CrCl, creatinine clearance; CV, cardiovascular outcomes; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; HF, heart failure; GI, gastrointestinal.

BP control

- HTN occurs in ~40% of T1DM and 70% of T2DM.
- Higher BP is associated with both development and progression of DKD.
- Progressive lowering of BP to 120 mm Hg was associated with improved renal and patient survival. However, SBP < 120 mm hg or diastolic bp (dbp) < 70 mm hg are poorly tolerated and associated with increased incidence of myocardial infarction and mortality. the latter is thought to

reflect reduced coronary perfusion during diastole, particularly in patients with underlying coronary artery disease (irbesartan diabetic nephropathy trial [idnt])

- Recommendations
  - Maintain SBP <130 mm hg and dbp < 80 mm hg
  - For DKD with albuminuria, one antihypertensive agent should include ACEI or ARB. For interested readers, see **Appendix A** for a discussion on the use of ACEI versus ARB.
    - Notes regarding RAAS inhibition:
      - T1DM and T2DM: Use ACEI or ARB in normotensive patients with uACR ≥ 30 mg/g who are at high risk for DKD or its progression. High risk for DKD or its progression is defined as increasing albuminuria in the microalbuminuria range, macroalbuminuria, declining GFR, increasing BP, presence of DR, elevated lipids and/or uric acid concentrations, or family history of HTN, macrovascular disease, or DKD.
      - Combination therapy of RAAS inhibition in DKD: not advised due to unacceptable increase in adverse events (i.e., impaired kidney function and hyperkalemia). Additionally, there was no significant benefit in primary end point (progression of kidney disease), mortality, or CVEs—Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) trial.
      - Aliskiren (renin inhibitor) should not be used in combination with either ACEI or ARB due to increased risk of stroke and adverse events (i.e., hyperkalemia, hypotension, and ESKD or death due to kidney disease)—Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE).

Lipid management

- Lowering low-density lipoprotein cholesterol (LDL-C) with statin-based therapies reduces risk of major atherosclerotic events, but not all-cause mortality, in patients with CKD including those with DM.
- Recommendations:
  - Use of LDL-C (statins or statin/ezetimibe combination) is recommended

to reduce risk of major atherosclerotic events with patients with diabetes and CKD, including kidney transplant recipients. There is no evidence to suggest improvement in kidney disease outcomes with statin therapy.

- *Initiating* statin in patients with diabetes who are about to receive or already receiving dialysis is *not* recommended. Statins provide little or no benefit in death rates due to CVD events in dialysis patients with diabetes and appear to increase risk of hemorrhagic stroke.

Other considerations in the management of DKD

- Nonmedical strategies to slow down progression of DKD: smoking cessation, weight loss
- The dose of insulin is typically reduced with declining eGFR.
- Autonomic neuropathy may mimic and thereby exacerbate uremic symptoms.
- In patients with macroalbuminuria without retinopathy, especially if DM has been present for < 10 years, consider evaluation for non-dkd.

Sickle Cell Nephropathy

Renal manifestations

- Sickle cell nephropathy (SCN) encompasses a wide range of tubular and glomerular functional and anatomic abnormalities summarized in Table 7.15.

Table 7.15 Renal abnormalities in sickle cell disease

Cortical Manifestations	Medullary Manifestations	Distal Tubular Manifestations
Early alterations • Hyperfiltration, glomerular hypertrophy • Supranormal proximal tubular function • ↑Reabsorption of Na^+, PO_4^{2-}, β2-microglobulin • ↑Secretion of uric acid and creatinine (hence, creatinine-	• Hematuria (micro or macro): • 10% bilateral, left four times more than right due to increased pressure in the left renal vein • More common in SCT than SCD • Obstructive uropathy (due to papillary	• Impaired concentrating ability with resultant isosthenuria (urine osmolality 450 mosm/kg). • Impaired K^+ secretion with resultant hyperkalemia. RAAS is intact. • Incomplete RTA: typically not clinically significant but can be unmasked with reduction in GFR. • Voltage-dependent hyperkalemia distal RTA: patients fail to secrete H^+ and K^+ ➔urine pH > 5.5

based GFR may be greatly overestimated)
Late alterations
• Microalbuminuria, proteinuria
• Progressive CKD and ESKD
  • Genetic risk factors: APOL1, MYH9, HMOX1 rs743811 gene variants[a]
  • Protective factors: higher HbF levels, co-inheritance of α-thalassemia
	necrosis)	• Selective aldosterone deficiency distal RTA; patients have hyperkalemia-induced suboptimal ammoniagenesis but can secrete H^+ ➔urine pH can be 5.5 (respond to fludrocortisone)

Pathologic findings Renal cortical infarctGlomerular lesions: • Focal segmental glomerulosclerosis (most common) • Others: MPGN, SCD glomerulopathy, TMA (associated with retinitis)	Pathologic findings • Medullary ischemic necrosis and infarction • Papillary necrosis • Medullary carcinoma (occurs almost exclusively in sickle cell trait)	

[a]HMOX1 rs743811 gene variant is associated with albuminuria and progression of CKD to ESKD in some, but not all, studies.

Abbreviations: CKD, chronic kidney disease; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; HbF, fetal hemoglobin; MPGN, membranoproliferative glomerulonephritis; SCD, sickle cell disease; TMA, thrombotic microangiopathy.

Cortical/glomerular manifestations

- Early alterations:
  - Hyperfiltration, glomerular hypertrophy
  - Supranormal proximal tubular function:
    - Increased reabsorption of sodium, phosphate, β2-microglobulin
    - Increased secretion of:
      - Uric acid (in early disease with good kidney function, serum uric

acid level may be normal despite increase uric acid production)

- Creatinine (thus eGFR based on SCr may be greatly overestimated). Studies comparing CystC-based or creatinine-based MDRD (modification of diet in renal disease study) *or* CKD-EPI equations suggested that CystC-based CKD-EPI equation best estimates GFR in sickle cell disease (SCD) patients. Further studies are needed.

NOTE Cystatin C levels may be increased in high cell turnover states (such as hyperthyroidism, steroid use, malignancy, advanced age, gender and ethnicity, fat mass, and diabetes, among others).

- Late alterations:
  - Similar to diabetic and other kidney diseases, glomerular hyperfiltration in patients with SCD can lead to albuminuria, proteinuria, glomerulosclerosis, and progressive CKD.
- Histopathology:
  - FSGS: most common glomerular lesion in SCD, associated with glomerular hypertrophy
  - MPGN: Both immune-complex and non-immune complex/non-complement TMA type MPGN have been described.
  - SCD glomerulopathy: glomerular hypertrophy with or without mesangial hypercellularity
  - TMA: associated with history of retinitis
  - Glomerular ischemia
  - Hemosiderin in tubular epithelial cells and interstitial macrophages

Medullary manifestations

- Hematuria (microscopic or macroscopic):
  - 10% bilateral, left kidney affected four times more than right due to increased venous pressure in the longer left vein when compressed between the aorta and the superior mesenteric artery (i.e., nutcracker phenomenon)
  - Pathogenesis:

Medullary low oxygen tension, low pH, and high osmolality predispose the vasa recta RBCs to sickle.
    - Sickling leads to increased blood viscosity, microthrombus formation, and ischemic necrosis with RBC extravasation and hematuria.
  - Histopathology: ischemic papillary infarction and necrosis, hemosiderin deposition
  - Management:
    - Conservative: bed rest, volume repletion, rule-out papillary necrosis
    - For persistent hematuria, consider vasopressin or aminocaproic acid (synthetic inhibitor of the plasmin-plasminogen system) 2 to 3 g daily over several days, not to exceed 12 g daily due to risk of thrombosis.
    - For medical therapy failure or life-threatening bleeding, arterial embolization or surgical intervention must be considered.
- Acute obstructive uropathy:
  - Sloughing of necrotic papillae into the renal pelvis can lead to obstructive uropathy.
  - Sloughed necrotic papillae can give the appearance of “egg in a cup” or “golf ball and a cup” on contrast CT urography. See **Fig. 6.4**.

Tubular manifestations

- Impaired concentrating ability despite volume depleted state (isothenuria with maximum urine osmolality <450 mosm/kg). may present as polyuria, hypovolemia prone with poor oral intake, and nocturnal enuresis in young patients. this defect may be reversible with blood transfusion in young patients but become uncorrectable by age 15.
- Impaired potassium secretion with resultant hyperkalemia. RAAS is intact.
- Incomplete RTA: typically not clinically significant but can be unmasked with reduction in GFR
- Voltage-dependent hyperkalemic distal RTA: Patients fail to secrete both H^+ and K^+, thus urine pH > 5.5.
- Selective aldosterone deficiency distal RTA: Patients have hyperkalemia-induced suboptimal ammoniagenesis, but can secrete H^+, thus urine pH can

be < 5.5. these patients respond to fludrocortisone.

CKD and ESKD

- Factors associated with progression of CKD to ESKD: HTN, nephrotic-range proteinuria, severe anemia, vasoocclusive crisis, acute chest syndrome, stroke, βS-gene haplotype, pulmonary HTN, and the presence of certain genetic variants (discussed below)
- Gene variants of APOL1 and MYH9 are associated with proteinuria, CKD, and loss of kidney function.
- Protective factors
  - Higher fetal hemoglobin (HbF) levels and α-globulin genotype have been suggested to be protective against SCN and vasoocclusive complications.
  - Coinheritance of α-thalassemia appears to be protective against proteinuria and SCN.
  - Some, but not all, studies suggest that hydroxyurea may reduce proteinuria and/or hyperfiltration.
- Special considerations of CKD in SCD: Hb target with erythropoiesis-stimulating agent use should not exceed 10.5 g/dL.

Kidney transplantation in SCD

- One-year graft survival ≥ 60% to 80+%
- Confers survival benefit: Although survival of SCD kidney transplant recipients is inferior to that of matched African American transplant recipients without SCD, survival of SCD transplant recipients is comparable with that of matched diabetic patients.
- Kidney transplant may be complicated by allograft venous thrombosis, deep vein thrombosis, and vasoocclusive crises.
- Although preoperative blood transfusion to decrease hemoglobin S (HbS) level has been suggested to decrease the incidence of posttransplant complications, aggressive RBC transfusion should be avoided because increasing RBC mass increases blood viscosity, thereby potentially precipitating RBC sickling.

Renal manifestations of sickle cell trait (SCT)

- Except for hematuria and renal medullary cancer (discussed below), renal manifestations of SCD are generally less common and less severe in patients with SCT than those with homozygous HbS.
- Renal medullary cancer
  - Seen almost exclusively in patients with SCT and occurs at a relatively young age, averaging 21 years (20 to 30 years old)
  - The presence of flank or abdominal pain, or continued or persistent macroscopic hematuria with or without clots should prompt further evaluation with both cystoscopy and ureteroscopy to exclude renal medullary cancer.
  - Aggressive metastatic disease is usually present at diagnosis and portends a poor prognosis (median survival 3 months following diagnosis).
- Whether SCT predisposes to CKD is not clear. However, among African Americans with polycystic kidney disease, cystic hemorrhage is more common and progression to ESKD is more rapid.

Fabry Disease

Background

- Second most prevalent lysosomal storage disease after Gaucher disease
- May be seen in all ethnics and races
- X-linked inborn error with deficiency or defect of lysosomal hydrolase α-galactosidase A (α-Gal A), an enzyme that catalyzes the hydrolytic cleavage of the terminal galactose from globotriaosylceramide (Gb3), thus leading to lysosomal accumulation of Gb3 in various cells, including vascular endothelium and smooth muscle cells, cardiac muscle cells and conduction fibers, kidneys, and nerve root ganglia.

Clinical manifestations

- Neurologic: neuropathic pain in extremities, stroke in early age
- Dermatologic: telangiectasias; angiokeratomas in groin, hip, periumbilical areas, corneal opacities; thickened lips; bullous nose; hypohidrosis or hyperhidrosis and associated heat or cold intolerance, respectively
- Cardiac: arrhythmias, left ventricular hypertrophy

- GI: abdominal pain, diarrhea
- Renal: proteinuria (both tubular and glomerular proteinuria possible), progressive CKD, Fanconi syndrome due to proximal tubular injury, polydipsia and polyuria due to distal tubular injury and associated defective urinary-concentrating ability, multiple renal sinus and parapelvic cysts on imaging studies

Histopathology (Fig. 7.20)

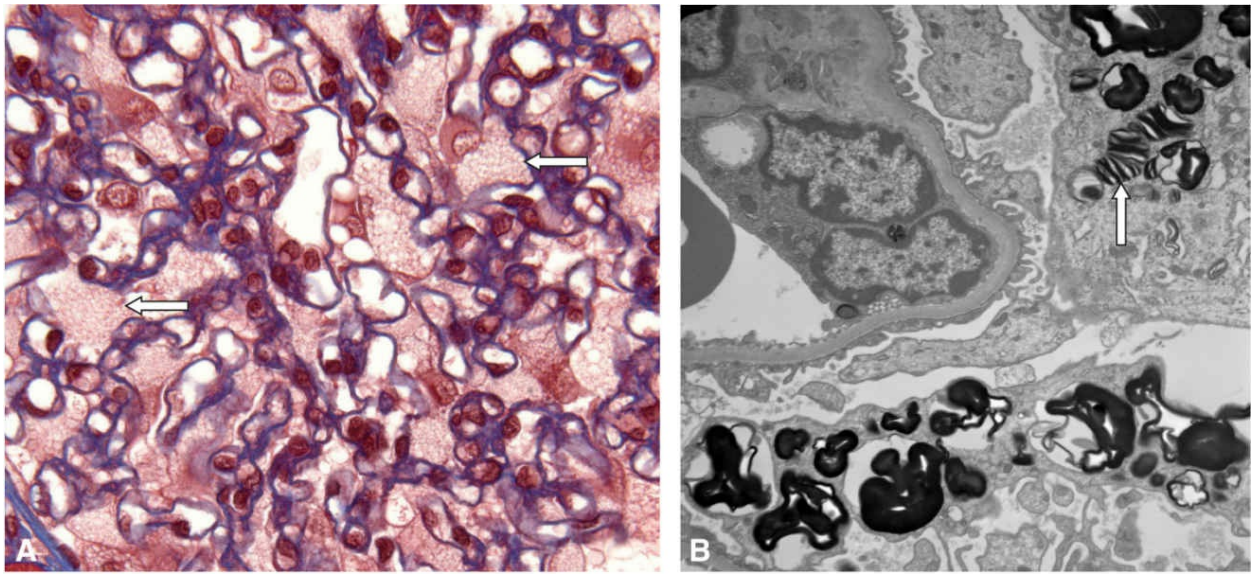

FIGURE 7.20 Fabry disease. **A.** Enlarged foamy podocytes (*arrows*) throughout the glomerulus (Masson trichrome ×600). **B.** Podocytes contain whorled and clumped electron-dense inclusions (myelin figures) composed of accumulated globotriaosylceramide. These inclusions may have a striped or "zebra-body" appearance (*arrow*) (×10,000).

- LM:
  - Vacuolization/foamy appearance of podocytes and rarely distal tubular epithelial cells due to glycolipid accumulation
  - Nonspecific findings: FSGS or global glomerulosclerosis, tubulointerstitial fibrosis
- EM:
  - Podocytes with "myeloid" or "zebra" bodies (concentric lamellated/striped inclusions of Gb3 within enlarged secondary lysosomes)
  - Similar myeloid inclusions may be seen with chloroquine or

hydroxychloroquine administration and less often in gentamicin toxicity or silicosis, predominantly in proximal tubules.

Diagnosis

- Low α-Gal A activity in leukocytes of plasma in males
- Female carriers may have normal to low levels of α-Gal A. Genetic analysis for the *α-Gal A* gene is required for diagnosis.
- Genetic analysis may also be required in males with marginally low α-Gal A activity levels.
- Tissue biopsy (skin or kidney) reveals characteristic findings, but is typically not necessary.

Management

- Genetic counseling
- Enzyme (α-Gal A) replacement therapy:
  - Recommended for all males and females with classic presentations
  - May be considered in asymptomatic female carriers or males with atypical presentations
  - Enzyme replacement therapy effectively reduces tissue deposition of Gb3 in most tissues, except for podocytes and vascular smooth muscle. Nonetheless, replacement therapy may slow kidney function decline in early-stage disease.
  - Replacement options: agalsidase alfa 0.2 mg/kg or agalsidase β 1.0 mg/kg infusion every 2 weeks. Notable side effects: infusion reactions, development of antibodies against the enzyme
- Kidney transplantation: improves survival compared to nontransplant

VIRAL NEPHRITIDES

Human Immunodeficiency Virus

- HIV may be associated with (1) HIV-associated nephropathy (HIVAN), (2) HIV-associated immune complex kidney disease (HIVICK), (3) combined antiretroviral treatment (cART) nephropathy, (4) TMA, and (5) others (tubulointerstial disease and diffuse infiltrative lymphocytosis syndrome).

HIV-Associated Nephropathy

Epidemiology

- Predominantly observed in African Americans
- Associated with severe/advanced HIV (i.e., CD4 < 200 cells/mm^3, high viral load)

Pathogenesis

- Genetic susceptibility: APOL1 risk alleles
- Both direct and indirect mechanisms involving HIV are thought to be contributory.

Clinical manifestations

- Nephrotic-range proteinuria, hematuria
- Normal to enlarged kidneys on ultrasound due to microcyst formation, edema

Histopathology (Fig. 7.21)

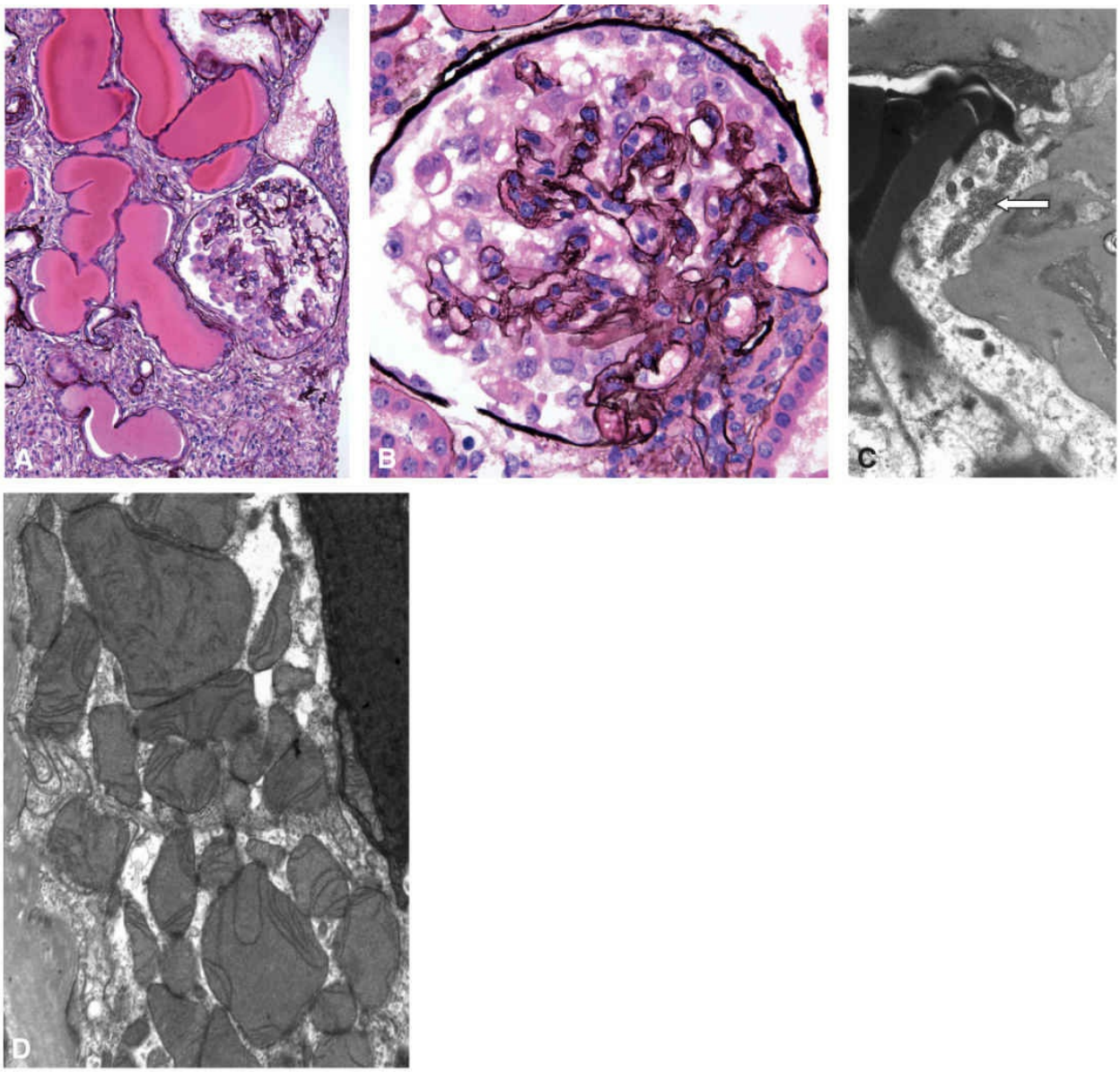

FIGURE 7.21 HIV-associated nephropathy. **A.** Cluster of dilated tubules with plasma protein casts and collapsing glomerulopathy (Jones silver ×100). **B.** Collapsing glomerulopathy showing capillary collapsing with podocyte hypertrophy, hyperplasia, and cytoplasmic vacuoles (Jones silver ×400). **C.** Tubuloreticular inclusion (*arrow*) in glomerular endothelial cell. These disappear with combined antiretroviral therapy (×15,000). **D.** Enlarged atypical proximal tubular mitochondria with broken cristae associated with nucleotide reverse transcriptase inhibitor (tenofovir) treatment (×10,000).

- LM: collapsing FSGS, tubular microcystic dilatation with proteinaceous casts, variable acute tubular injury, tubular atrophy, lymphocytic infiltrates, interstitial fibrosis
- EM: presence of tubuloreticular inclusions in endothelial cell cytoplasm in untreated patients

Natural history/prognosis

Rapid progression to ESKD if untreated.

Management

cART regardless of CD4 count, renin–angiotensin system inhibition, corticosteroid therapy only if rapid decline in kidney function despite cART *and* absence of superimposed/opportunistic infections

HIV-Associated Immune Complex Kidney Disease(HIVICK)

Background

- Typically occurs in patients with HIV duration ≥ 10 years
- Reported lesions: IgAN, lupus-like GN, MN, membranous/mesangial proliferative GN, postinfectious GN, immunotactoid/fibrillary GN

NOTE Since IgAN is rare in African Americans, the presence of IgAN should raise the possibility of concurrent HIV infection.

Clinical manifestations

Nephrotic syndrome is common. Others include hematuria, HTN; Patients with HIVICK may have positive ANA and low C3.

Histopathology

- LM: related to the type of disease as detailed above
- IF: variable Ig/complement staining related to the different glomerulopathies, “full house” of Ig may be present.
- EM: presence of endothelial cell tubuloreticular inclusions

cART nephropathy

- Nucleotide analog reverse transcriptase inhibitors: mitochondrial dysfunction, Fanconi syndrome, AKI/ATN:
  - Most well recognized: tenofovir

NOTE Mitochondrial injury may be seen on EM as giant mitochondria with atypical shapes and broken or absent cristae (**Fig. 7.21**).

- Protease inhibitors with associated crystal-induced nephropathy/urolithiasis (e.g., indinavir, atazanavir)
- The fusion inhibitor enfuvirtide may be associated with MPGN.
- See Table 10.1 for a complete list of cART effects on the kidneys.

Thrombotic microangiopathy

- May be seen with advanced HIV, not treated with cART
- Pathogenesis thought to involve direct HIV attack of endothelial cells.
- Affected individuals may have low ADAMTS13 levels.
- Response to corticosteroids and PLEX may be expected.

Other lesions associated with HIV

- Tubulointerstitial diseases
- Diffuse infiltrative lymphocytosis syndrome: a rare Sjögren-like sicca complex (e.g., bilateral parotid gland enlargement, xerostomia, and keratoconjunctivitis) seen in patients with HIV. The pathogenesis of this autoimmune disease is thought to be due to HIV antigen mimicry to host antigens, leading to the production of autoantibodies or cytotoxic T-cell clones targeting host tissues. Kidney involvement may be characterized by marked infiltration by mononuclear cells, predominantly CD8 lymphocytes, with tubulitis.

Kidney transplantation in patients with HIV

- May be considered if undetectable viral load *and* CD4 > 200 cells/mm^3

NOTE Major drug interaction: Protease inhibitors (e.g., darunavir, ritonavir) can markedly increase CNI levels. Less than 5% of usual CNI dose is typically given to achieve therapeutic level.

- Also see **Chapters 9 Kidney Transplantation and 10 Pharmacology** for cART and immunosuppressive drug–drug interactions.

Hepatitis A

- Most common kidney presentation is ATN.
- Other possible lesions: tubulointerstitial disease, IC-mediated proliferative GN

- Renal recovery typically parallels liver recovery.

Hepatitis B

Associated lesions

- MN without concurrent anti-PLA2R antibodies is most common, but MN associated with +anti-PLA2R is possible.
- Other associated lesions: IC MPGN, IgAN (in association with chronic liver disease, particularly with alcoholism), FSGS, and, rarely, crescentic GN
- Extrarenal lesions associated with hepatitis B: Polyarteritis nodosa (IC deposits formed by HBsAg and anti–hepatitis B antibody [IgM] along vessel walls), cryoglobulinemia

Management

- Antiviral therapy:
  - Patients with replicative HBV infection (i.e., HBV DNA level > 2,000 IU/mL) and associated glomerulonephritis, treatment with nucleos(t)ide analogs similar to those recommended for the general population is recommended.
  - Pegylated interferon regimens should not be used to treat patients with replicative HBV infection and GN because interferon may exacerbate autoimmune response in this subgroup.
- Immunosuppression in HBV-associated GN:
  - The use of CNI has been suggested to be safe for use in patients with HBV infection and HBV-associated MN and FSGS because CNI may reduce viral replication.
  - CYC or RTX may accelerate HBV replication and should be avoided in patients with untreated replicative HBV infection and GN.
- Nonspecific therapies: RAAS inhibition, BP control
- PLEX with either 5% albumin or FFP may be considered in patients with symptomatic cryoglobulinemia and cryocrit > 5% or > 500 mg/dL.

Hepatitis C

For a detailed description of the prevention, diagnosis, evaluation, and

treatment of hepatitis C, see the 2018 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines at https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2018-Hep-C-GL.pdf.

Clinical extrahepatic manifestations of hepatitis C

- Cryoglobulinemia, IC and lymphoproliferative disorder with associated arthralgias, fatigue, palpable purpura, digital ischemia, renal disease, peripheral neuropathy, central nervous system (CNS) vasculitis, hypocomplementemia
- IC-mediated MPGN with or without cryoglobulinemia is the most common glomerular lesion.
  - Cryoglobulins are Igs directed against the Fc portion of anti-HCV antibody. That is, these cryoglobulins have rheumatoid factor activity.
  - Laboratory findings: positive rheumatoid factor, elevated cryocrit, hypocomplementemia
  - Chronic active HCV infection may be associated with B-cell lymphoproliferative diseases, with the most common monoclonal gammopathy being IgM, κ light chain.
  - Clinical manifestations: asymptomatic hematuria and proteinuria, NS, slowly progressive CKD, or RPGN
  - EM: Cryoglobulins resemble “fingerprint” pattern of fibrils of 30 nm.
- Other HCV-associated renal lesions: MN, fibrillary/immunotactoid GN, PAN

Clinical impact of hepatitis C

- Chronic hepatitis C correlates with the incidence of T2DM and adverse outcomes.
- Successful antiviral therapy against HCV is associated with improved insulin resistance and reduced incidence of new-onset T2DM.
- The incidence of ESKD, ischemic stroke, and acute coronary syndrome is reduced among successfully treated HCV patients with T2DM in a large prospective cohort from Taiwan.
- Patients with T2DM and insulin resistance are at increased risk for hepatocellular carcinoma.

- HCV in the dialysis patient:
  - Prevalence is 8% to 9%.
  - Seroprevalence of HCV increases with dialysis vintage.
  - HCV-infected hemodialysis patients have decreased quality of life and increased mortality compared to their noninfected counterpart.
  - HCV infection may reduce both patient and allograft survival in the kidney recipient. However, the advent of direct-acting agent (DAA) should improve outcomes in hepatitis C–positive kidney transplant recipients. See **Chapter 9**.

Management

- Testing for hepatitis B should be done before treating for hepatitis C. Patients with both hepatitis B and C should be referred to a hepatologist.
- Antiviral therapy: American Association for the Study of Liver Diseases and Infectious Diseases Society of America, http://www.hcvguidelines.org
  - Antiviral therapy is recommended for all patients with chronic HCV infection, except for those with short life expectancies.
  - Treatment recommendations for patients with hepatitis C associated glomerular diseases (KDIGO 2018):
    - If stable kidney function and/or non-nephrotic proteinuria, treat with DAAs.
    - If cryoglobulinemic flare, NS, or rapidly progressive kidney failure, treat with DAA plus IST with or without PLEX.
    - If patients have histologically active HCV-associated glomerular disease and do not respond to DAA, particularly those with cryoglobulinemic kidney disease, treat with immunosuppressive therapy.
    - RTX is the recommended first-line immunosuppressive treatment as long as hepatitis B is not present.
  - The specific DAA regimen chosen should be based on the HCV genotype, the viral load, prior treatment history, drug interactions, GFR, stage of hepatic fibrosis, kidney and liver transplant candidacy, and comorbidities.

Patients with GFR ≥ 30 mL/min/1.73 m^2 (CKD G1-G3b) should be
  - treated with any licensed DAA-based regimen.
  - Patients with GFR < 30 ml/min/1.73 m^2 (ckd g4-g5d) should be treated with a daa regimen without sofosbuvir or ribavirin.
- Kidney transplant candidates should be treated in collaboration with the transplant center to optimize the timing of therapy.

Other Viral Nephritides

Parvovirus

- Collapsing FSGS, MPGN, diffuse proliferative GN

Hantavirus

- Hemorrhagic nephritis, see tubulointerstitial diseases

BK nephropathy

- See Kidney Transplantation.

CMV

- Rarely proliferative GN or collapsing FSGS. In kidney transplants, tubular cell or macrophage infection may result in intranuclear and/or intracytoplasmic viral inclusions.

Corona virus disease 19 (COVID-19)

- A small case series involving 17 patients (12 men, 12 black, median age of 54) with nephrotic range proteinuria reported collapsing FSGS as the most common GN. Other GN included MCD, MN, crescentic transformation of LN, and anti-GBM disease. Three kidney allograft biopsies revealed grade 2A acute T cell-mediated rejection, cortical necrosis, or ATN. APOL1 high risk variant was positive in all cases of collapsing FSGS and the one patient with MCD. There was no evidence of the virus in kidney cells.

THROMBOTIC MICROANGIOPATHY

Background

- TMAs are clinical syndromes characterized by the following triad:
  - Thrombocytopenia < 15,000/µl or >25% decline in platelet count from

baseline,

- Microangiopathic hemolytic anemia (MAHA), and
- End-organ dysfunction involving one or more organs (e.g., brain, kidneys, GI tract)

Histopathology

- The features of TMA are similar, regardless of pathogenesis, and biopsy does not differentiate among the different underlying causes (**Fig. 7.22**).

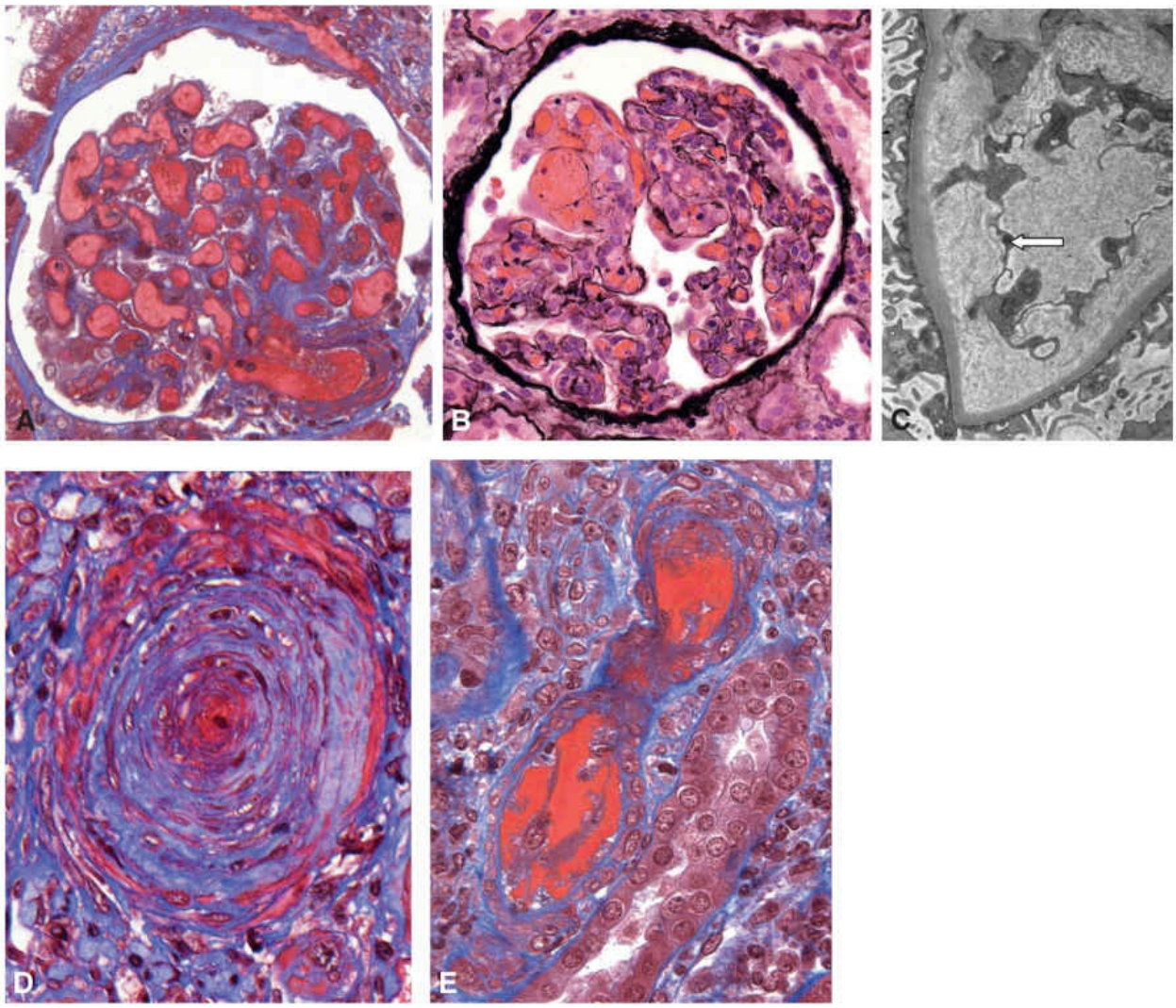

FIGURE 7.22 Antiphospholipid syndrome. **A.** Bland thrombosis of arteriole and glomerular capillaries (Masson trichrome ×400). **B.** Glomerular capillary thrombosis with irregular, ischemically wrinkled capillary walls and segmental double contours (Jones silver ×400). **C.** Arrow: Wide subendothelial lucency (which stains for fibrin) corresponding to thickened capillaries on light microscopy (×14,000). **D.** Arteriole with "onion-skin" appearance due to muscular hypertrophy, with a thrombus in the very

narrowed lumen (Masson trichrome ×600). **E.** Thrombosed arteriole (Masson trichrome ×400). Arterial/arteriolar fibrin thrombi and/or fibrin extending into the vascular intima and endothelial cell swelling with narrowed lumens.

- LM: glomerular arterial/arteriolar fibrin thrombi and/or fibrin extending into the vascular intima and endothelial cell swelling with narrowed lumens
- Fragmented RBCs in vessel lumens, walls, or in areas of glomerular mesangiolysis
- Concentric thickening (onion skinning + mucoid subendothelial widening of arterial/arteriolar walls)
- Glomerular ischemic wrinkling, sometimes with double contours
- IF: fibrin in glomerular capillaries and/or vessel walls lumens
- EM: subendothelial electron lucent widening between glomerular capillary basement membrane and swollen endothelium

Clinical Disorders Associated With TMA

- TMA may be seen in various clinical disorders:
  - Shiga-toxin–mediated HUS (i.e., diarrhea-associated HUS or diarrhea-associated HUS)
  - Complement-mediated TMA (i.e., atypical HUS). Historically, the term *atypical HUS* was used to distinguish it from Shiga-toxin–mediated HUS. However, such term does not reflect a specific cause.
  - TTP
  - Pregnancy-associated TMA syndromes (HELLP syndrome, TTP, complement- mediated TMA)
  - TMA associated with other clinical disorders: disseminated intravascular coagulation (DIC); systemic infections; drugs; cobalamin C deficiency; malignancies; autoimmune disease such as SLE, scleroderma, and APS; and malignant HTN, among others
- **Figure 7.23** summarizes the diagnostic criteria, clinical manifestations, pathogenesis, and therapy of Shiga-toxin–mediated HUS, complement-mediated TMA, and TTP.

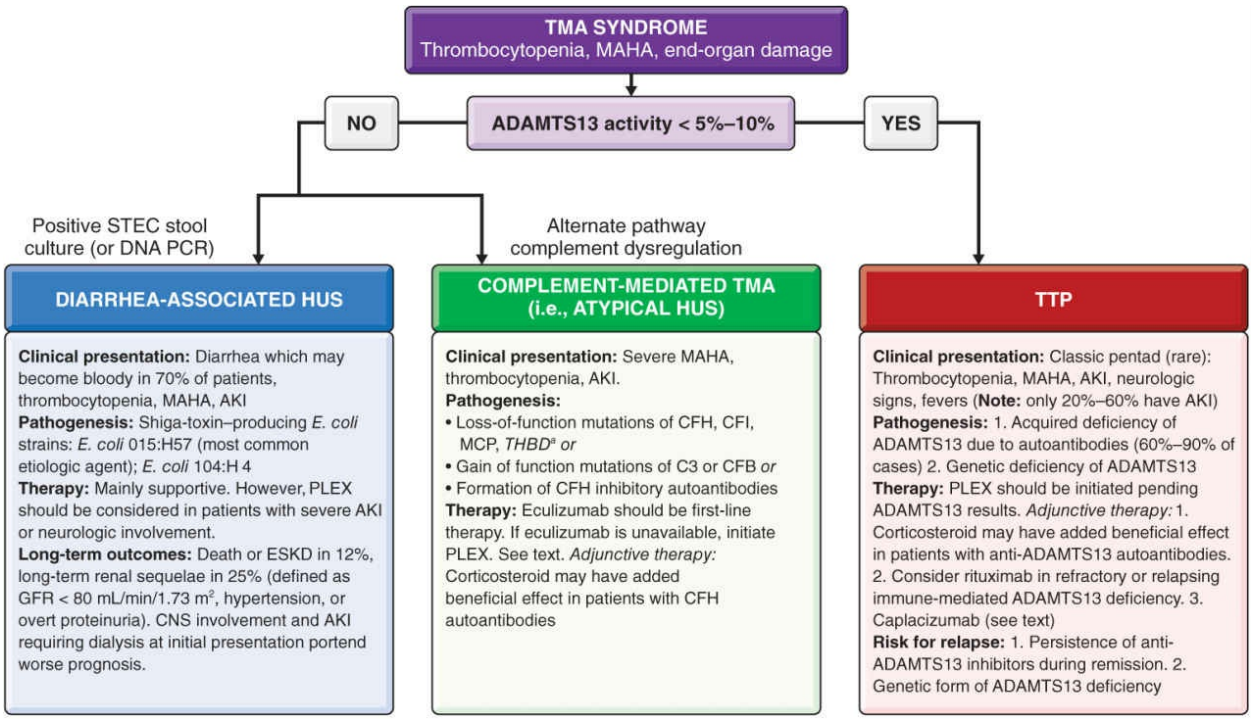

FIGURE 7.23 Differential diagnoses of the primary forms of thrombotic microangiopathy.

[a]Cells expressing THBD gene variant inactivate C3b less efficiently.

Abbreviations: AKI, acute kidney injury; CFB, complement factor B; CFH, complement factor H; CFI, complement factor I; CNS, central nervous system; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; HUS, hemolytic uremic syndrome; MAHA, microangiopathic hemolytic anemia; MCP, membrane cofactor protein; PCR, polymerase chain reaction; PLEX, plasma exchange; STEC, Shiga-toxin–producing enterohemorrhagic *E. coli*; THBD, thrombomodulin; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

Shiga-Toxin–Mediated HUS (Diarrhea-Associated HUS)

Clinical manifestation

- Bloody diarrhea. HUS usually occurs 5 to 10 days after the onset of diarrhea.

Pathogenesis

- Caused by Shiga-toxin-producing enterohemorrhagic *Escherichia coli* strains.
  - Usually *E. coli* O157:H7. Other: *E. coli* O104:H4 (large HUS outbreak in Germany in 2011)
  - Toxin-mediated endothelial cell damage leads to endothelial injury, thrombosis, cell death, and, occasionally, extensive cortical necrosis.

Therapy

- Mainly supportive
- Plasmapheresis should be considered in patients with severe AKI or neurologic involvement.

Long-term outcomes

- Death or ESKD in 12%, long-term renal sequelae in 25% (e.g., GFR < 80 ml/min/1.73 m^2, htn, or overt proteinuria at 4.4 years)
- CNS involvement and AKI requiring dialysis at initial presentation portend worse prognosis.

Complement-Mediated TMA (i.e., Atypical HUS)

- Most cases of complement-mediated TMA are sporadic; Familial cases occur in <20%.

Clinical manifestations

- Severe hemolytic anemia, thrombocytopenia, and AKI
- CNS and GI involvement occurs in 20% of cases.
- A preceding infection including a diarrheal illness may occur in 80% of children and 50% of adult patients.

- Other extrarenal manifestations: cardiac ischemic events, pulmonary hemorrhage, and hypoxemia

Pathogenesis

- Dysregulated (or uncontrolled) activation of the alternative complement pathway due to genetic mutations of or autoantibody formation against various complement regulatory proteins
  - Loss-of-function mutations of CFH, complement factor I (CFI), membrane cofactor protein (MCP), or thrombomodulin (*THBD*). Thrombomodulin is an endothelial surface anticoagulant protein that also modulates complement on cell surfaces. Cells that express *THBD* variants inactivate C3b less efficiently.
  - Gain-of-function mutations of C3 or CFB
  - Formation of CFH inhibitory antibodies
  - *Potential triggering factors*: pregnancy (usually postpartum),

gastroenteritis, upper respiratory tract infections, organ transplantation, and malignant HTN among others

Therapy

- An anti-C5 monoclonal antibody that inhibits C5 activation, such as eculizumab, should be first-line therapy.
- If eculizumab is unavailable, initiate PLEX. Plasma infusion provides normal complement factors to individuals with *CFH* or *CFI* gene mutations, whereas PLEX may remove the mutants CFH or CFI. Plasma infusion or PLEX may also be beneficial in those with *C3* or *CFB* gene mutation. The rate of remission with PLEX varies with mutation types. Note, however, PLEX is ineffective in *MCP* gene mutation because MCP is a cell-associated protein. Spontaneous remission may occur in individuals carrying the MCP mutation.
- Adjunctive therapy: Corticosteroid may have added beneficial effect in patients with CFH autoantibodies.

Thrombotic Thrombocytopenic Purpura

Background

- ADAMTS13 (**A** **D**isintegrin **A**nd **M**etalloproteinase with a **T**hrombospondin type 1 motif, member **13**) is a protease that cleaves ultra-large von Willebrand factor (vWF) multimers on endothelial cell surface into smaller fragments to make them “less sticky” to circulating platelets. Without functional ADAMTS13, there are dysfunctional ultra-large vWF multimers, increased platelet trapping, and intravascular microthrombi formation.

Clinical manifestation

- Presence of the classic pentad for TTP (thrombocytopenia, MAHA, kidney failure, neurologic signs, and fever) is rare.
- TTP and Shiga-toxin-mediated HUS may have significant overlapping clinical signs and symptoms at presentation. While Shiga-toxin-mediated HUS can also present with CNS involvement and diarrheal illness, 20 to 60% of patients with TTP may present with kidney failure.

Diagnosis

- May not be obvious at presentation and requires testing for ADAMTS13 activity.

Pathogenesis and therapy

- *Acquired TTP*: severe functional deficiency of ADAMTS13 due to inhibitory autoantibodies (ADAMTS13 activity < 5% to 10%)
  - PLEX should be initiated pending ADAMTS13 activity test results.
    - Plasma replaces defective protease activity.
    - PLEX (vs. infusion alone) may additionally remove ADAMTS13 antibodies.
  - Adjunctive corticosteroid therapy may provide added benefit for autoimmune forms of TTP by inhibiting anti-ADAMTS13 autoantibody synthesis.
  - RTX should be considered in refractory or relapsing immune-mediated ADAMTS13 deficiency.
  - Novel drug therapy: Caplacizumab is a monoclonal antibody fragment (nanobody) that binds to vWF inhibiting platelet adhesion. It was approved by the FDA in February 2019 for use in acquired TTP in conjunction with PLEX and immunosuppressive therapy.
- *Genetic TTP:* genetic deficiency of ADAMTS13 due to homozygous or compound heterozygous *ADAMTS13* gene mutation
  - Plasma therapy replaces ADAMTS13. Relapse is common.
  - PLEX is often required during acute episodes.

Therapy considerations when diagnosis may not be obvious at presentation and ADAMTS13 activity testing is pending

- Immediate PLEX initiation is recommended, if TTP is suspected pending ADAMTS13 result.
- Eculizumab should be initiated when there is a high index of suspicion for complement-mediated TMA.

Pregnancy-Associated TMA Syndromes (Also see Chapter 11)

Pregnancy-associated TTP due to ADAMTS13 deficiency

- May occur early in pregnancy, but typically occurs in the late second and third trimesters, at median gestational age of 23 weeks

- During pregnancy, plasma vWF including the ultra-large multimers increase steadily up to 20% to 500% of normal at term, while ADAMTS13 activity declines gradually from the end of the first trimester to the end of early puerperium.

Pregnancy-associated complement-mediated TMA

- Typically occurs postpartum (80%) but may occur early in pregnancy
- Complement dysregulation has been reported in 75% of patients with pregnancy-associated TMA syndrome.
- Late (i.e., postpartum) occurrence is thought to be due to the loss of placental protective complement inhibitory factors against mother's underlying complement dysregulation.
- Patients with complement dysregulation may have a 20% risk of pregnancy-associated TMA syndrome.
- Pregnancy-associated complement-mediated TMA is associated with a higher incidence of fetal losses (4.6% vs. 2% to 3%) and preeclampsia (7.4% vs. 4% to 5%) compared to the general population.
- Two-thirds of affected patients develop ESKD within a month of diagnosis.
- Infection is thought to be a potential triggering factor.

Severe preeclampsia associated with HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome

- HELLP diagnostic criteria defined by the American College of Obstetricians and Gynecologists:
  - MAHA
  - LDH ≥ 600 IU/L
  - Elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) to more than twice the upper limit of normal
  - Platelet count < 100,000 cells/µl

TMA Associated With Other Clinical Disorders

- Disseminated intravascular coagulation (DIC)
  - Associated with sepsis, liver failure, malignancy, tissue death, obstetric complications such as preeclampsia, septic abortion

- Classic presentation: elevated prothrombin time/partial thromboplastin time (PT/PTT), increased fibrinogen-degradation product (FDP), increased D-dimer
- Low-grade or chronic DIC: PT/PTT and fibrinogen may be normal, but MAHA will be present and FDP and D-dimer will be increased.

NOTE While Shiga-toxin–mediated HUS, TTP, and complement-mediated TMA have reduced platelet survival and normal plasminogen and fibrinogen turnover, DIC has reduced platelet survival and increased fibrinolysis and plasminogen activator. Unlike DIC where PT/PTT are typically elevated and fibrinogen levels are reduced, these levels are normal in HUS and TTP.

- Infections: HIV, CMV, parvovirus, *Streptococcus pneumoniae*
- Drugs: ticlopidine (off-market), quinine (off-market), clopidogrel, valacyclovir, oral contraceptives, chemotherapy, mitomycin C, CSA, TAC, sirolimus, everolimus
- Other causes of TMA: autoimmune disease such as SLE or APS (discussed below), systemic sclerosis, malignant HTN, stem cell transplant, cobalamin C deficiency

SLE and TTP

Epidemiology

- TTP typically precedes the diagnosis of SLE in children. Six percent of patients with TTP have SLE.
- SLE typically precedes the diagnosis of TTP in adults. Less than 5% of SLE patients have TTP.
- Differential diagnoses of MAHA other than TTP in patients with SLE:
  - DIC
  - Malignant HTN
  - Catastrophic antiphospholipid antibody syndrome (multiorgan thromboses)
  - Active lupus complicated by hemolytic anemia
  - Small-vessel vasculitis with end-organ damage

Clinical manifestations

- Presence of MAHA, anemia, thrombocytopenia
- Patients with SLE-associated TTP tend to be younger males, have worse kidney function (both proteinuria and SCr), class IV diffuse proliferative LN, lower C3 levels, and other complications such as APS, serositis, pulmonary HTN, nephritis, and CNS involvement.
- Mortality in SLE-associated TTP is approximately 50% and is commonly associated with infections.

Diagnosis

- Diagnosis is based on clinical assessment, serologic and coagulation tests, and exclusion of all other differential diagnoses above.
- Reduced ADAMTS13 levels and/or the presence of ADAMTS13 antibodies may be detected in SLE patients *without* overt TMA. However, SLE patients with TTP do have severely depressed ADAMTS13 levels or high titers of anti-ADAMTS13 antibodies.

Management

- Data for the management of TTP in SLE are lacking.
- PLEX plus immunosuppressive therapy (e.g., corticosteroids and CYC) to control both TTP and active SLE, respectively , may be used. Anticoagulation should be added if APS nephropathy is present. APS nephropathy is discussed in a later section.
- RTX may be considered if above fails. Data are lacking.

SLE and Thrombosis

- Arterial thromboembolic events are increased in patients with SLE: increased risks for myocardial infarction and stroke after adjustments for traditional risk factors
- Reported risks for arterial thromboembolic events:
  - Traditional factors: age, male, gender, smoking, dyslipidemia, HTN, obesity, hyperhomocysteinemia
  - Nontraditional factors: SLE disease duration, presence of antibodies (aPLs), higher SLE damage scores, duration and cumulative dose of corticosteroid use

- Reported risks for venous thromboembolic events: male gender, higher body mass index, aPLs, low serum high-density lipoprotein (HDL), hemolytic anemia, kidney disease
- Leukopenia has been reported to be associated with a decreased risk of both arterial and venous thromboembolic events.
- The coexistence of the three aPLs lupus anticoagulant, anticardiolipin, and anti–β2-glycoprotein I is especially high risk for thromboembolic events.
- The use of antimalarials (hydroxychloroquine) is protective against both arterial and venous thromboembolic events. Adverse effects of antimalarials: retinopathy, cardiotoxicity, neuromyopathy, cutaneous hyperpigmentation, transaminitis, and/or increased SCr
- The use of aspirin is inconclusive but warranted due to its low adverse effect profile.
- Routine evaluation for other genetic conditions must also be considered (e.g., factor V Leiden, methylenetetrahydrofolate reductase, fibrinogen γ mutations).

Antiphospholipid Syndrome

Systemic APS

- Systemic APS is defined as having ≥ one of the following clinical manifestation *and* ≥ one of the following laboratory criteria (Sapporo/Sydney classification criteria):

Clinical manifestations

- Imaging or histologic evidence of venous, arterial, or small-vessel thrombosis in any tissue or organ (e.g., deep vein thrombosis, pulmonary embolism, strokes, myocardial infarction, APS nephropathy)
- ≥ one unexplained death of a morphologically normal fetus at ≥10 weeks' gestation, ***or*** ≥ one premature birth of a morphologically normal neonate before 34 week gestation because of eclampsia, preeclampsia, or placental insufficiency, ***or*** ≥ three consecutive spontaneous pregnancy losses at < 10 week gestation, unexplained by chromosomal abnormalities or by maternal anatomic or hormonal causes

Laboratory criteria

- positive aPLs detected on ≥ two occasions ≥ 12 weeks apart (aPLs are autoantibodies directed against plasma proteins bound to anionic surfaces. aPLs are typically IgG or IgM, but can be IgA)
  - aPLs of interest: lupus anticoagulant, anticardiolipin antibodies, and anti-β2-glycoprotein I. Lupus anticoagulant is thought to carry the highest risk for thrombosis and has been reported to be the primary predictor of adverse pregnancy outcome in patients with aPLs.
  - Antibodies against cell membranes including phosphatidylserine, phosphatidylinositol, phosphatidylethanolamine, phosphatidic acid, and autoantibodies to prothrombin are not routinely tested due to lack of standardized testing and their presence is of unclear clinical significance.
  - The prevalence of aPLs is 1% to 5% of general population but may be as high as 16% to 40% in patients with SLE and 16% in those with rheumatoid arthritis.
- Systemic APS may be classified as primary or secondary APS. Primary APS has no associated systemic disease, whereas secondary APS is associated with a systemic disease, typically autoimmune (e.g., SLE).

Renal APS

- Renal APS may present with renal artery or vein thrombosis or APS nephropathy.
- APS *nephropathy* is a vasoocclusive kidney injury due to TMA and is a subset of renal APS. APS nephropathy per se is not generally considered a clinical manifestation required for the diagnosis of systemic APS.
  - APS nephropathy has been reported in 10% of patients with LN and in 20% to 30% of those with SLE.
  - Up to one-third of patients with APS nephropathy does not have systemic APS.
- Other renal APS lesions: renal vascular fibrointimal hyperplasia, renal artery or vein thrombosis with or without associated HTN, cortical ischemia/necrosis, hematuria, kidney injury, tubulointerstitial fibrosis, glomerulosclerosis, and any glomerular lesions noted below:
  - Primary APS: membranous, MCD, FSGS
  - Secondary APS: typically LN of any World Health Organization class

Pathogenesis of APS

- Inciting events is thought to arise from aPL-mediated blood vessel injury, followed by endothelial disruption, formation of β2-glycoprotein I IC, activation of endothelial cells, platelets, and circulating monocytes, all leading to a thrombogenic state.
- Other downstream effects that would favor thrombus formation:
  - Release of tissue factor, followed by activation of the extrinsic coagulation pathway, and production of vasoconstrictive thromboxane A2
  - Reduction of endothelial NO production, leading to increased endothelial monocyte adhesion, superoxide generation, and decreased arterial relaxation
  - Activation of classic complement pathway, increased expression of C5a, leading to neutrophil recruitment to area of tissue injury

Management of APS

- Lifetime anticoagulation for APS, even APS nephropathy alone, with goal INR 2 to 3.5. Aspirin or clopidogrel alone is inadequate therapy for patients with symptomatic APS.

NOTE INR > 3.0 may be associated with warfarin-related nephropathy (WRN-AKI associated with glomerular hemorrhage and intratubular RBC obstruction). Underlying CKD is thought to be a risk factor for WRN (**Fig. 7.24**).

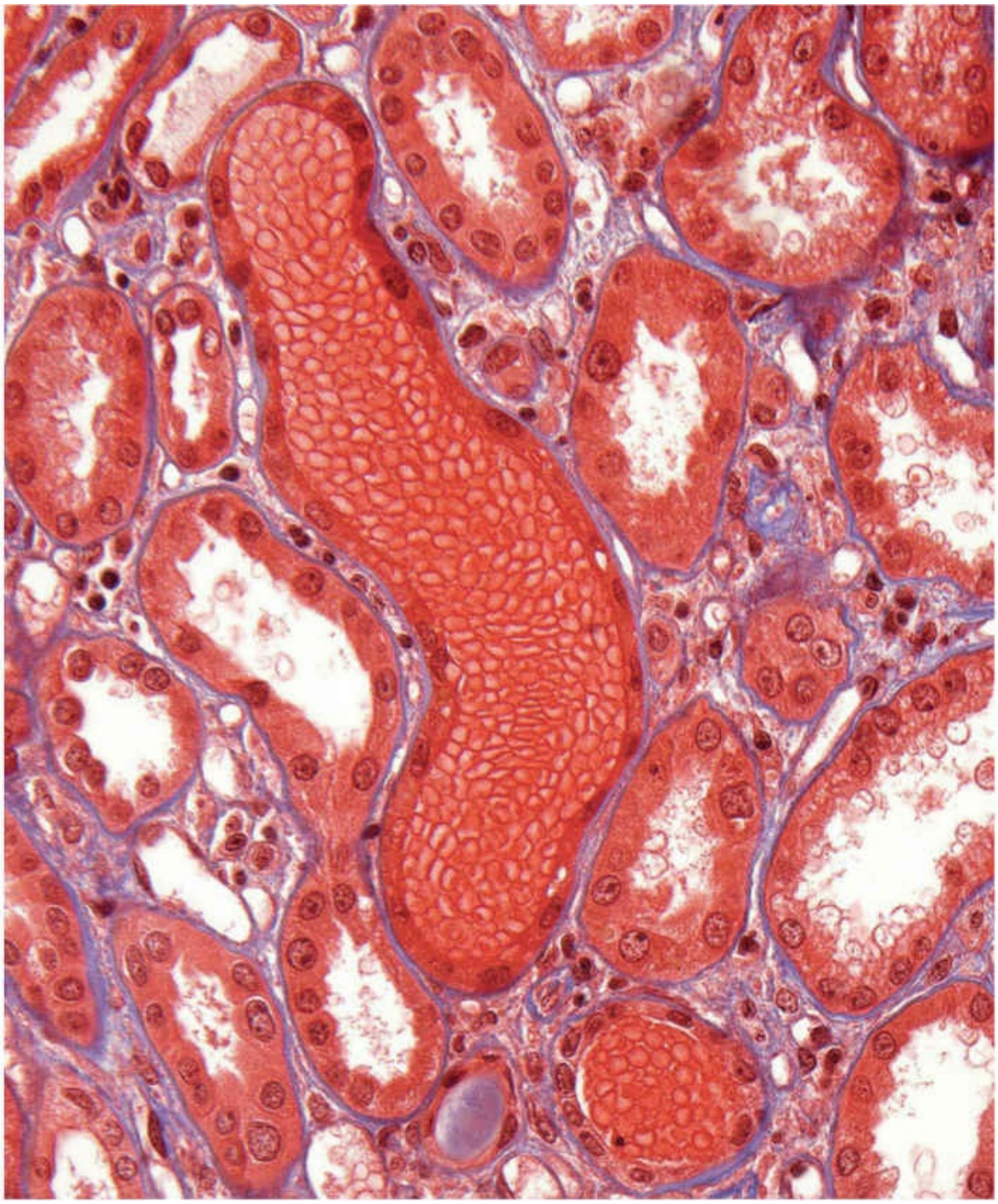

FIGURE 7.24 Anticoagulant related nephropathy. Red blood cells are within and occluding the lumen of distal tubules (Masson trichrome ×400). This form of kidney injury may also be seen with direct-acting oral anticoagulants (DOAC). “Warfarin-related nephropathy” may be replaced by the more general term “Anticoagulant related nephropathy” to include all anticoagulants as the inciting agent.

- Direct-acting oral anticoagulants (DOACs)
  - Evidence-based recommendations are lacking at the time of this writing.
  - 2019 European League Against Rheumatism (EULAR) guidelines:
    - Rivaroxaban should not be used in patients with triple aPLs positivity because of high recurrence risks.
- DOACs could be considered in patients not able to achieve a target INR despite good adherence to vitamin K antagonist (VKA) or those with contraindications to VKA (e.g., allergy or intolerance to VKA).
- Switching patients from VKA to DOACs due to poor adherence to VKA treatment or INR monitoring should be avoided.
  - Further studies are needed.
- LMWH is the treatment of choice for pregnancy complicated by APS. Its use may also alleviate symptoms of migraine headache.
- Hydroxychloroquine can be beneficial in patients with APS without evidence of SLE.

Access the eBook for self-assessment questions.

CHAPTER 8

Transplant Immunobiology

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BACKGROUND

ABO blood group is the most important tissue barrier to successful kidney transplantation, followed by major histocompatibility complex (MHC) antigens. Non-MHC molecules, referred to as minor histocompatibility antigens or non–human leukocyte antigens (non-HLAs), can also mediate rejection (discussed below and summarize in Table 8.1).

Table 8.1 Transplantation antigens and their role in kidney allograft rejection

Transplantation Antigens (listed in order of importance in allograft rejection)	Comments
ABO blood group	• ABO blood group antigens are strong transplantation antigen. • ABO-incompatible transplantation results in hyperacute rejection and graft loss.
Major histocompatibility antigens (also known as human leukocyte antigens [HLA])	• HLAs are classified into class I (HLA-A, HLA-B, HLA-C) and class II (HLA-DR, HLA-DQ, HLA-DQA, HLA-DP, HLA-DPA). • Fewer HLA mismatches between donor and recipient correlate better with graft survival. • 1-y graft survival is more related to HLA class II mismatching than to class I mismatching. • Repeat HLAs mismatch in the setting of a re-allograft transplantation may trigger reactivation of memory cells and production of donor-specific antibodies.

Minor histocompatibility antigens	• MHC-related chain A (MICA) and MHC-related chain B (MICB) are examples of minor antigen expressed on endothelial cells. • Unlike the classic HLA classes I and II, they do not bind peptides and do not engage T-cell receptor. Antibodies against MICA have been shown to be associated with antibody-mediated rejection.
Non-HLAs	• Examples of non-HLAs: MICA and MICB (discussed above), AT1R, anti–endothelin-1 type A receptor (ETAR), vimentin, cardiac myosin, collagen V, and agrin • Antibodies to non-HLAs have been shown to be associated with graft rejection. • Currently, clinical tests are available to test for antibodies to MICA, AT1R, and reactivity to antigens expressed on donor endothelial cells.

Abbreviation: AT1R, angiotensin II type 1 receptor.

ABO BLOOD GROUP ANTIGENS

- ABO blood group antigens are expressed on the surface of red blood cells as well as in the kidneys, gastrointestinal, respiratory, and other organ systems.
- ABO-incompatible kidney transplantation results in hyperacute rejection and graft loss.
- A number of variant A antigens are known, with the A1 antigen providing more potent antigenicity than the antigen A2. Successful transplantation can be performed using A2 kidneys into O recipients and A2 and A2B kidneys into B recipients.
- Various desensitization protocols have allowed successful ABO-incompatible kidney transplantation. Discussion is beyond the scope of this chapter.

MHC, HLA MOLECULES

- The major histocompatibility (*MHC*) genes are located on the short arm of chromosome 6 and represent the most polymorphic genes in human genome.
- HLAs are glycoproteins encoded by the *MHC* genes (**Fig. 8.1**). In human, the MHC molecule was first discovered in leukocytes; therefore, it is also called the human leukocyte antigen (HLA).

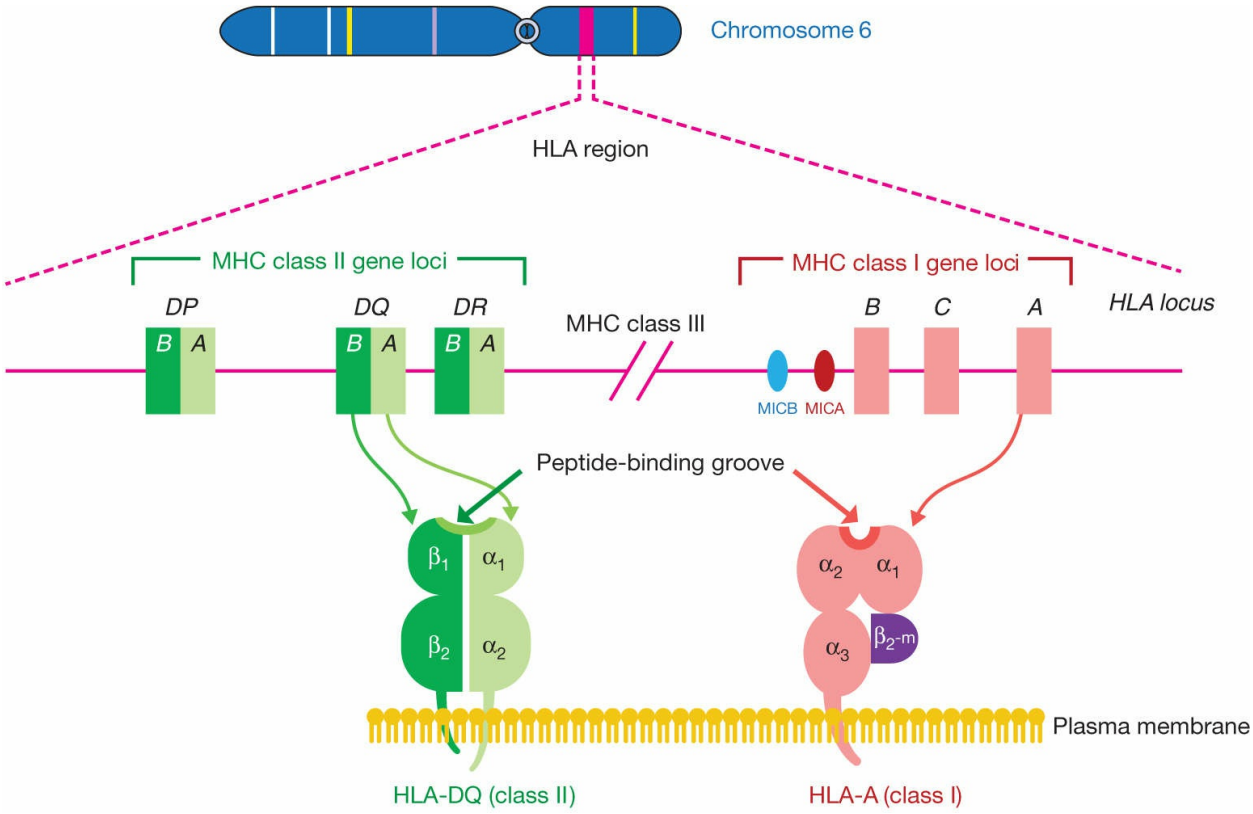

FIGURE 8.1 Major histocompatibility complex, human leukocyte antigen molecules.

Class I HLA antigens (HLA-A, HLA-B, and HLA-C) heterodimers consisting of a polymorphic α or heavy chain (encoded by *HLA-A*, *HLA-B*, and *HLA-C* genes) that is noncovalently bound to a nonpolymorphic light-chain, β2-microglobulin. Class II HLA antigens (HLA-DP, HLA-DQ, and HLA-DR) consist of two noncovalently bound glycoproteins: an α chain (encoded by *DPA1*, *DQA1*, or *DRA1*) and a β chain (encoded by *DPB1*, *DQB1*, or *DRB1*, *DRB3/4/5*). Note: All HLA-DR types have the *DRB1* gene, and some contain an additional functional gene, *DRB3*, *DRB4*, or *DRB5*. The majority of polymorphisms that stimulate alloactivation of the recipient's immune system are located in the α_1 and α_2 domains of HLA class I and α_1 and β_1 domains of HLA class II. Abbreviations: β2-m, β2-microglobulin; MICA, MHC class I–related chain A; MICB, MHC class I–related chain B.

- The primary role of Class I and II HLA is to present foreign antigen to the immune system.
- In kidney transplantation, HLAs are the predominant antigens that form the targets for the immune response.
- Over 25,000 distinct HLA alleles have been defined through DNA sequencing. Despite significant diversity at the level of DNA, the majority of polymorphisms that stimulate alloreactivity of the recipient's immune system are located in the α_1 and α_2 domains of the α chain of HLA class I, and the α_1 and β_1 domains of the α and β chains of HLA class II, respectively (discussed below).

- HLA class I (**Fig. 8.1**):
  - The classic HLA class I antigens (HLA-A, HLA-B, and HLA-C) are heterodimers composed of a polymorphic, membrane-spanning α or heavy chain of 44 kDa with three external domains (α_1, α_2, and α_3), noncovalently bound and stabilized by a nonpolymorphic light-chain, β2-microglobulin (β2-m) of 12 kDa. β2-Microglobulin is encoded by a non-*MHC* gene located on chromosome 15.
  - The HLA class I antigens are encoded by the *HLA-A*, *HLA-B*, and *HLA-C* genes.
  - They are expressed on all nucleated cells and platelets, but not on red blood cells.
  - Class I molecules generally present peptides derived from intracellular proteins (e.g., viral proteins) to cytotoxic $CD8^+$ T cells (**Fig. 8.2**).

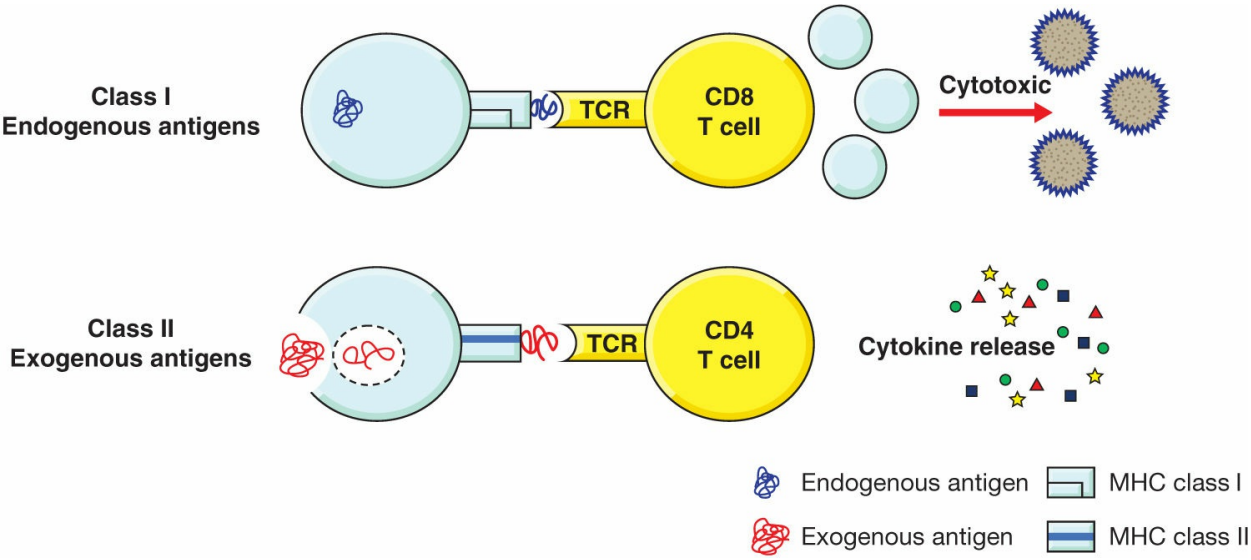

FIGURE 8.2 Antigen presentation. **The endogenous pathway:** Endogenous antigens are digested into peptides and loaded into class I MHC. The MHC–peptide complex is assembled within the cell's endoplasmic reticulum, transported through the Golgi apparatus and expressed on the cell surface where it is recognized by $CD8^+$ TCR, leading to T-cell activation. **Exogenous pathway:** Exogenous antigens are degraded within endosomes and loaded into class II MHC. The MHC–peptide complex is ultimately expressed on the cell surface where it is recognized by $CD4^+$ TCR, leading to T-cell activation. Abbreviations: MHC, major histocompatibility complex; TCR, T-cell receptor.

- HLA class II (**Fig. 8.1**):
  - The classic class II antigens (HLA-DP, HLA-DQ, and HLA-DR) are composed of two membrane-spanning, noncovalently bound

glycoproteins: an α chain of 35 kDa (encoded by *DPA1*, *DQA1*, or *DRA1*) and a β chain of 31 kDa (encoded by *DPB1*, *DQB1*, or *DRB1*).

- The majority of polymorphic sites on class II antigens that stimulate alloactivation of the recipient's immune system are located in the α_1 and β_1 domains of HLA class II.
- HLA class II antigens are constitutively expressed on professional antigen-presenting cells (APCs), including dendritic cells, macrophages, and B lymphocytes. Their expression may be upregulated on activated T cells and epithelial and vascular cells (e.g., renal tubular cells, glomerular endothelium, and capillaries) after exposure to proinflammatory cytokines.
- Class II molecules present larger peptides derived from extracellular proteins (e.g., bacterial proteins) to $CD4^+$ T cells (**Fig. 8.2**).

- Kidney donors and recipients in the United States are typed for HLA-A, HLA-B, HLA-Bw4/6, HLA-C, HLA-DRB1, HLA-DRB3/4/5, HLA-DQB1, HLA-DQA1, and HLA-DPB1.
- *For interested readers:*
  - HLA-B antigens are distinguished by either the immunogenic Bw4 or Bw6 epitope encoded on this antigen between amino acids 77 and 83.
  - The *DRB3*, *DRB4*, or *DRB5* genes encode HLA-DR52, HLA-DR53, and HLA-DR51, respectively. Some *HLA-DRB1* genes are commonly linked to one of these additional *DRB345* genes. For example, DR17 is commonly linked to DR52; DR7 is commonly linked to DR53; DR15 is commonly linked to DR51. However, DR8, and members of the DR1 group, are not commonly linked to a *DRB345* gene (**Fig. 8.3**).

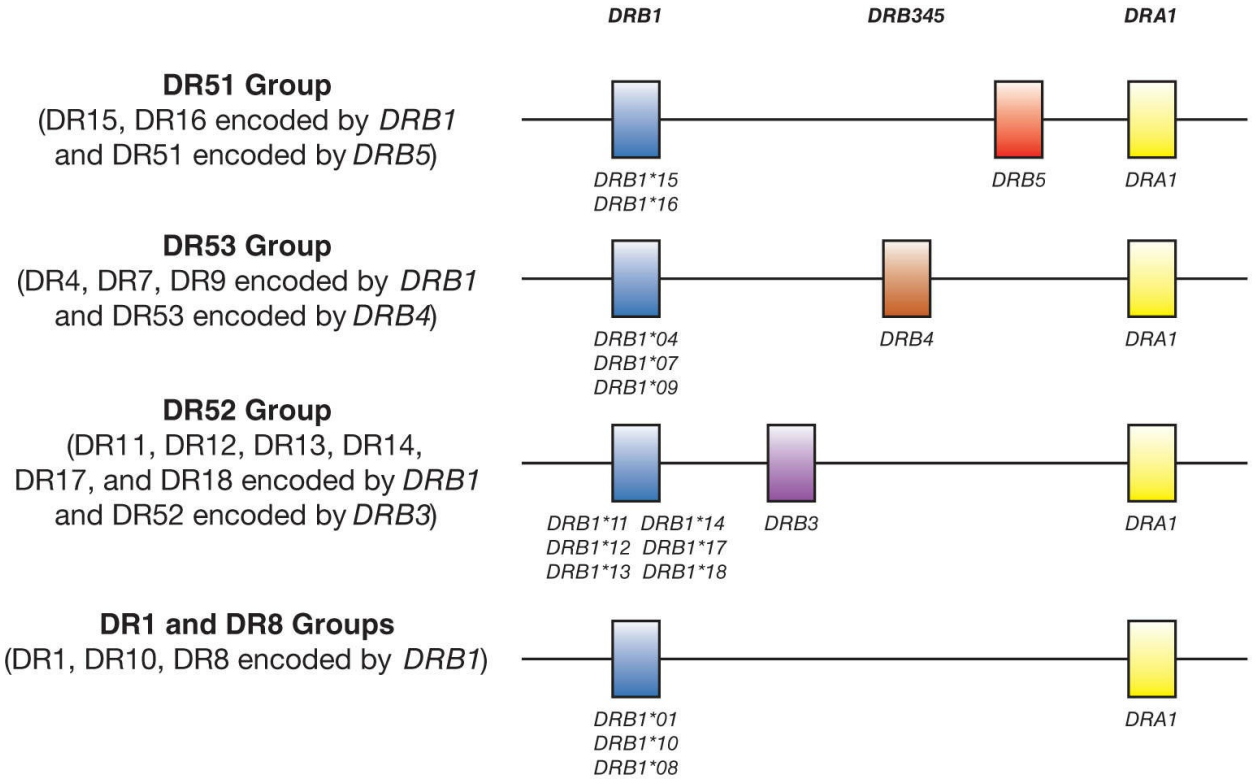

FIGURE 8.3 HLA-DR genomic region (*for interested readers*). Most *DRB1* genes are associated with *DRB3*, *DRB4*, or *DRB5* gene. The *DRB345* genes encode the DR52, DR53, and DR51 antigens, respectively. The DR51 group includes the DR15 and DR16 antigens (encoded by the *DRB1* gene depicted in teal; blue-green) that are commonly associated with the DR51 antigen (encoded by the *DRB5* gene). Antigens in the DR1 and DR8 groups (DR1, DR10, and DR8) are not commonly associated with *DRB345* gene. The majority of polymorphisms in DR antigens are encoded in the *DRB1/345* genes (such as DR15, DR51, or DR17). The protein translated from these genes is noncovalently bound to the protein produced by translation of the *DRA1* gene (depicted in *yellow*).

- Terms used for HLA match (or mismatch) when considering HLA-A, HLA-B, and HLA-DR:
  - *Kidney from a parent or a sibling:* Each parental chromosome 6 provides a linked set of *MHC* genes (called a haplotype) to the offspring in a Mendelian codominance inheritance. Statistically, there is a 25% chance that siblings share the same two haplotypes (two-haplotype match), a 50% chance they share one same haplotype (one-haplotype match), and a 25% chance they do not share any of their parental haplotypes (zero-haplotype match or two-haplotype mismatch). By definition, a child is a haplotype match to each parent unless recombination has occurred (**Fig. 8.4**).
    - Example: a kidney from a parent donor (father or mother) to a

recipient offspring: one-haplotype match.

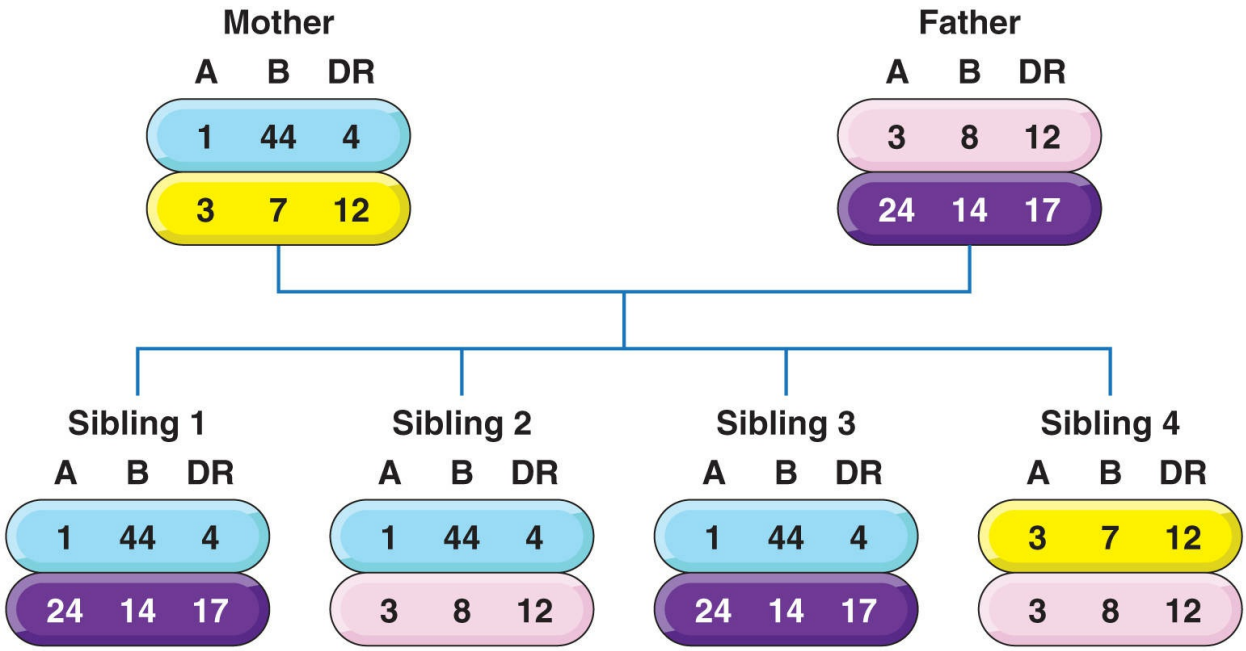

FIGURE 8.4 Inheritance of haplotypes and human leukocyte antigen profile in four theoretical siblings. Sibling 1 is a one-haplotype match to sibling 2, a two-haplotype match to sibling 3, and a zero-haplotype match to sibling 4 (or a two-haplotype *mismatch* to sibling 4).

- Example: a kidney from a sibling donor to sibling recipient: will be either a zero-haplotype match, one-haplotype match, or two-haplotype match (**Fig. 8.4**).

- *Kidney from a deceased donor*
  - Deceased donors are HLA typed at HLA-A, HLA-B, HLA-C, HLA-DRB1/3/4/5, HLA-DQB1, HLA-DQA1, and HLA-DPB1.
  - The United Network for Organ Sharing (UNOS) uses HLA-A, HLA-B, and HLA-DRB1 matching as part of the donor allocation algorithm. In the current UNOS allocation system, points are given to patients without HLA-DR mismatch: 2 points if there are no HLA-DR mismatches with the donor and 1 point if there is one HLA-DR mismatch with the donor. Allocation of “zero mismatch” deceased donor kidneys is based on HLA-A, HLA-B, and HLA-DR matching between patient and donor.
  - Terms used for HLA match (or mismatch) when considering HLA-A, HLA-B, and HLA-DR:

- 0 of 6 HLA-A, HLA-B, HLA-DR mismatch (or a 6 of 6 HLA match)
- 1 of 6 HLA-A, HLA-B, HLA-DR mismatch (or five HLA match)
- 2 of 6 HLA mismatch (or four HLA match)
- 3 of 6 HLA mismatch (or three HLA match)
- 4 of 6 HLA mismatch (or two HLA match)
- 5 of 6 HLA mismatch (or one HLA match)
- 6 of 6 HLA mismatch (or zero HLA match)
- Example: Consider the HLA phenotype of the following recipient/donor pair:
  - Recipient:**A** 1, 2; **B** 8, 51; **DR** 17, 11
  - Donor:**A** 1, 3; **B** 8, 37; **DR** 11, 17
  - The donor is a 2 of 6 HLA mismatch with the recipient (or 4 HLA match).

- Terms used for HLA match (or mismatch) when considering HLA-A, HLA-B, HLA-DR, HLA-DQ, and HLA-DP:
  - A donor/recipient pair with 0 of 6 HLA-A, HLA-B, HLA-DR antigen mismatches can be mismatched at other HLA loci, such as HLA-C, HLA-DQ, HLA-DQA, HLA-DP, or HLA-DPA.
  - Example: Consider the HLA phenotype of the following recipient/donor pair:
    - Recipient:**A** 2, 24; **B** 17, 51; **C** 9, 16; **DR** 11, 4; **DQ** 8, 5; **DP** 23, 28
    - Donor:**A** 2, 24; **B** 17, 51; **C** 10, 16; **DR** 11, 4; **DQ** 7, 5; **DP** 23, 18
    - The donor is a 0 of 6 HLA-A, HLA-B, and HLA-DR antigen mismatch, but is mismatched with the recipient for 3 HLA-C, HLA-DQ, and HLA-DP antigens. Therefore, the donor is also considered a 3 of 12 HLA mismatch with the recipient (or a 9 of 12 HLA match).

- The degree of HLA mismatch between donor and recipient plays an important role in rejection risk and graft loss. In the setting of kidney transplant, fewer HLA mismatches correlate better with graft survival.

One-year graft survival is more related to HLA class II mismatching than to class I mismatching. Repeat HLA mismatch in the setting of reallograft transplantation (second or third transplant) may trigger reactivation of memory cells and production of donor-specific antibody (DSA). DSAs are antibodies that are specific for donor antigens and can be formed prior to transplant due to pregnancy, blood transfusion, or prior transplant (referred to as preformed) or developed posttransplant (referred to as de novo). Further discussion on identification of anti-HLA antibodies is presented in a later section.

HLA-TYPING TECHNIQUES

Serotyping

- HLA serotyping by serologic methods was previously performed using the complement-dependent microlymphocytotoxicity test; however, more accurate and higher resolution molecular typing of DNA (described below) has replaced these methods.
  - The test is performed in a microtiter plate with multiple small wells.
  - Each well is loaded with a selected antiserum, and lymphocytes from the individual to be typed are added. The antiserum is well characterized and contains strong HLA antibodies with known antigen specificity.
  - After an incubation period, complement is added.
  - If anti-HLA antibody from the antiserum binds to its specific HLA target antigen on the cell surface, the complement cascade is activated, leading to cytotoxic injury. A vital dye is added to permit visualization of the proportion of dead cells in each well when the tray is examined under phase-contrast microscopy.
  - The HLA-typing antiserum does not recognize all antigens and is considered low resolution.

DNA Typing

- Generally, DNA isolated from blood anticoagulated with acid citrate dextrose (ACD) is preferred for DNA-based HLA-typing methods; however, any source of cells can serve as a sample for molecular-based

tissue typing, including samples isolated from biopsy.

- DNA-based tissue typing uses standardized probes, primers, or sequencing to determine an individual's HLA tissue type.
- DNA probes hybridize to the complementary DNA nucleotide sequence that is unique to an HLA locus, allele, or groups of alleles. DNA hybridization probe techniques allow identification at the "antigen level" with varying levels of resolution based on the method used (low-to-intermediate resolution), whereas sequencing provides high-resolution "allele-level" HLA typing.
- Molecular-based HLA typing reveals a much greater degree of polymorphism of the individual HLA than that detected by serologic tests.

HLA Nomenclature

- The level of resolution provided by various molecular HLA-typing methods leads to complex HLA nomenclature. Methods that produce low-resolution typing results distinguish an antigen such as "A2," whereas high-resolution probes make it possible to distinguish alleles of that antigen such as "A*02:01:01:02" (**Fig. 8.5**). Intermediate-resolution HLA-typing results may include a "string" of alleles that cannot be ruled out by the method such as A*02:01/03/09/212 (for explanation, see **Fig. 8.5**).

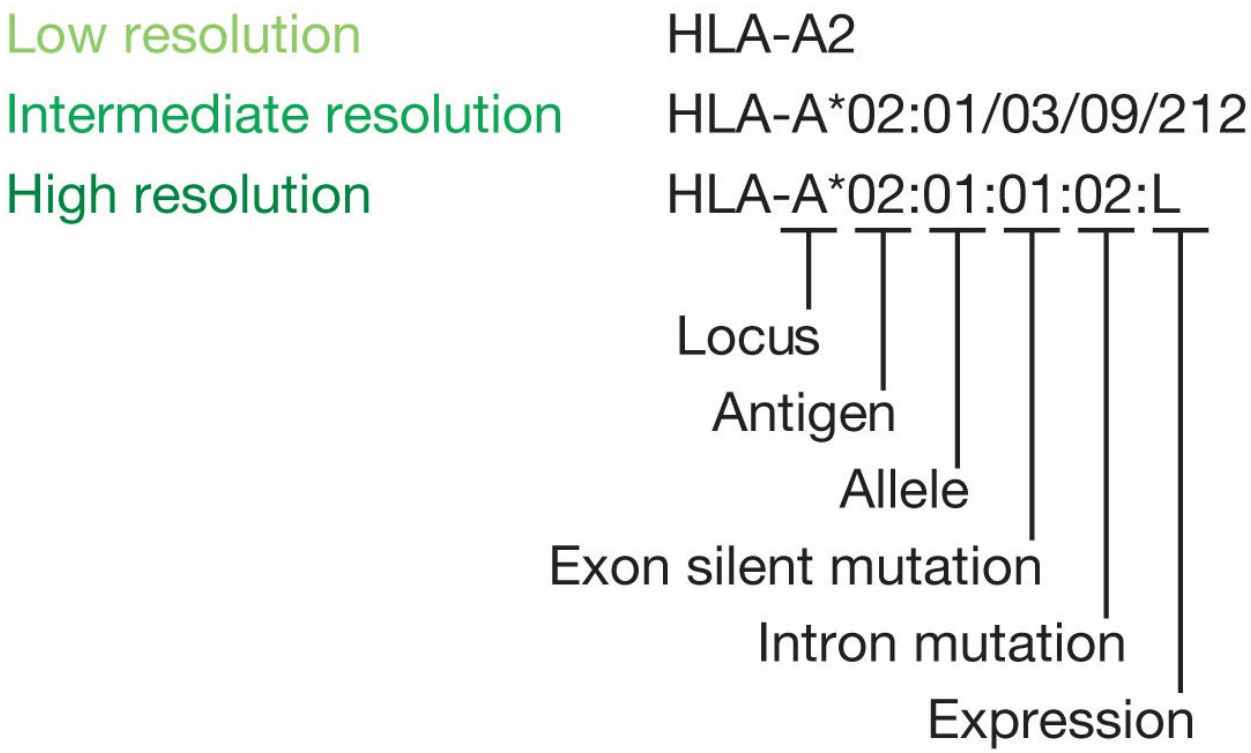

FIGURE 8.5 Human leukocyte antigen (HLA) nomenclature. Low-resolution HLA typing, performed by serology during the early days of tissue typing, defines the HLA locus (e.g., A, B, C, DR) and antigen, shown here as "A2." HLA typing performed by state-of-the-art molecular methods is denoted by "*." Intermediate-resolution HLA typing defines the locus, antigen, and a string of alleles that cannot be ruled out by the method ":01/03/09/212," whereas high-resolution methods define the allele as well as nucleotide substitutions in exons, resulting in silent mutations and intronic mutations. Some typing results include a letter, such as "L," indicating that the antigen is known to be of "low" expression. Intermediate-resolution HLA typing is generally sufficient for solid organ transplant patients and donors, whereas high-resolution typing is required for bone marrow and peripheral blood stem cell transplant.

MINOR HISTOCOMPATIBILITY ANTIGENS

- Minor histocompatibility antigens are small endogenous peptides that occupy the antigen-binding site of the donor MHC molecules. They are encoded by genes located on different chromosomes.
- Minor histocompatibility antigens are usually recognized by $CD8^+$ cytotoxic T cells in the context of self-MHC (indirect allorecognition), leading to graft rejection.
- The nonclassic MHC class I–related chain A (MICA) and MHC class I–related chain B (MICB) are examples of minor antigen expressed on endothelial cells. The *MICA* and *MICB* genes are located on chromosome

6, close to HLA-B (**Fig. 8.1**). However, unlike the classic HLA class I, they do not bind peptides and do not engage with the T-cell receptor. Antibodies against MICA have been shown to be associated with antibody-mediated rejection (ABMR).

- While transplant from an identical twin may be accomplished in the context of no immunosuppression, two-haplotype matched siblings (fraternal twins or non-twin siblings) require immunosuppression (albeit at reduced dose) to prevent rejection due to differences in minor histocompatibility antigens.

NON-HLAs

- Non-HLAs are antigens expressed on the allograft endothelium and are distinct from HLA.
- Non-HLAs can be classified as:
  - Alloantigens, such as MICA and MICB (discussed earlier)
  - Tissue-specific autoantigens, such as the angiotensin II type 1 receptor (AT1R), anti–endothelin-1 type A receptor (ETAR), vimentin, cardiac myosin, collagen V, and agrin
- Antibodies to non-HLAs are associated with poor graft outcomes. Currently, clinical tests are available to test for antibodies to MICA, AT1R, and reactivity to antigens expressed on donor endothelial cells. For example, the endothelial cell crossmatch identifies non-HLA immunoglobulin G (IgG) antibodies reactive to antigens expressed on endothelial cells. The XM-ONE crossmatch identifies non-HLA IgG and IgM antibodies that bind to donor endothelial precursor cells. Identification of antibodies to non-HLAs that may be associated with graft rejection is an area of intense research because graft rejection and graft loss can occur in the absence of detectable HLA DSAs.

ALLORECOGNITION PATHWAYS: DIRECT, INDIRECT, AND SEMIDIRECT ALLORECOGNITION

- In the direct pathway, recipient T cells recognize intact allogeneic HLAs expressed by donor cells (**Fig. 8.6**).

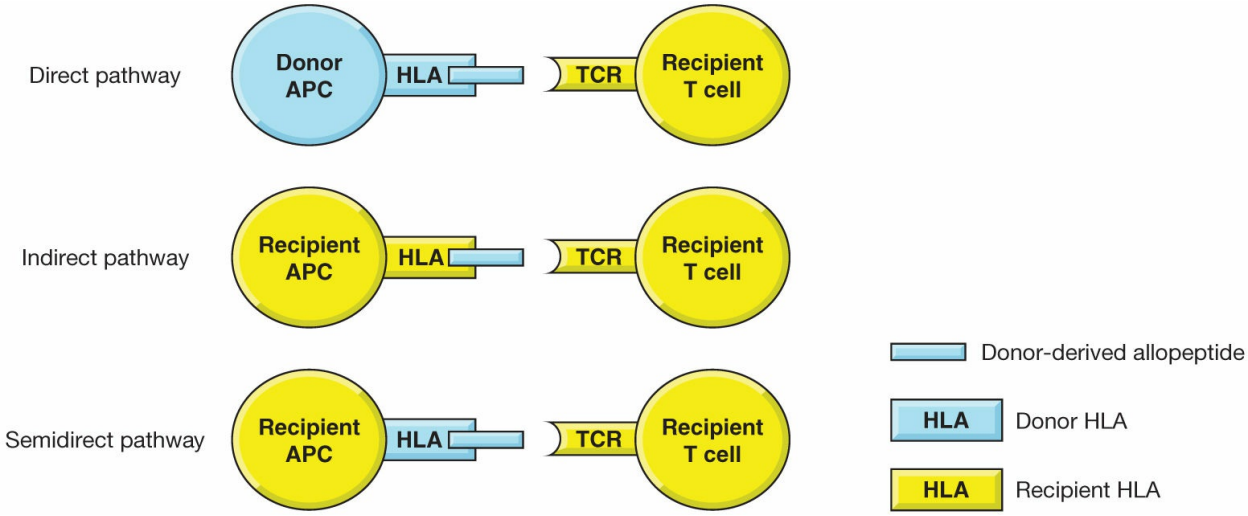

FIGURE 8.6 Direct, indirect, and semidirect allorecognition pathways. In the direct allorecognition pathway, recipient's T cells recognize intact allogeneic HLAs expressed by donor cells. In the indirect pathway, the recipient's T cells recognize peptides derived from donor HLAs that are presented by recipient APCs. In the semidirect pathway, intact donor HLA is transferred to recipient APC and presents donor antigen to recipient T cells. Abbreviations: APCs, antigen-presenting cells; HLA, human leukocyte antigen; TCR, T-cell receptor.

- In the indirect pathway, recipient T cells recognize peptides derived from donor HLAs presented by recipient APCs (**Fig. 8.6**).
- In the semidirect way, intact donor HLAs are presented on the recipient APCs (through either membrane exchange or exosome uptake) to the recipient T cells (**Fig. 8.6**).
- Acute rejection of an allograft is primarily dependent on direct allorecognition, whereas the indirect pathway may play a greater role in chronic rejection thought to be due to the continuous shedding of donor MHC–allopeptide complexes from the graft. Such complexes are processed by recipient APCs and presented as allopeptide to recipient T cells.
- The semidirect pathway also plays an important role in chronic allograft rejection. However, the relative contribution of the direct, indirect, and semidirect allorecognition pathways to the alloresponse in the early and late posttransplantation period remains to be elucidated.

HLA ALLOSENSITIZATION

- More than 30% of patients awaiting a kidney transplant in the United

States are sensitized to HLAs.

- Anti-HLA antibodies are formed after exposure to allogeneic HLAs through pregnancy, blood transfusion, or prior transplantation.
- HLA sensitization can also develop following immune activation in patients with implantable ventricular assist devices, infections, or following a proinflammatory event such as surgery.

- Alloantibody specificities:
  - The specificities of HLA antibodies an individual produces upon exposure to allogeneic HLA molecules are influenced by the individual's immunologic history as well as the individual's HLA type.
  - Antibodies can be directed against "private" HLA specificities or "public" HLA specificities.
    - Antibodies to "private" specificities recognize an epitope that is unique to one particular HLA molecule.
    - Antibodies to "public" specificities recognize an epitope that is shared by more than one HLA molecule. HLAs that share epitopes can be grouped into the major cross-reactive groups, also known as CREGs (e.g., a patient's serum containing HLA-A2 antibodies may react with HLA-A2 as well as HLA-A68, HLA-A69, HLA-B57, and HLA-B58 because these antigens share amino acid sequence motifs with HLA-A2).

TECHNIQUES FOR DETECTION OF ANTI-HLA ANTIBODIES: GENERAL CONCEPT

- Preformed HLA antibodies of the IgG isotype may prohibit successful organ transplantation.
- The tests used to identify anti-HLA antibodies are based on assessment of reactions of anti-HLA IgG subclass antibodies present in the patient's serum with well-characterized panels of donor lymphocytes (cell-based screening—complement-dependent cytotoxicity [CDC]) or HLAs coupled to microspheres (solid-phase screening—phenotype or single-antigen Luminex bead-based assays). Patient's serum can be treated with dithiothreitol (DTT) to remove or reduce the effects of confounding

factors, such as antibody of the IgM subclass. IgM antibody is often an autoantibody detected in sera of patients with autoimmune disorders, such as systemic lupus erythematosus.

- Cell-based assays can detect strong HLA antibody but do not always allow identification of specific antigens to which the patient has antibodies, especially in cases of broad sensitization.
- Solid-phase, bead-based Luminex technology revolutionized the field of HLA antibody identification, allowing for superior sensitivity and specificity that is not possible with cell-based assays. Luminex-based antibody detection is used to identify HLA antibodies pretransplant to guide donor selection and risk assessment at the time of transplant and in posttransplant immune monitoring to identify DSA and correlate to biopsy findings when rejection is suspected.
- Single-antigen C1q-binding assay is a modification of the single-antigen Luminex assay (discussed in a later section).

CELL-BASED CDC PANEL REACTIVE ANTIBODY

- The cross section of donors that a patient displays strong HLA DSA to, and therefore would be avoided, can be understood by incubating the patient's serum with a panel of lymphocytes that display HLAs representative of the local donor population in the cell-based cytotoxic panel reactive antibody (PRA) test.
- In the cell-based cytotoxic PRA, the patient's serum is incubated with a panel of HLA-typed T or B lymphocytes that represent the local donor pool. HLA antibody in the serum binds the cell, and unbound HLA antibody is removed. Complement and a vital dye are then added. One molecule of complement binds to two bound HLA antibodies, and the complement cascade is initiated, resulting in perforation of the cell membrane by the membrane attack complex (MAC) and cell lysis. Qualitative/semiquantitative results are read microscopically. Prolonging the complement incubation time increases the sensitivity of the test and enhances the detection of low-titer antibodies.
- In a positive result, the cells take up the vital dye, indicating the presence

of *strong, complement-binding HLA DSA* and initiation of the complement cascade, resulting in cell death.

- The percentage of positive cells over the panel, referred to as percentage panel reactive antibody (%PRA), is calculated by dividing the number of positive wells (indicated by dead cells) by the total number of wells on the panel.
- Separate panels of T and B lymphocytes identify antibodies to HLA class I or II.
- The %PRA estimates the percentage of organ donors who would be crossmatch incompatible with a transplant candidate in a given donor pool. A PRA of 80% on the HLA class I panel of cells indicates that patient has a 20% chance to receive a negative cytotoxic crossmatch.
- A limitation of the assay is the inability to determine antibody specificities in broadly sensitized patients.

SOLID-PHASE LUMINEX PRA

- Solid-phase assays employing Luminex technology use HLA-coated beads to detect and identify preformed HLA antibodies before transplantation as well as to monitor for de novo development of anti-HLA antibodies after transplantation.
- Generally, two platforms are used to identify HLA antibodies:
  - Screening or phenotype beads are engineered to display HLA class I or II antigens in their *native conformation*. These are produced by affixing the cell membrane harvested from a transformed cell line onto a microsphere. Each screening bead displays two haplotypes of HLAs. A "panel" of beads constructed from an array of cells bearing various HLA phenotypes is representative of the donor pool (**Fig. 8.7A**).
  - Single-antigen beads differ in that each microsphere is affixed to only one single HLA molecule (**Fig. 8.7B**). Instead of harvested from cell lines, the HLA molecules are *recombinantly generated*.

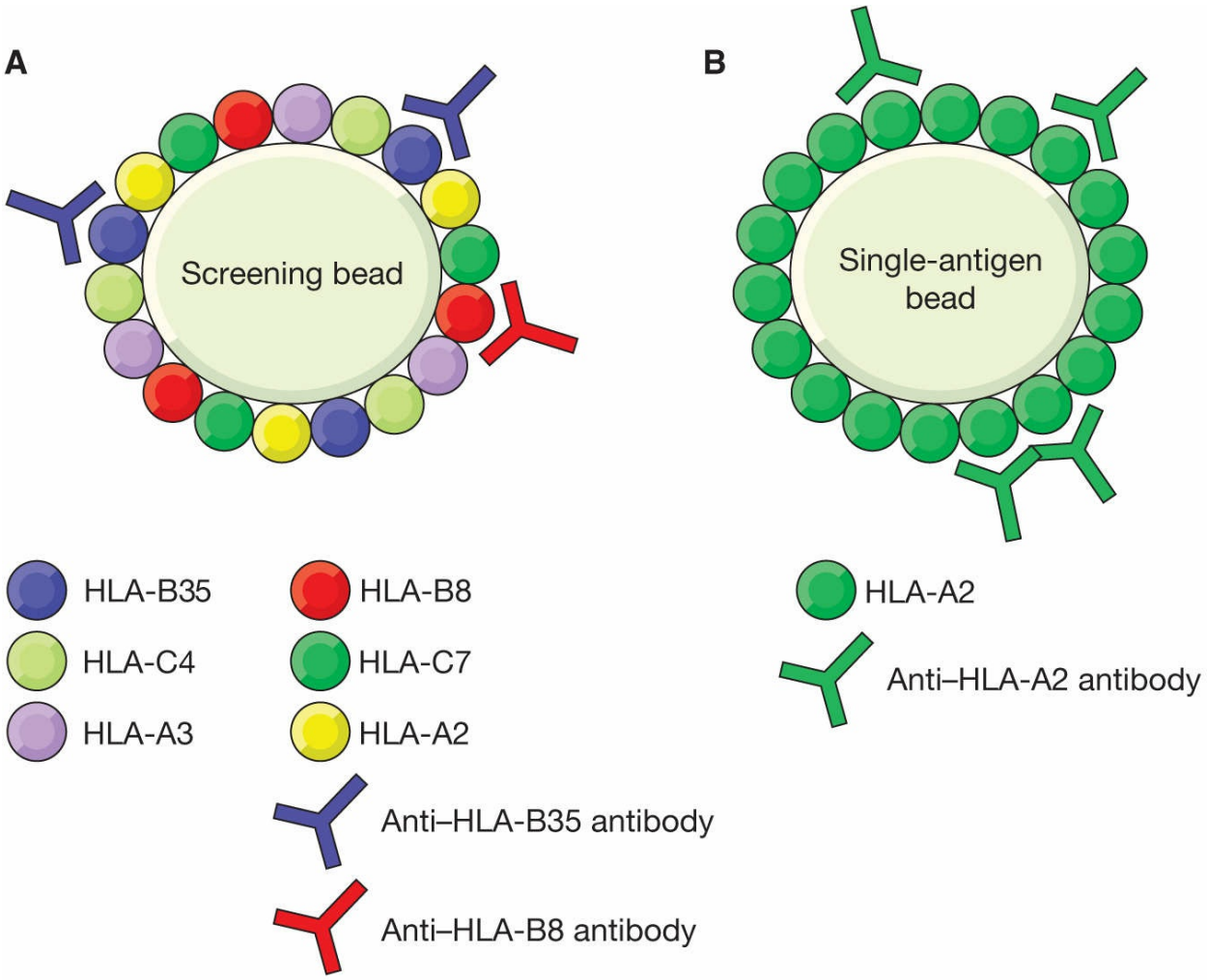

FIGURE 8.7 Solid-phase human leukocyte antigen–antibody detection methods. **A.** Screening/phenotype beads: Microspheres are coated with two haplotypes of human leukocyte antigen (HLA) class I or class II antigens. Here, the HLA-A3, HLA-B35, HLA-C4, HLA-A2, HLA-B8, and HLA-C7 haplotypes are isolated from the surface of transformed cell lines and affixed to microspheres in their native conformation. The panel of beads is constructed from an array of cells bearing various HLA phenotypes representative of the donor pool. In this example, the bead identifies HLA antibody to B35 and B8. **B.** Single-antigen beads: A panel of single-antigen beads is constructed such that each bead contains one single recombinant antigen. In this example, single HLA-A2 antigen is affixed to the bead.

- To identify HLA antibodies, the patient's serum is mixed with antigen-coated beads. HLA antibodies in the serum bind the beads. The beads are then washed, and an anti-IgG detection reagent is added. HLA antibody bound to the beads is identified on a Luminex analyzer (for **Single-Antigen Beads**, see **Fig. 8.8**).

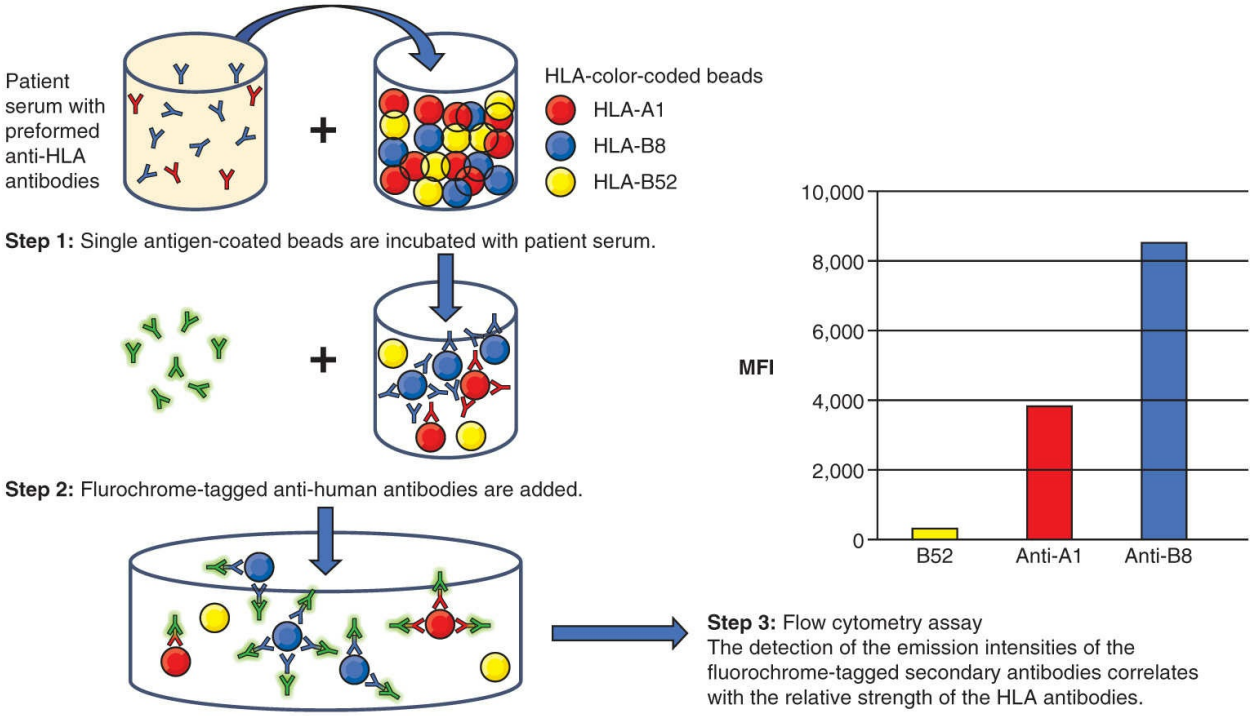

FIGURE 8.8 The single-antigen bead assay. Patient serum is mixed with single-antigen beads. Preformed antibodies in the serum bind the beads and are detected with a fluorescent detection reagent on a Luminex analyzer. The strength of the antibodies correlates quantitatively to the mean fluorescence intensity (MFI). Abbreviation: HLA, human leukocyte antigen.

- The results of the assays are semiquantitative as the mean fluorescence intensity (MFI) correlates with the strength of the anti-HLA antibody but is limited to the dynamic range of the test.
- The percentage of microspheres on the panel that react with HLA antibodies in the patient's serum is referred to as percentage panel reactive antibody (%PRA).
- Both platforms have known advantages and disadvantages. A balanced approach may be to test patient sera using both platforms to accurately establish the patient's immunologic profile.
  - Single-antigen bead
    - Advantages:
      - Most sensitive and specific platform for identifying HLA antibodies. Identifies antibodies to HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DR51/52/53, HLA-DQ, HLA-DQA, HLA-DP, and HLA-DPA, even when the patient is very broadly sensitized

- Disadvantages:
  - Prone to false-positive reactions due to expression of cryptic epitopes that are generated due to misfolding of the recombinant proteins
  - Can generate false-negative, or falsely low, antibody strength when there are interfering factors in the sera or when antibody is in strong excess (referred to as prozone, discussed below). To minimize the potential for interference, sera can be treated with reducing agents such as DTT or ethylenediaminetetraacetic acid (EDTA) or treated with other methods such as heat inactivation.

- Screening bead
  - Advantages:
    - Generally less costly than single-antigen bead test
    - HLAs are in their native conformation and can, therefore, be used to validate suspicious results identified in the single-antigen bead test that may be due to cryptic epitopes.
  - Disadvantages:
    - Less sensitive than single-antigen beads
    - Do not identify antibodies to HLA-C, HLA-DQA, HLA-DP, or HLA-DR51/52/53
    - Less specific than single-antigen beads and do not permit accurate identification of antibody specificities when the patient is broadly sensitized

- Both the single-antigen bead test and the screening beads are limited by:
  - The antigens encompassed in the panel
  - Identification of total IgG, and not subclass specific ($IgG_{1–4}$), HLA antibodies
  - The dynamic range of the Luminex analyzer. In the single-antigen bead test, saturation of the beads occurs around 12,000 to 15,000 MFI. Antibody strength above this range cannot be accurately assessed without modifications to the test (discussion is beyond the scope of this chapter. However, for interested readers, see **Modifications of the Single-Antigen Bead Assay** section).

Unacceptable HLAs and Calculated PRA

- Unacceptable HLAs are HLAs that a transplant program is unwilling to cross. They are defined by:
  - Transplant center practice
  - The strength of the HLA antibodies present in the patient's serum as measured by solid-phase assay
  - The immunologic history of the transplant patient
- Transplant centers define unacceptable antigens by the MFI (strength) of an HLA antibody to that antigen. Unacceptable antigens are then entered into UNet to prevent donor offers if the donor displays that antigen. For instance, if a patient has a strong antibody (high MFI) to HLA-B8 and HLA-B8 is listed as an unacceptable antigen, potential donors expressing HLA-B8 will not be offered to that patient due to a predicted positive crossmatch or unacceptable risk (i.e., HLA-B8 is an "unacceptable HLA").
- Entry of unacceptable antigens into UNet results in a calculated percentage PRA (cPRA), indicating the percentage of donors to which the patient is unacceptably sensitized in the UNOS donor pool. Example: A cPRA of 80% means that 80% of donors will not be acceptable to the patient.
- cPRA is calculated based on known HLA frequencies from the actual UNOS donor pool; therefore, it permits a uniform measurement of sensitization for all patients across geographic regions. The cPRA calculator based on HLA frequencies found in the US donor population is available at: https://optn.transplant.hrsa.gov/resources/allocation-calculators/cpra-calculator.
  - Example: If a patient has antibodies against the HLA-A2 antigen, which is found in 48% of the US population, the patient's cPRA would be 48%. If the patient has antibodies against the B8 antigen, which is present in 17 percent of the population, the cPRA would be 17%. If the patient has antibodies against ***both*** the HLA-A2 and B8 antigens, the cPRA would be 58%. The resulting cPRA is less than the frequency of the HLA-A2 and B8 antigens combined because some donors express both A2 and B8 antigens.
- Because unacceptable antigens are defined by transplant center practice,

patients who are listed at more than one center may have two different cPRAs.

- Patients with DSA or anti-HLA antibodies in the serum have been shown to have poorer graft survival compared with those without DSA or anti-HLAs.

Modifications of the Single-Antigen Bead Assay

NOTE This section is for interested readers. Readers must have basic knowledge about the concept of antibody excess and prozone effect.

- As noted in the previous section, one limitation of the single-antigen bead assay is the limited dynamic range of the Luminex analyzer that results in the inability to accurately assess the strength of strong antibodies. This limitation can affect the clinical interpretation of test results. For example, the efficacy of plasmapheresis-based desensitization therapy on strong antibodies can be difficult to assess.
  - Single-antigen testing with serum dilution can, therefore, be used to aid in interpretation of results. Retesting of diluted sera can more accurately assess the strengths of strong antibodies that are saturating single-antigen beads.
  - Example: An antibody identified at baseline to A2 in the single-antigen bead test at 18,000 MFI in undiluted sera may appear unchanged after serial rounds of plasmapheresis (10,500 MFI; Table 8.2). However, single-antigen testing of the baseline and post-plasmapheresis samples with dilution may show that the same antibody in the post-plasmapheresis sample was significantly less strong at 2,500 MFI (Table 8.2). A significant change in the single-antigen bead test is considered to be at least a 50% change in MFI. (The C1q modification of the single-antigen bead test is discussed below.)

Table 8.2 Single-antigen bead antibody assessment with serum dilution and C1q testing

	Baseline Serum			Post-Plasmapheresis Serum		
HLA	Undiluted	Diluted 1:10 MFI	C1q	Undiluted	Diluted 1:10 MFI	C1q
A2	18,000	14,000	Positive	10,500	2,500	Negative
A68	8,500	15,500	Positive[a]	16,000	13,000	Positive

[a]Testing of this baseline sera indicates prozone of A68 antibody in the undiluted serum.
Abbreviations: HLA, human leukocyte antigen; MFI, mean fluorescence intensity.

- Another noted limitation of the single-antigen bead assay is false-negative, or falsely low, antibody strength due to antibody excess. This phenomenon is referred to as *prozone*.
  - False-negative/low antibody strength is identified when the results of testing methods are unexpectedly divergent. For example, single-antigen bead testing identified a weak antibody, but that same sera tested by another method identified a strong antibody.
  - Single antigen with serum dilution, or single-antigen C1q testing, can be used as a supplementary method to rule out prozone (discussed below).
- Single-antigen C1q:
  - The single-antigen C1q test is a modification of the single-antigen class I and class II Luminex assay that detects the ability of HLA antibodies to bind C1q (the first component of the classic complement cascade) after incubation with Luminex beads. The presence of bound complement is detected using a fluorescent-conjugated anti-C1q antibody. The C1q-binding assay enables characterization of strong antibodies that are potentially able to fix complement in the CDC assay discussed above.
  - Antibodies first identified to be weak/moderate in strength in the single-antigen bead test and significantly stronger after serum dilution, or positive in the single-antigen C1q test, indicate prozone in the first test. Importantly, the single-antigen C1q test is generally performed on undiluted serum.
  - Example: An antibody to A68 is identified at 8,500 MFI in the single-antigen bead test (Table 8.2). Dilution of the serum at 1:10 shows the strength of the antibody to be much stronger (15,000 MFI) and C1q positive in the modification of the test. Taken together, these results indicate that the antibody is “prozoned” in the single-antigen bead test

and much stronger than 8,500 MFI. In this example, after repeated rounds of plasmapheresis-based desensitization therapy, the strength of the A68 antibody is identified at 16,000 MFI in undiluted serum. Dilution of the serum does not result in a significant change in MFI (13,000 MFI), and the antibody remains C1q positive. The antibody is no longer referred to as prozoned, but is still very strong.

- Although HLA DSA of the IgG3 and IgG4 subclasses have been suggested to be associated with a higher incidence of ABMR, current solid-phase antibody detection methods routinely used in clinical laboratories identify total IgG HLA antibodies.

VIRTUAL CROSSMATCH

- A virtual crossmatch is a prediction of a physical crossmatch result at the time of a donor offer. Virtual crossmatching also allows for a risk assessment prior to transplant. Because the UNOS National Kidney Allocation System (KAS) allocates organs to patients outside the donor service area with regional and national priority, the virtual crossmatch is used to speed allocation.
- A virtual crossmatch requires:
  - Complete molecular HLA typing of the donor (HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DRB3/4/5, HLA-DQB1, HLA-DQA1, and HLA-DPB1)
  - Molecular HLA typing of the recipient
  - The recipient's history of solid-phase anti-HLA antibody specificities
- At the time of virtual crossmatch, physical crossmatch results can be accurately predicted based on the strength (MFI) of preformed DSA. Accurate virtual crossmatch is important to help in facilitating import of deceased donor kidneys from outside a patient's local donor service area to reduce cold ischemia time and speed allocation.
- At the time of a virtual crossmatch, a risk assessment can also be performed. The patient's history of sensitizing events (pregnancy, transfusion, prior transplant) is essential to provide an accurate risk assessment. Donor factors, such as quality and cold ischemic time, are also

considered.

- The national KAS allocates donor organs to patients outside the donor's local area according to policy. Currently, patients who are very highly sensitized with a cPRA of 99% or 100% are eligible for the regional and national share of donor offers.
- Acceptance or decline of the regional or national offer is made, in part, on the interpretation of a virtual crossmatch.
- **Figure 8.9** compares virtual crossmatch with physical crossmatch.

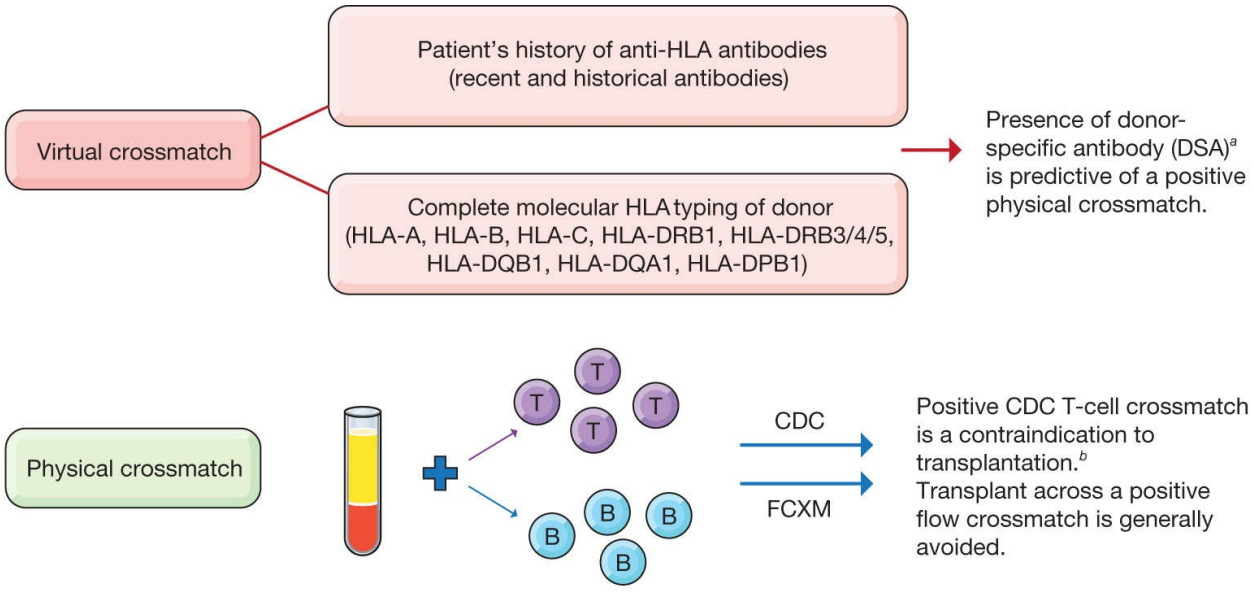

FIGURE 8.9 Virtual crossmatch versus physical crossmatch. Virtual crossmatch uses the patient's human leukocyte antigen (HLA) and immunologic history, and the donor's HLA typing, to predict the results of a physical crossmatch and provide a risk assessment prior to transplant.

[a]Discussion of DSA MFI threshold for the prediction of a positive crossmatch is beyond the scope of this chapter.

[b]Transplantation in the face of a positive B-cell crossmatch and detectable DSA should be avoided

Abbreviations: CDC, complement-dependent cytotoxicity; FCXM: flow cytometry crossmatch; MFI, mean fluorescence intensity.

PHYSICAL CROSSMATCH

- The physical crossmatch test is generally performed prior, or perioperative, to transplantation to determine whether the patient has HLA antibody directed against a potential donor, also known as DSA.
- Testing method is determined by center practice, but generally includes the

flow and/or CDC crossmatch (Table 8.3).

Table 8.3 Different crossmatch methods

	Methods	Comments
Standard complement-dependent cytotoxic (CDC) crossmatch	1. Recipient serum mixed with donor lymphocytes (T or B cells) 2. Complement and vital dye are added. • If recipient antidonor antibodies bind to the antigens on the donor lymphocytes, added complement will kill donor lymphocytes. • Cells that are killed are evaluated microscopically using fluorescent dyes that identify live and dead cells. Results are recorded using a semiquantitative score (e.g., negative, weakly positive, strongly positive).	Detect high titer of IgG HLA antibodies that fix complement Serum can be treated with DTT to inactivate IgM. A positive CDC T-cell crossmatch is a contraindication to kidney transplantation. Transplant across a positive flow crossmatch is generally avoided (FCXM is discussed below).
AHG-augmented CDC crossmatch	1. Recipient serum mixed with donor lymphocytes 2. AHG reagent added 3. Complement and vital dye are added	Adding AHG or prolonging the incubation time increases the sensitivity of the test and enhances the detection of low-titer antibodies.
Flow cytometry crossmatch (FCXM)	1. Recipient serum mixed with donor lymphocytes 2. Fluorochrome-coated antihuman IgG detection reagent is added followed by CD3 and CD19 antibodies to distinguish T and B cells. 3. Assess with flow cytometer	Most sensitive crossmatch test. Identifies anti-HLA IgG donor-specific antibodies binding to T and B lymphocytes. Cells can be treated with pronase[a] to increase the sensitivity or remove Fc receptors or the CD20 molecule to produce more accurate results in some settings.

[a]False-positive FCXMs are often caused by nonspecific immunoglobulin binding to Fc receptors on lymphocytes. Patients treated with antibodies such as rituximab (an anti-CD20 antibody) may also have false-positive FCXM results due to the presence of the administered antibody in their serum. Pronase is a nonspecific peptidase that preferably digests Fc receptors and other cell-surface proteins (including CD20) without substantially destroying HLA molecules under certain conditions.

Abbreviations: AHG, antihuman globulin; CDC, complement-dependent cytotoxicity; DTT,

dithiothreitol; HLA, human leukocyte antigen; IgG, immunoglobulin G; IgM, immunoglobulin M.

- The CDC crossmatch test is used to determine the presence of preformed high-titer IgG HLA DSA in patient serum.
- The potential donor's lymphocytes serve as the target cells for the patient's serum.
  - The CDC assay was described previously. Briefly, the patient's serum is incubated with donor T and B lymphocytes to allow HLA DSA to bind the cells. Unbound antibody is washed away, and complement and vital dye are added. Cell death is visually assessed under phase-contrast microscopy.
  - A positive CDC crossmatch due to IgG antibodies directed against HLA class I antigens (HLA-A, HLA-B, HLA-C) is a contraindication to transplantation.
  - A positive T- or B-cell CDC test in the absence of strong HLA DSA is likely due to the presence of confounding antibodies of the IgM isotype in the patient's sera. Treatment of the patient's serum with DTT inactivates IgM by eliminating the disulfide bonds required to give IgM its shape, therefore removing the confounder from the test. Positive B-cell CDC assays are found in the context of rituximab therapy. Rituximab is a chimeric antibody composed of a murine anti-CD20 variable region and the human IgG1k constant region. DTT treatment of the sera does not remove the binding capacity of rituximab in the CDC assay. Therefore, close communication between the clinical program and HLA laboratory is essential for crossmatch interpretation.
  - The sensitivity of the CDC assay is increased with the addition of antihuman globulin.
- The flow crossmatch test is more sensitive compared to the CDC crossmatch for HLA antibody detection.
  - Antibodies directed against HLA class I can result in a positive crossmatch with both B and T cells.
  - Antibodies directed against class II will only cause a positive crossmatch with B lymphocytes.
  - Therefore, a positive T-cell flow crossmatch is an indication of anti–

class I DSA in the patient, whereas a positive B-cell crossmatch could be caused by either anti–class I or anti–class II DSA.

- Positive B flow crossmatches observed in the absence of DSA can be due to nonspecific antibody binding to Fc receptors on the surface of B cells or the presence of therapeutic biologicals such as rituximab.
- Pronase treatment of lymphocytes prior to flow crossmatch enzymatically cleaves off Fc receptors and the similarly shaped CD20 molecule while leaving the HLA molecule intact, therefore increasing the sensitivity of the B flow crossmatch and removing confounding factors.

- The different pretransplantation crossmatch methods are summarized in Table 8.3.

IMMUNOLOGIC EVALUATION OF THE TRANSPLANT CANDIDATE

- Evaluation of a transplant candidate is according to center practice but generally will include molecular HLA typing of the patient and detection of HLA antibodies by solid-phase and/or cell-based methods.
- The patient's ABO and HLA typing and unacceptable antigens are entered into the UNOS national KAS, with additional transplant candidate information. (The UNOS KAS is discussed in **Chapter 9 Kidney Transplantation**.)
- The frequency of solid-phase antibody testing and subsequent update of unacceptable antigens is according to transplant center practice. Testing frequency may differ based on the sensitization or risk category of the patient.
- The average wait time until a patient begins frequently receiving donor offers differs by UNOS region.
- When a donor becomes available, the donor blood is sent to an immunogenetics laboratory for HLA typing. The donor's HLA typing is entered into UNOS DonorNet, and a match run is performed.
- Due to the structure of the UNOS KAS, a very highly sensitized patient in a UNOS region outside the donor's service area may receive the organ

offer.

A virtual crossmatch and risk assessment are performed. If the patient does not display any DSA to the donor in the most recent sera, the physical crossmatch is predicted to be negative with that serum. Alternatively, the patient may have preformed HLA DSA to the donor in the current sera. Based on the strength of the DSA, the physical crossmatch may be predicted to be positive. The predicted strength of the physical crossmatch, patient's clinical status and history of sensitizing events, and donor factors such as organ quality and cold ischemic time are taken into account. The patient's clinical providers will accept or decline the donor based on the collected data. If the donor is accepted, the organ is imported/shipped to the patient's transplant center and the patient is prepared for transplant. Generally, a pretransplant physical crossmatch is performed using cells isolated from donor blood or tissue shipped with the organ.

- After the transplant, the patient is removed from UNET.
- Suggested algorithm for pretransplant immune monitoring is shown in **Figure 8.10**.

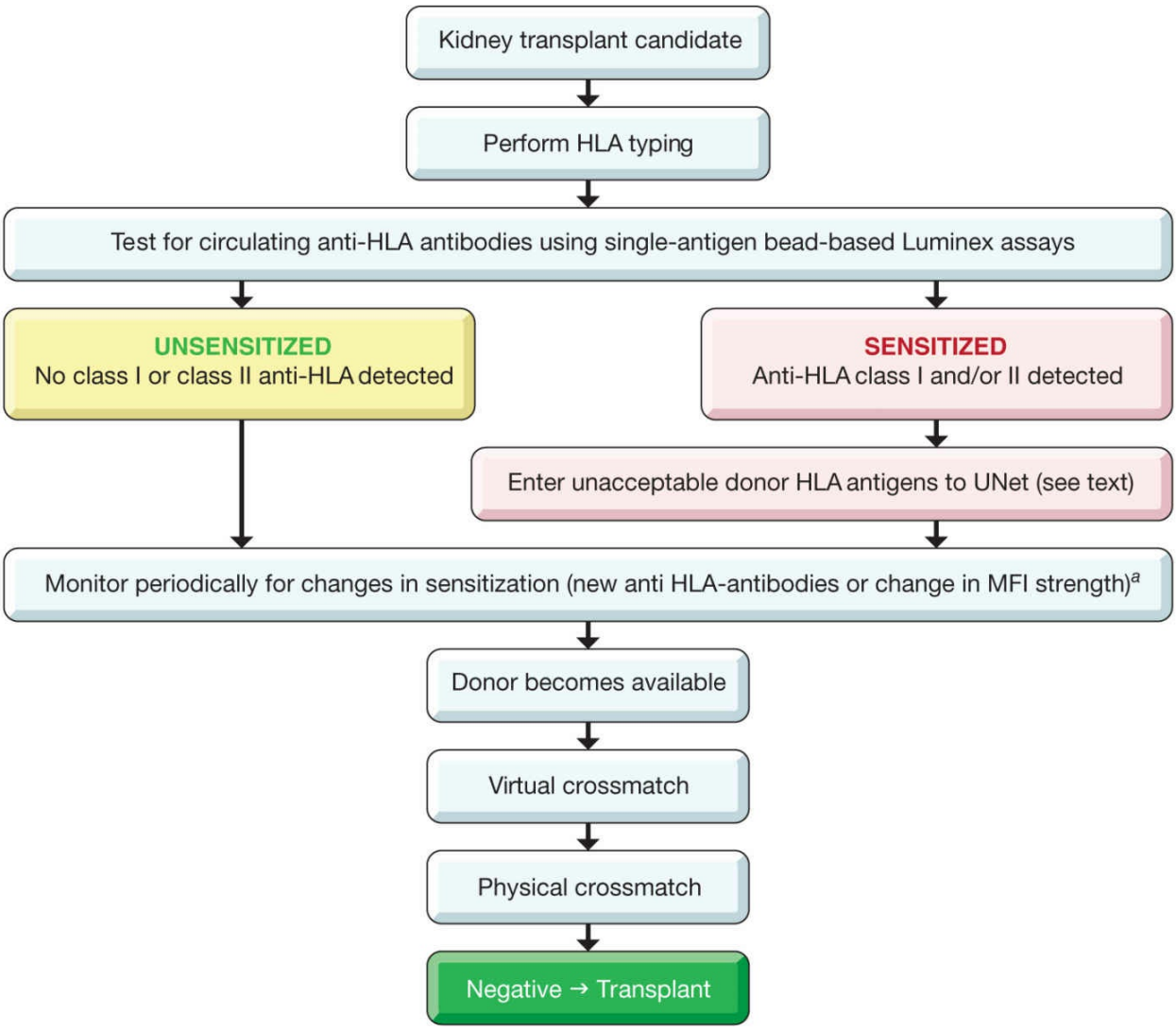

FIGURE 8.10 Suggested algorithm for pretransplant immune monitoring.
[a]Obtain blood sample from patient every 3 months (or per center protocol) if not yet transplanted.
Abbreviation: HLA, human leukocyte antigen; MFI, mean fluorescence intensity.

- The patient is followed after transplant with solid-phase antibody detection methods to identify and longitudinally track the presence and strength of DSA that were either present prior to transplant or developed de novo posttransplant.

Access the eBook for self-assessment questions.

CHAPTER 9

Kidney Transplantation

Phuong-Thu T. Pham, Phuong-Chi T. Pham, Michelle J. Hickey, Jonathan E. Zuckerman

EVALUATION OF THE POTENTIAL KIDNEY TRANSPLANT CANDIDATE

- Kidney transplantation is the treatment of choice for suitable candidates with end-stage kidney disease (ESKD).
  - It confers survival advantage over remaining on dialysis across all ages and in both diabetic and nondiabetic transplant recipients.
  - It offers long-term economic benefits compared to dialysis.
  - Although there has been no consensus on the upper age limit at which patients are accepted for kidney transplantation, 80 years of age has been suggested to be a sensible biologic limit. Suitability for transplantation should be assessed on a case-by-case basis.
- The routine assessment of a kidney transplant candidate includes thorough history and physical examination, psychosocial evaluation, and psychiatric evaluation as needed. In addition, patients should attend a patient education session and undergo a number of routine laboratory testing and imaging studies as outlined in Table 9.1.

Table 9.1 Pretransplant routine laboratory testing and imaging studies

Laboratory evaluation
Comprehensive metabolic panel

Complete blood count with platelets

Prothrombin time panel (INR and PTT)

Urinalysis and urine culture

Hepatitis B (surface Ag, IgM and IgG core Ab, and surface Ab)

HCV Ab screening (if positive, check PCR confirmatory test)

HIV-1/HIV-2 Ag/Ab screening, fourth generation with reflex confirmation

CMV-specific IgG

EBV-VCA IgM/EBNA1 IgG panel

RPR or VDRL (FTA-ABS confirmatory test if positive RPR or VDRL)

Iron and iron-binding capacity, ferritin

Type and screen

Coccidioides IgG/IgM EIA (recommended for patients with history of valley fever or those who live in endemic areas)

Optional: serum immunofixation electrophoresis if age > 60 y old (Currently, routine testing transplant candidates for MGUS is not recommended. However, practice may differ among centers.)

Special laboratory evaluation

Hypercoagulability panel in patients with history of recurrent thrombosis or spontaneous fetal losses

PSA screening for men with family history, obstructive voiding symptoms, or hematuria[a]

Serologic testing based on risk factors (endemic mycoses or travel history): Coccidioides IgM and IgG antibody, histoplasma immunodiffusion antibody antigen, *Strongyloides stercoralis* antibody, *Leishmania* spp., *Trypanosoma cruzi* antibody, human T-cell lymphotropic virus (HTLV-1/2) antibody

Other evaluation

Electrocardiogram

Chest X-ray

PPD skin test or preferably the interferon-γ release assays (QuantiFERON-TB Gold Test)

Renal ultrasound to assess for acquired cystic disease or mass

Abdominal ultrasound in diabetics to evaluate for gallstones

Cardiac evaluation (myocardial perfusion study or stress test with imaging—choice of cardiac studies differs among centers); echocardiogram to assess ejection fraction

Colonoscopy screening[b]

Pap smear and mammogram screening (appropriate for age similar to the general population)

Urologic evaluation if history of bladder/voiding dysfunction, recurrent urinary tract infections, or history of urologic abnormalities

Immunologic studies

Blood group and HLA typing

Bead-based single-antigen antibody, class I and II (see **Chapter 8 Transplant Immunobiology**)

Sera for crossmatch

[a]Routine screening may be more harmful than protective because it does not appear to confer a survival benefit and may delay listing and decrease transplantation rates (single-center study, =3,782 men > 18

years of age undergoing primary kidney transplant evaluation).
[b]Appropriate for age or at the discretion of the clinician (for a detailed discussion, see Pham and Pham [2020]).
Abbreviations: Ab, antibody; Ag, antigen; CMV, cytomegalovirus; EBNA1, Epstein–Barr nuclear antigen 1; EBV, Epstein–Barr virus; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption; HCV, hepatitis C virus; HLA, human leukocyte antigen; IgG, immunoglobulin G; IgM, immunoglobulin M; INR, international normalized ratio; MGUS, monoclonal gammopathy of undetermined significance; PCR, polymerase chain reaction; PPD, purified protein derivative; PSA, prostate-specific antigen; PTT, partial thromboplastin time; RPR, rapid plasma reagin; VCA, viral capsid antigen; VDRL, venereal Disease Research Laboratory.

- The absolute and relative contraindications to transplantation are outlined in Table 9.2.

Table 9.2 Contraindications to kidney transplantation

Absolute contraindications
Recent[a] or active malignancy, metastatic malignancy
Untreated current infection or ongoing nonhealing ulcers
Severe irreversible extrarenal disease (e.g., severe cardiovascular disease not amenable to intervention or severe pulmonary disease)
Life expectancy 2 y
recalcitrant treatment nonadherence
poorly controlled psychiatric illnesses
active substance abuse
aggressive native kidney disease[b]
Limited, irreversible rehabilitation potential
Decompensated liver cirrhosis (unless simultaneous liver-kidney transplantation)
Primary oxalosis (consider simultaneous liver-kidney transplantation)
Chronic severe and uncorrectable hypotension (may compromise posttransplant graft perfusion potentially leading to graft primary nonfunction)
Relative contraindications
Morbid obesity (center dependent)
Advanced age (center dependent—consensus on the upper age limit is lacking)
History of multiple myeloma or plasma cell dyscrasia (Assess on a case-by-case basis. Hematology/Oncology consultation strongly recommended)
Other evaluation
ABO incompatibility[c]
Positive T- and/or B-cell flow cytometry crossmatch[c]
Post-percutaneous coronary intervention patients[d]
Transplant surgery not recommended:

- Within 4 wk of coronary revascularization with balloon angioplasty
- Within 1 mo of bare metal stent placement
- Within 6 mo of drug-eluting stent (DES) placement (with the newer generation DES)

[a]See Table 9.3.

[b]See Table 9.28—Glomerular disease recurrence after transplant.

[c]Pretransplant preconditioning regimen or desensitization may allow successful transplantation across these barriers (discussion is beyond the scope of this chapter). See **Chapter 8 Transplant Immunobiology** for different crossmatch methods. *Other options:* paired donor exchange or kidney-paired donation (KPD) at the internal (involving one single-transplant center), regional (involving multiple transplant centers within close geographical or system networks), or national level (via the National Kidney Registry).

Interested readers are referred to Pham, McGuire et al. (2020).

[d]The following recommendations are for patients who had undergone elective percutaneous coronary intervention (PCI) procedure. Patients with acute coronary syndrome must wait for one year regardless of stent type. Cardiology consult is recommended.

- The United Network for Organ Sharing (UNOS) listing criteria for deceased donor kidney: chronic kidney disease (CKD) with glomerular filtration rate (GFR) ≤ 20 mL/min or ESKD
- Transplant candidates with a history of malignancies: Table 9.3 provides general guidelines for minimum tumor-free waiting periods for common malignancies.

Table 9.3 Tumor-free waiting period for common pretransplant malignancies[a,b]

No waiting time	
Long-standing history of MGUS. Hematology/Oncology consult is advisable in patients with newly diagnosed monoclonal gammopathy	
No waiting time if cure at the time of transplantation	
Incidental renal cell carcinoma, in situ carcinoma of bladder, in situ carcinoma of cervix, basal cell carcinoma	
Waiting time varies with staging, tumor size	
Breast cancer	2–5 y 2 y waiting time for ductal carcinoma in situ Patients with stage III or IV breast cancer should be advised against transplantation
Prostate cancer	Old paradigm: 2 y tumor-free waiting time Current trend[b]: Shorter waiting time is acceptable for patients with grade group 1 or 2 prostate cancer (Gleason score ≤ 6 or Gleason 3 + 4, respectively)
Renal cell carcinoma	2 y if 5 cm 5 y if >5 cm or 5 cm with invasion
Skin squamous cell carcinoma[b,c] (SCC)	Old paradigm: 0–2 y waiting time New paradigm[d]: Low-risk SCC: surgical excision with clear margins or Mohs

	surgery and no waiting time High-risk SCC: no perineural invasion: surgical excision with clear margins or Mohs surgery and 2 y waiting time High-risk SCC with perineural invasion: surgical excision with clear margins or Mohs surgery and/or adjuvant radiation therapy and waiting time of 5 y High-risk SCC with local nodal disease: surgical excision, lymph node dissection, adjuvant radiation therapy, and 5 y waiting time
Melanoma[b,c]	Old paradigm: 5 y waiting time New paradigm[d]: In situ: wide excision and no waiting time Stage Ia: wide local excision and 2 y waiting time Stage Ib/IIa: wide local excision and/or sentinel lymph node biopsy and 2–5 y waiting time Stage IIb/IIc: wide local excision and/or sentinel lymph node biopsy and 5 y waiting time Stage III or IV: not a transplant candidate
PTLD (retransplantation)	At least 1–2 y[b]
Waiting time 2–5 y[b] 2 y waiting time: invasive bladder, uterine body, Wilms tumor 2–5 y waiting time: lymphoma, invasive cervical carcinoma, colorectal carcinoma (at least 5 y for Dukes B1 or higher)	

[a]Certain cancers may recur despite a tumor-free waiting period.

[b]Oncology evaluation or consultation with the Israel Penn International Transplant Tumor Registry at https://ipittr.uc.edu may be invaluable.

[c]Dermatology consultation is recommended.

[d]Mittal A, Colegio OR. Skin cancers in organ transplant recipients. *Am J Transplant*. 2017;17(10):2509–2530.

Abbreviations: MGUS, monoclonal gammopathy of undetermined significance; PTLD, posttransplantation lymphoproliferative disorder.

- Disease recurrence after transplantation: Patients should be informed of the risk of disease recurrence after transplantation and the risk of graft loss associated with disease recurrence (discussed in a later section).

Candidates With Preexisting Infectious Diseases

Hepatitis B

- Diagnostic tests for hepatitis B virus (HBV) are listed in Table 9.4. Patients with hepatitis B surface antigen (HBsAg) positive with or without evidence of active viral replication should be referred to hepatology (the latter as assessed by the detection of HBV DNA by reverse transcriptase polymerase chain reaction [PCR]).

Diagnostic tests for hepatitis B and hepatitis C

Hepatitis Type	Diagnostic Tests and Interpretation
Hepatitis B	• Hepatitis B surface antigen (HBsAg): HBV infection • IgM antibody to hepatitis core antigen (IgM anti-HBc): acute or recent HBV infection • IgG antibody to hepatitis B core antigen (IgG anti-HBc): chronic or remote HBV infection • Antibody to hepatitis B surface antigen (HBsAb): immunity to HBV (prior infection or through vaccination) • Hepatitis B e-antigen (HBeAg): can persist in carriers and is usually associated with detectable HBV DNA (HBV viremia): active viral replication

Hepatitis C	• Anti-HCV: used for initial screening. The third-generation ELISA 3.0 has excellent sensitivity and specificity
	• Nucleic acid testing for detection of HCV RNA
	• HCV qualitative
	  • More sensitive than quantitative test
	  • Used to confirm HCV infection in anti–HCV-positive patients
	  • Useful in immunocompromised patients (dialysis patients, transplant recipients)
	• HCV quantitative
	  • More reproducible than qualitative tests
	  • Used to assess viral load
	  • Useful in monitoring response to therapy
	• HCV genotyping: may predict response to treatment (helpful in treatment decision)

Abbreviations: ELISA, enzyme-linked immunosorbent assay; HBV, hepatitis B virus; HCV, hepatitis C virus; IgG, immunoglobulin G; IgM, immunoglobulin M.

- Assessment of severity of liver disease
  - Liver biopsy is often indicated to assess the severity of liver disease (grade and stage) because liver enzymes may be spuriously normal in patients with CKD despite advanced liver disease.
  - Transient elastography (FibroScan) is increasingly being used to assess the severity of fibrosis, but liver biopsy remains gold standard.
- Hepatocellular carcinoma screening with the following studies is recommended every 6 months (particularly in high-risk patients such as those with high HBV viral load, hepatitis B e-antigen [HBeAg] positive, HBsAg positive, HBV genotype C, Asian or African ethnicity):
  - Abdominal ultrasound
  - α-Fetoprotein before and after transplant

- Transplant considerations
  - Kidney-alone transplantation is acceptable after sustained viral response in patients with precirrhosis or compensated liver cirrhosis (defined as absence or mild portal hypertension with hepatic portal venous gradient < 10 mm hg). *Hepatology consult is recommended.*
  - Patients with decompensated liver disease should be referred for simultaneous liver-kidney transplant (SLKT).
- Antiviral therapy considerations
  - Transplant candidates with active HBV replication (i.e., detectable HBV DNA)
    - Initiate antiviral therapy pretransplant.
  - Transplant recipients with HBV infection (i.e., positive HBeAg or HBsAg)
    - All patients should be placed on antiviral therapy after transplantation to avoid HBV reactivation and progression of liver disease associated with the use of immunosuppressive therapy.
    - Risk factors for posttransplant progression of HBV-related liver disease: duration of infection, genotype C, higher HBV DNA titer, hepatitis C or hepatitis D coinfection, immunosuppressive therapy
  - The authors advocate antiviral prophylactic therapy in all HBsAg-positive candidates at the time of transplantation.

Hepatitis C

- Diagnostic tests for hepatitis C virus (HCV) are presented in Table 9.4. Serologic testing is the initial screening tool for HCV infection. The third-generation enzyme-linked immunosorbent assay (ELISA 3.0) has excellent sensitivity and specificity even for patients with CKD. Confirmation of chronic HCV infection requires detection of HCV RNA by reverse transcriptase PCR.
- All patients should be referred to hepatology.
- Assessment of severity of liver disease: Liver biopsy is often indicated to assess the severity of liver disease (grade and stage) because liver enzymes may be spuriously normal in patients with CKD despite advanced liver disease.

- Transplant considerations
  - Kidney-alone transplantation is acceptable with HCV treatment in patients with precirrhosis or compensated liver cirrhosis (absence or mild portal hypertension with hepatic portal venous gradient < 10 mm hg). *Hepatology consult is recommended.*
  - Patients with decompensated liver disease should be referred for SLKT.
  - Kidney transplantation from hepatitis C–positive donors may be offered to hepatitis C–positive candidates (who are viremic) and who have consented to receive such kidney (informed consent should preferably be obtained at the time of pretransplant evaluation).
  - Hepatitis C–positive donors to hepatitis C–negative candidate and preemptive therapy with direct-acting antiviral agents (DAAs) after transplantation is a potential therapeutic option for waitlisted transplant candidates who consent to receive such kidney. Further studies are needed. Discussion is beyond the scope of this chapter.
- Antiviral therapy considerations
  - Active viral replication at the time of transplant has been shown to be associated with a higher incidence of long-term clinical liver disease and worse allograft function and graft survival compared with HCV-positive recipients with persistently negative viremia. The advent of DAA in ribavirin- and interferon (INF)-free regimen should improve outcomes in hepatitis C–positive kidney transplant recipients.
  - In HCV-positive transplant candidate without a living donor, consider delaying DAA therapy until after transplant due to a considerably shorter waiting time for a deceased HCV-positive transplant candidate. Nonetheless, among those with advanced fibrosis, treatment before transplant is recommended by experts in the field. In those with mild-to-moderate fibrosis, treatment can be deferred until after transplant.

Human immunodeficiency virus

- Highly active antiretroviral therapy (HAART) regimen has allowed successful transplantation of stable human immunodeficiency virus (HIV) patients, defined as:
  - Undetectable HIV viral load

  - CD4 lymphocyte count > 200/mm^2
  - Absence of opportunistic infections in the previous year
- Specific recommendations may vary from center to center.
- Clinicians should remain vigilant to significant drug–drug interactions between HAART and immunosuppressive drugs metabolized by CYP450, such as the calcineurin inhibitors (CNIs) and mammalian target of rapamycin (mTOR) inhibitors (see also **Immunosuppressive Agents** section). Raltegravir is the first integrase inhibitor approved by the Food and Drug Administration (FDA) for use in the treatment of HIV-1 infection in combination with other antiretroviral agents. It is not a cytochrome P450 substrate and, therefore, lacks drug–drug interactions with the CNIs (see also **Chapter 10 Pharmacology**).

Latent tuberculosis

- All potential kidney transplant candidates should undergo a purified protein derivative (PPD) skin test or preferably the INF-γ release assays (QuantiFERON-TB Gold test) because the latter has lower false-positive rates associated with prior BCG vaccine.
- A positive skin test or INF-γ released assay result or a prior history of tuberculosis (TB) mandates further evaluation to rule out active disease.
- Obtain chest X-ray (part of routine pretransplant workup).
- Isoniazid (INH) prophylaxis for a total of 9 months is recommended for those with evidence of latent TB.
- Clinical, radiologic, or culture evidence of active TB infection is a contraindication to transplantation.

Pregnancy After Transplantation

- Patient must be at least 1-year posttransplant and on stable immunosuppression.
- Allograft function:
  - No acute rejection episodes in the previous year
  - Serum creatinine < 2.0 mg/dl, preferably < 1.5 mg/dl (higher creatinine level increases the risk of allograft loss and maternal and fetal

complications)
  - Minimal or no proteinuria/albuminuria (minimal proteinuria defined as < 500 mg/24 hours)
  - Normal kidney allograft ultrasound
- Well-controlled hypertension (HTN) on minimal antihypertensive regimen
- No acute infections that may impact fetal growth and well-being (e.g., congenital cytomegalovirus [CMV] infection can cause birth defect and/or developmental delays)
- Drug safety in pregnancy:
  - Drugs that may be used during pregnancy:
    - Cyclosporine, tacrolimus, and azathioprine (AZA)
  - Drugs that should not be used during pregnancy:
    - Mycophenolic acid (MPA) derivatives (mycophenolate mofetil [MMF] or mycophenolate sodium) due to increased risk of first-trimester pregnancy loss and congenital malformation
    - mTOR inhibitor sirolimus or everolimus has been shown to be associated with increased fetal mortality, decreased fetal weights, and delayed ossification of skeletal structures.
    - Use reliable contraception while on MPA derivatives or mTOR inhibitors and for 3 months after discontinuation.
  - Belatacept: Clinical studies on belatacept use in pregnancy are currently limited. To date, only two cases of successful pregnancy and delivery have been reported to the Transplant Registry International (US FDA pregnancy category: not assigned).
  - Breastfeeding (see **Appendix A**)

Male Fertility

- Fertility, as assessed by sperm counts, improves in half of patients.
- There is no increased incidence of neonatal malformations in pregnancies fathered by kidney transplant recipients.

LIVING DONOR EVALUATION

Options

- Living related, living unrelated, kidney-paired donation (KPD), paired kidney chain donation, altruistic, voucher donation
  - KPD, paired kidney chain donation:
    - Approximately 30% of potential living donors are incompatible to their recipients due to blood group incompatibility or the presence of preformed donor-specific human leukocyte antigen (HLA) antibody or both.
    - KPD is a program in which an incompatible donor–recipient pair is swapped with another incompatible donor–recipient pair. A number of transplant centers in the United States offer KPD and/or desensitization protocols to such willing but incompatible healthy donor–recipient pairs. Sometimes, these "swaps" may include multiple pairs.
    - Paired kidney chain donation (formerly known as domino-paired kidney donation or never-ending altruistic donation [NEAD]). The nondirected donor donates a kidney to a compatible recipient who has an intended but incompatible living donor. The recipient's incompatible living donor will, in turn, donate his or her kidney to the next incompatible pair, generating a domino effect. The chain can terminate when the final donor donates to a recipient on the deceased donor waiting list. Alternatively, the final donor can wait until a suitable match is found with a new incompatible pair. As such, the final donor becomes a bridge donor to continue the chain until no match can be identified through paired kidney donation, and the final donor's kidney is directed to a recipient on the deceased donor waitlist.
  - Voucher donation:
    - Novel concept whereby the donor donates a kidney at a time that is optimal for the donor, whereas the intended recipient is not yet in need of a transplant or may never need a transplant.
      - Example: A 66-year-old grandmother can donate a kidney to a nondirected recipient now to allow her 7-year-old grandson with CKD to receive priority for a future living donor kidney transplant if needed later in life.

    - Advantages: Vouchers for future kidney transplantation overcome "chronologic incompatibility" between living donors and recipients.
- The Declaration of Istanbul on organ trafficking and transplant tourism and the World Health Organization (WHO) prohibit and condemn the exploitation of vulnerable living donors (defined as illiterate or impoverished individuals, undocumented immigrants, and political or economic refugees).

General Assessment

- Complete history and physical examination, and psychosocial assessment
- Psychosocial assessment by the transplant center psychiatrist or social worker is recommended to evaluate for any significant psychiatric problem and any possibility of coercion. The presence of either of these would preclude donation.
- Suggested routine evaluation and optional testing are listed in Table 9.5.

Table 9.5 Suggested routine evaluation and optional testing[a]

Laboratory tests
ABO blood group, HLA tissue typing, crossmatch testing
Urinalysis and urine culture
24-h urine for albumin, protein,[b] and creatinine clearance (or GFR determination by nuclear medicine test)
CBC with platelets, INR, and PTT
Comprehensive metabolic panel (electrolytes, transaminase levels, albumin, bilirubin, calcium, phosphorous, alkaline phosphatase, fasting blood glucose)
Fasting lipid profile
Serologies: Hepatitis B (surface Ag, IgM and IgG core Ab, and surface Ab). HCV Ab screening (if positive, check PCR confirmatory test), HIV-1/HIV-2 Ag/Ab screening, fourth generation with reflex confirmation,[c] CMV, EBV, HSV, West Nile antibodies (IgG and IgM), RPR or VDRL (FTA-ABS confirmatory test if positive RPR or VDRL), *Strongyloides stercoralis* antibodies
Geographic residence or environmental exposure that may require additional testing: coccidioidomycosis, schistosomiasis, malaria, HHV-8, HHV-6. *Trypanosoma cruzi*
Women 55 y: human chorionic gonadotropin quantitative pregnancy test
prospective donors > 60 y: Serum protein electrophoresis and serum immunofixation electrophoresis
African Americans: Hemoglobin electrophoresis (to rule out sickle cell trait)
Other tests

Electrocardiogram
Chest X-ray
Pap smear appropriate for age similar to the general population
Mammogram appropriate for age similar to the general population
Renal imaging: spiral computed tomography (CT), CT angiogram, or magnetic resonance angiogram
Further testing depending on age, history, abnormal laboratory findings, family history
Cardiac screening: exercise treadmill or nuclear medicine stress test, echocardiogram
Colonoscopy for prospective donors ≥ 50 y
24-hour ambulatory blood pressure monitoring
Renal biopsy
Cystoscopy
PPD skin test or preferably QuantiFERON-TB Gold test
Screening for hypercoagulability
Oral glucose tolerance test in patients with family history of diabetes or in those with risk factors for diabetes
Prostate-specific antigen screening for men with family history at the discretion of the clinician (routine screening may be more harmful than protective)
African Americans: screening for APOL1 G1/G2 mutation (see text)

[a]May vary among centers.

[b]KDIGO guidelines recommend that donor proteinuria should be measured as albuminuria, not total urine protein. In the authors' opinion, both urine albumin and total protein should be measured because the former does not detect light-chain immunoglobulins.

[c]HIV-1/HIV-2 screening as close as possible but within 28 days prior to organ recovery and HCV RNA by nucleic acid testing (NAT) as close as possible but within 28 days prior to organ recovery.

Abbreviations: Ab, antibody; Ag, antigen; CMV, cytomegalovirus; EBV, Epstein–Barr virus; FTA-ABS, fluorescent treponemal antibody absorption; GFR, glomerular filtration rate; HCV, hepatitis C virus; HHV, human herpes virus; HLA, human leukocyte antigen; HSV, herpes simplex virus; IgG, immunoglobulin G; IgM, immunoglobulin M; INR, international normalized ratio; PCR, polymerase chain reaction; PPD, purified protein derivative; PTT, partial thromboplastin time; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.

Absolute and relative contraindications to living kidney donation are listed in Table 9.6.

Table 9.6 Absolute and relative contraindications to living kidney donation (criteria may vary among centers)

Absolute Contraindications (At Most Transplant Centers)	Relative Contraindications
• Evidence of kidney disease (GFR 80 ml/min/1.73 m^2 and/or microalbuminuria ≥ 30 mg/24 hr [or equivalent]) (see relative contraindication regarding kdigo	• Age 18 y (seldom performed) or >70 y (need to evaluate on a case-by-case basis) • Borderline or mild hypertension • Borderline urinary abnormalities in the absence of

guidelines)
- significant renal or urologic abnormalities
- transmissible infectious disease (hiv,[a] hepatitis B infection, hepatitis C infection,[b] *Trypanosoma cruzi* infection [Chagas disease])[c]
- Active malignancy
- Chronic illness that places patient at significant risk of undergoing surgery
- Poorly controlled psychiatric illness or active substance abuse
- Cognitive deficit
- Current pregnancy
- Hypertension (clinically significant)
- Diabetes mellitus
- Recurrent nephrolithiasis or bilateral stones
- History of thrombotic disorders with risk factors for future events or inherited hypercoagulable states (e.g., the presence of lupus anticoagulant or anticardiolipin antibody, factor V Leiden, or prothrombin gene mutation FII-20210)
- High suspicion for covert coercion
- BMI > 30–35 kg/m^2 (center dependent)
- Urologic abnormalities of donor kidney

renal function impairment
- Single prior episode of kidney stone without evidence of secondary risk (see Table 9.7)
- Obesity (center dependent, generally defined as BMI > 30 kg/m^2)
- Metabolic syndrome and fatty liver (must resolve or demonstrate significant improvement through lifestyle changes before donation)
- Young donor with risk factors for future development of diabetes mellitus
- Jehovah Witness
- African Americans with two mutated alleles of APOL1 G1/G2
- Sickle cell trait (sickle cell trait is considered as an absolute contraindication to living donation at some centers)
- Cigarette smokers (must stop at least 4 wk prior to surgery to decrease pulmonary complications). At some centers, current cigarette smoking is considered a contraindication to donation.
- KDIGO guidelines for GFR between 60 and 80 mL/min/1.73 m^2 and/or albumin excretion rate between 30 and 100 mg/d: Decision should be individualized based on demographic and health profile in relation to the transplant center's acceptance risk threshold.

[a]The first living donor HIV-to-HIV kidney transplant was performed in the United States in March 2019 (HIV Organ Policy Equity [HOPE] in Action is an ongoing prospective multicenter, clinical trial of HIV-to-HIV deceased donor kidney transplantation).
[b]Kidneys from hepatitis C–positive donors may be offered to hepatitis C–positive transplant candidates (who are viremic) who have consented to receive such kidneys.
[c]UNOS policy: If transplantation from an infected donor is planned, recipients should receive specific information regarding risk of transmission and limited data regarding the risk, especially pertaining to live donors, posttransplantation monitoring, potential toxicities associated with treatment for Chagas disease. Detailed discussion is beyond the scope of this chapter.
Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

Evaluation for Specific Conditions

Diabetes mellitus

- *2015 American Society of Transplantation (AST) Living Donor Community of Practice*
  - Prediabetes increase future risk for diabetes-associated kidney disease in

the donor.
  - Potential donors with diabetes mellitus are excluded from donation per UNOS.
  - Potential donors with prediabetes need to make lifestyle changes including diet change and increased exercise and weight loss to normalize glucose metabolism and reduce future diabetes risk.
- *2017 Kidney Disease: Improving Global Outcomes (KDIGO) inclusion and exclusion criteria for donation*
  - Donor candidates with type 1 diabetes should not donate.
  - Donor candidates with prediabetes or type 2 diabetes
    - Decision for kidney donation should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold.
    - Donor candidates should be counseled that their condition may progress over time and may lead to end-organ complications.

Hypertension

- *2015 AST Living Donor Community of Practice*
  - Medical evaluation of potential donors suspected to have HTN should include:
    - Ambulatory blood pressure monitoring
    - Evaluation of end-organ damage (e.g., retinal evaluation, echocardiogram)
  - Caucasian donors with HTN should not be precluded from donation if the following criteria are met:
    - HTN is well controlled (per Amsterdam guidelines).
    - Candidates are reliable and agree to long-term follow-up.
  - Living donation among young African Americans with HTN is generally discouraged due to their possible genetic predisposition to ESKD and higher rates of ESKD.
- *2017 KDIGO Clinical Practice Guidelines*
  - Donor candidates with HTN that can be controlled to systolic blood pressure < 140 mm hg and diastolic blood pressure < 90 mm hg using

one or two antihypertensive agents, who do not have evidence of end-organ damage, may be acceptable for donation.

- Donors candidates should be informed that:
  - Blood pressure may rise with aging.
  - Donation may accelerate the rise in blood pressure and the need for antihypertensive treatment over that expected with normal aging and among those with high-normal blood pressure before donation (particularly in African Americans).
  - Antihypertensive medication is more likely to be prescribed after donation.

Donor with history of nephrolithiasis

See Table 9.7.

Table 9.7 Prospective donors with history of kidney stones

Kidney Donation Acceptable	Contraindications to Donation if One or More of the Following Risk Factors Are Present

• Distant history of stone (>10 y) without metabolic abnormalities associated with stone formation (e.g., hypercalcemia, hyperuricemia, hyperoxaluria, hypocitraturia, or metabolic acidosis)
• Current asymptomatic single stone if:
  • Stone is 1.5 cm or potentially ureteroscopically removable from explanted donor kidney (before transplantation), *and*
  • Further evaluation must reveal no evidence of metabolic abnormalities, urinary tract infection, or nephrocalcinosis.
• Single stone episode associated with treated primary hyperparathyroidism and normocalcemia does not necessarily preclude donation (must evaluate on a case-by-case basis).
 	
AST Living Donor Community of Practice Guideline
• The following are considered acceptable for donation:
  • Small incidental stones (2–3 mm) and negative metabolic stone evaluation
  • Candidates with a distant history of a single passed stone without recurrent stone on imaging and negative metabolic evaluation
	• Cystinuria
	• Sarcoidosis
	• History of struvite stones
	• Inflammatory bowel disease
	• Evidence of nephrocalcinosis
	• Primary or enteric hyperoxaluria
	• History of bilateral stones, multiple stones, recurrent stones despite preventive therapy

Abbreviation: AST, American Society of Transplantation.

Online calculator that may be used to predict stone recurrence: http://www.qxmd.com/calculate-online/nephrology/recurrence-of-kidney-stone-roks.

Hereditary Renal Disease

Autosomal dominant polycystic kidney disease

- Most commonly encountered hereditary renal disease
- Diagnostic criteria are age and genotype dependent (i.e., polycystic kidney disease 1 or 2 [PKD1 or PKD2]).
  - PKD1
    - Younger than 30 years of age: ≥ one cysts in each kidney or ≥ two cysts in one kidney
    - 30 to 59 years of age: ≥ two cysts in each kidney
    - 60 years of age: ≥ four cysts in each kidney
  - PKD2
    - May present later in life. The use of PKD1 diagnostic criteria may lead to false-negative results. Asymptomatic patients from families with known and well-characterized pathogenic mutations in the *PKD2* locus, genetic testing is more definitive than ultrasound.
  - At risk but unknown familial genotype
    - Between the ages of 15 and 39 years: at least three unilateral or bilateral kidney cysts
    - 40 to 59 years of age: ≥ two cysts in each kidney
    - 60 years or older: ≥ four cysts in each kidney
- Ultrasound screening is acceptable for prospective donors older than 30 years of age.
- Magnetic resonance imaging (MRI)–based criteria for disease exclusion in at-risk individuals younger than 40 years of age. The finding of < five cysts is sufficient for disease exclusion.
- For prospective donors with positive family history and age < 30 years, direct mutation analysis for pkd1 and pkd2 is required at some centers.

Apolipoprotein L1 gene mutations

- Two risk allele mutations (homozygous G1/G1, homozygous G2/G2, or compound heterozygous G1/G2) are found in 13% of African Americans

and are associated with increased risk of nondiabetic glomerulosclerosis and focal segmental glomerulosclerosis (FSGS) and more rapid CKD progression compared with their non-black counterparts. African American kidney donors are at higher risk of developing ESKD than their European American counterparts. The UNOS data demonstrated that the risk of ESKD 15 years postdonation was 74.4 per 10,000 African American donors compared with 22.7 per 10,000 European American donors.

- Prospective younger African American donors and those with significant family history of ESKD should be tested for the presence of two risk alleles for apolipoprotein L1 (APOL1) variants (G1 and G2).
- Final kidney phenotypes may not yet manifest in young adults and must be considered when potential young African American donors are being evaluated.
- Donor candidates with two APOL1 risk alleles should be informed of the increased lifetime risk of kidney failure, but the precise kidney failure risk after donation cannot currently be quantified.
- Renal allograft from living and deceased donors with two risk alleles for APOL1 variants has an increased risk for rejection and transplant failure.

Pregnancy

- Desire to become pregnant is not a contraindication to donation. However, prospective female donor of childbearing age should be informed to avoid becoming pregnant from the time of approval for donation (or preferably from the time of donor evaluation to the time of recovery after nephrectomy).
- Female donor candidate should not donate while pregnant.
- Evaluating for donation 6 months postpartum is reasonable.
- Prospective female donor candidates of childbearing age should be informed that kidney donation may increase the risk of gestational HTN and preeclampsia (11% vs. 5% among healthy nondonors counterparts).
- 2017 KDIGO Clinical Practice Guidelines:
  - Women with prior history of hypertensive disorders of pregnancy (e.g., gestational HTN, preeclampsia, or eclampsia) may be acceptable for

donation if their long-term postdonation risks are acceptable.

- Women with childbearing potential who proceed with donation should be counseled on how to reduce the risk of complications in future pregnancies (close follow-up with a nephrologist during pregnancy is advisable).

Donor Safety and Long-Term Renal Function

- Surgical mortality within 90 days of live kidney donation: 3.1 in 10,000 donors (UNOS database consisting of 80,347 live kidney donors)
- Despite the loss of 50% renal mass, unilateral nephrectomy only reduces renal function by approximately 20% to 30% at long-term follow-up because of compensatory hyperfiltration. The degree of compensation is determined by age-related reserve.
- One-third of healthy donors will have estimated GFR (eGFR) < 60 ml/min/ 1.73 m^2. however, the fall in egfr usually does not decrease with time beyond the rate associated with natural aging.
- Systematic review and meta-analysis of 52 studies involving more than 110,000 living kidney donors (average follow-up of 1 to 24 years):
  - The relative risk (RR) for ESKD was nearly ninefold higher among living donors compared with their nondonor counterparts. However, the absolute risk was low, with an estimated incidence rate of less than 1 case per 1,000 person-years (RR, 8.83 [95% confidence interval or CI, 1.02 to 20.93]. Incidence rate, 0.5 event [CI, 0.1 to 4.9 events] per 1,000 person-years).
  - The RR for preeclampsia in female donors was twofold higher among living donors compared with their nondonor counterparts, with an estimated incidence rate of nearly 6 cases per 100 pregnancies (RR, 2.12 [CI, 1.06 to 4.27]. Incidence rate, 5.9 events [CI, 2.9 to 8.9 events] per 100 pregnancies).
- Risk for ESKD: male sex, greater body mass index (BMI), donors with first-degree biologic relationship to the recipient, lived in lower socioeconomic status neighborhoods, younger ages at donation for Blacks, and older ages at donation for Whites. (data source: Organ Procurement Transplantation Network [OPTN] database with ESKD ascertained via

Centers for Medicare & Medicaid Services linkage; *n* > 120,000 living kidney donors)

- African Americans have higher rates of developing postdonation CKD due to HTN and use of antihypertensive medication compared to white donors.
- Systematic review, meta-analysis, and meta-regression study (*n* > 5,000 donors from 27 countries): Kidney donation resulted in small increases in urinary albumin, which increased with time after donation. An initial decrement in GFR was not followed by accelerated losses over the subsequent 15 years.
- The OPTN policy requires informing donor candidates that the risk of ESKD after donation may exceed that of healthy nondonors with medical characteristics similar to living kidney donors.
- For interested readers, a calculator to assess the risk of developing kidney disease in the absence of donation can be found at http://www.transplantmodels.com/esrdrisk/. This risk model is intended for low-risk adults considering living donation in the United States. **This risk calculator should not replace clinical judgment.**
- May increase risk of HTN, hyperuricemia, gout, and hyperthyroidism
- Association between living kidney donation, race, HTN, and eGFR:
  - Study design: Longitudinal multicenter study of 1,295 living kidney donors. Controls: *n* = 8,233 healthy nondonors drawn from the ARIC (Atherosclerosis Risks in Communities) and CARDIA (Coronary Artery Risk Development in Young Adults) studies
  - Results:
    - Median follow-up: 6 years
    - Black race was associated with a 27% higher risk of HTN, regardless of whether the individual donated a kidney. Although the baseline risk of HTN was higher for blacks, donation was associated with a 19% higher risk of HTN compared with healthy nondonor controls, regardless of race (white or black).
    - Although kidney donors experienced an increase in eGFR over time after donation (attributed to adaptive hyperfiltration), their eGFR plateaued after they developed HTN.

        - The study finding suggests that incident HTN adversely affects GFR after kidney donation.
    - Study limitations: Factors that might impact the effect of HTN on eGFR such as blood pressure control, quality of care for subjects with HTN, and use of antihypertensive medications were not assessed.
- Impact of age on long-term safety:
    - Study design: Single-center study: *N* = 539 consecutive live kidney donors (422 donors were <60 years and 117 were 60 years or older). older donors had lower mean predonation gfr (80 vs. 96 ml/min/1.73 m^2), higher bmi, and higher american society of anesthesiologists (asa) classification compared with younger donors.
    - Results:
        - There was no difference in the mean maximum decline in eGFR between the two groups at a median follow-up of 5.5 years (maximum decline in eGFR was 38% ± 9%).
        - The percentage maximal decline was comparable between the two groups.
        - At 5 years follow-up, significantly more elderly had an eGFR < 60 ml/min/1.73 m^2 compared with younger donors (94% vs. 80%, p < 0.001). however, renal function stabilized during follow-up, and no donor had an egfr of < 30 ml/min/1.73 m^2.
    - Conclusion: After kidney donation, decline in eGFR is similar in younger and older donors. As kidney function does not progressively decline, live kidney donation by elderly is considered safe.
- No apparent adverse effect on life expectancy. However, obese living kidney donors might be at increased risk of long-term mortality.
    - In a study using the Scientific Registry of Transplant Recipients database (*n* = 119,769 living kidney donors with a maximum follow-up of 20 years), obese living kidney donors (BMI ≥ 30) were found to have a 30% increase risk of long-term mortality compared with their nonobese counterparts (adjusted hazard ratio: 1.32, p = 0.006).
        - Study limitations:
            - Of the 119,769 living kidney donors, BMI data at donation were

only available in approximately two-thirds of the study cohort (*n* = 78,592). Multiple imputation was used for one-third of the cohort with missing BMI data at donation.
- Lack of data on predonation metabolic syndrome
- Lack of data on postdonation development of other comorbidities such as HTN, diabetes, or cardiovascular disease (CVD)

KIDNEY ALLOCATION SYSTEM

- Kidney donor profile index (KDPI)
  - Deceased donor kidneys are given a KDPI value ranging from 0% to 100% based on longevity-matching concepts. Ten donor characteristics used to calculate KDPI:
    - Donor age
    - Height
    - Weight
    - Ethnicity
    - History of HTN
    - History of diabetes
    - Serum creatinine
    - Cause of death
    - Hepatitis C status
    - Donation after circulatory death status
  - Lower KDPI values are associated with longer estimated function, whereas higher KDPI values are associated with shorter estimated function (e.g., a kidney with KDPI of 20% is expected to have longer longevity than 80% of recovered kidneys).
- UNOS listing criteria:
  - CKD with eGFR ≤ 20 mL/min or
  - On dialysis
- Factors determining kidney allocation:
  - Waiting time
    - Preregistration dialysis time allows transplant candidates to gain

waiting time upon listing (e.g., patient who has been on dialysis for 5 years prior to UNOS registration will have 5 years of waiting time upon listing).
    - Candidates not yet on dialysis at the time of registration will still begin to accrue waiting time once they are registered on the waiting list.
- Geographic area: allocation prioritized to candidates in areas closest to donor
- Degree of allosensitization (calculated panel reactive antibody [cPRA] ≥ 20%)
    - Higher cPRA scores indicate increasing difficulty in getting a kidney with a negative or acceptable crossmatch (discussion is beyond the scope of this chapter).
    - Prioritization points will be assigned based on a sliding scale, beginning with a cPRA score of 20%. Examples:
        - Candidates with a cPRA of 20% will receive 0.08 points, which is equivalent to about 1 month of waiting time.
        - Candidates with cPRA of 75% to 79% will receive 1.58 points (equivalent to 1.5 years of waiting time).
        - Candidates with cPRA of 80% to 84% will receive 2.46 points (equivalent to 2.5 years of waiting time).
        - Candidates with cPRA of 98%, 99%, or 100% will receive 24.4, 50.09, and 202.10 points, respectively. Such candidates will also receive local, regional, and national priority.
        - The cPRA-based allocating points improve access for highly sensitized candidates.
- Pediatric candidate
- Prior living donor
- Patient/donor HLA-A, HLA-B, and HLA-DR mismatch at the time of allocation
    - Prioritization of zero HLA-A, HLA-B, HLA-DR mismatch (also known as 0MM)
    - Zero-DR mismatch: 2 points

    - One-DR mismatch: 1 point
  - Estimated posttransplant survival (EPTS) score
    - The EPTS score is designed to ensure that those kidneys expected to function the longest are transplanted into those candidates expected to live the longest. It is based on four factors: candidate's age, length of time on dialysis, prior transplant of any solid organ, and current diabetes status. A lower EPTS score is associated with longer posttransplant longevity.
    - Candidates with EPTS scores of ≤20% will receive increased priority for offers of kidneys with KDPI scores of ≤20% before other candidates at the local, regional, and national levels of distribution.
    - The EPTS score will only be used in kidney allocation when the donor has a KDPI of ≤20%.
    - EPTS scores will not be calculated for pediatric candidate until the candidate turns 18 years.
- The kidney allocation system also provides greater access to deceased donor kidneys for blood type B candidates who can safely accept a kidney from an A2 or A2B blood type donor.
- *Anticipated kidney allocation policy change (not yet implemented at the time of this writing)*:
  - Under the new allocation system, kidneys will be offered first to candidates listed at transplant hospitals within 250 nautical miles of the donor hospital. Offers not accepted for any of these candidates will then be made for candidates beyond the 250 nautical mile distance.
  - Candidates will also receive proximity points based on the distance between their transplant program and the donor hospital. The point assignment will be highest for those closest to the donor hospital and will decrease as the distance increases.

IMMUNOSUPPRESSIVE AGENTS

The Three-Signal Model of the Alloimmune Response

- T-cell activation requires three signals (**Fig. 9.1**).

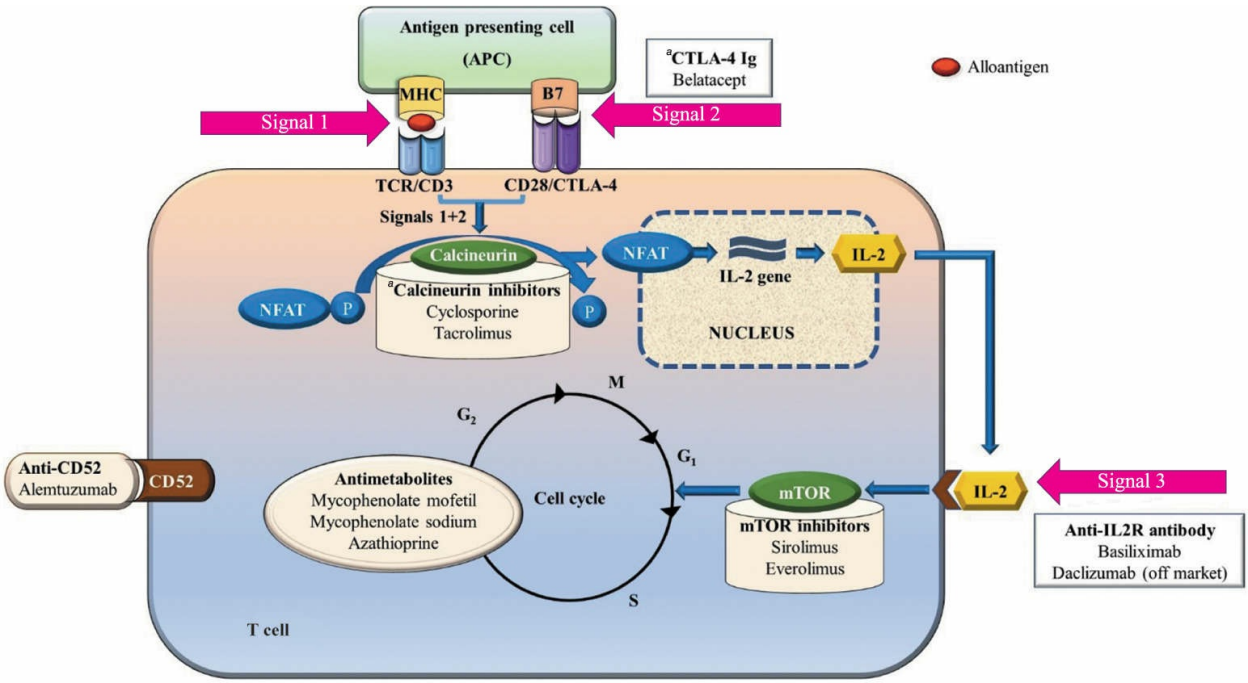

FIGURE 9.1 The three-signal model of the alloimmune response and targets of different immunosuppressive agents. **Signal 1:** binding of alloantigen (red oval) on the surface of the APC to TCR/CD3 complex on T cell. **Signal 2:** binding of B7 on the surface of APC to CD28 on T cell. These dual signals (i.e., signals 1 and 2) activate the intracellular pathways that trigger T cells to activate the transcription of IL-2 and other growth-promoting cytokines. **Signal 3:** binding of IL-2 to its receptor leads to activation of mTOR, which leads to T-cell proliferation.

[a]**Calcineurin** is a phosphatase that dephosphorylates and facilitates the translocation of NFAT (and other nuclear factors) to the nucleus. Inhibition of *calcineurin* impairs the expression of IL-2 (and other growth-promoting cytokines), thereby reducing the proliferation of T cells.

Abbreviations: Anti–IL-2R, anti–IL-2 receptor; APC, antigen-presenting cell; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cells.

- **Signal 1** is initiated by the binding of the alloantigen on the surface of antigen-presenting cell (APC) to the T-cell receptor (TCR)–CD3 complex.
- **Signal 2** is a nonantigen-specific costimulatory signal provided by the engagement of B7 on the surface of APC with CD28 on T cell. These dual signals activate the intracellular pathways that trigger T cells to activate the transcription of interleukin-12 (IL-2) and other growth-promoting cytokines.
- **Signal 3:** Engagement of IL-2 to its receptor activates the mTOR pathway to provide signal 3, which leads to cell proliferation. If a TCR is triggered without the accompanying costimulatory signal 2, the T cell

is driven into an anergic state.

- Lymphocyte proliferation, which requires the synthesis of purine and pyrimidine nucleotides, is inhibited by the antimetabolites MMF, enteric-coated mycophenolate sodium, and AZA.
- T cells also express cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4), a cell surface molecule that is homologous to CD28. However, unlike CD28, the binding of B7 to CTLA-4 produces an inhibitory signal that inhibits T-cell proliferation and helps terminate the immune response.

Targets of Various Immunosuppressive Agents

- The targets of various immunosuppressive agents are shown in **Figure 9.1**.
  - Agents targeting both signals 1 and 2:
    - Cyclosporine and tacrolimus are termed *calcineurin inhibitors* (CNIs) due to their common mechanism of action.
    - *Calcineurin* is a phosphatase that dephosphorylates and facilitates the translocation of the nuclear factor of activated T cells (NFAT) and other nuclear factors to the nucleus. Once translocated into the nucleus, NFAT promotes the translation of specific genes, including that of the growth-promoting cytokine IL-2. Inhibition of *calcineurin* impairs the expression of IL-2 (and other growth-promoting cytokines), thereby reducing the proliferation of T cells.
  - Agents targeting signal 2:
    - Belatacept (Nulojix) is a humanized fusion protein, composed of CTLA-4 fused with the Fc domain of human immunoglobulin G1 (CTLA-4Ig). Belatacept binds to B7 with high affinity and inhibits the costimulatory pathway.
  - Agents targeting signal 3:
    - Basiliximab is a humanized monoclonal antibody that targets against the α chain of the IL-2 receptor (also known as anti–IL-2 receptor or anti-CD25 antibody), blocking IL-2–mediated responses.
    - mTOR inhibitors: sirolimus and everolimus
      - The mTOR is a key regulatory kinase in the cell division process. Its inhibition reduces cytokine-dependent cellular proliferation at

the G1 to S phase of the cell division cycle.

- Lymphocyte-depleting agents:
  - Thymoglobulin is a polyclonal antibody preparation made by immunization of rabbits with human lymphoid tissue. The purified immunosuppressive product contains cytotoxic antibodies directed against a variety of T-cell markers.
  - Alemtuzumab is a humanized monoclonal antibody targeting against CD52 on the surface of both B and T lymphocytes, leading to a rapid and profound depletion of peripheral and central lymphoid cells.
- Antimetabolites:
  - Mycophenolic acid (MPA) derivatives (MMF, mycophenolate sodium)
    - MMF (Cellcept) is a prodrug that must be hydrolyzed to the active agent—MPA—in the gastric acidic milieu. MPA is a reversible inhibitor of the enzyme inosine monophosphate dehydrogenase (a rate-limiting enzyme in the de novo synthesis of purines). Depletion of guanosine nucleotides by MPA has a relatively selective antiproliferative effect on lymphocytes due to their reliance on the de novo pathway of nucleotide synthesis.
    - Mycophenolate sodium (Myfortic) is an enteric-coated formulation of MPA that dissolves at pH > 5.5. Therefore, unlike MMF, mycophenolate sodium bypasses the acidic milieu of the stomach and is absorbed in the intestines.
    - The use of antacids or proton-pump inhibitors (PPIs) can reduce the dissolution of MMF by increasing pH. In contrast, the bioavailability of mycophenolate sodium is not affected by antacids or PPIs.
  - Azathioprine (AZA)
    - AZA is a precursor of 6-mercaptopurine.
    - AZA inhibits DNA replication and subsequent T-cell proliferation. MMF/mycophenolate sodium has largely replaced AZA due to its greater efficacy in reducing acute rejection.
- Corticosteroid:
  - Key component of all immunosuppressive regimens
  - Modulates inflammatory mediators

- Blocks IL-1 and IL-2 production, thereby suppressing the early phase of the immune response

Basic Principles of an Immunosuppressive Protocol

Standard immunosuppressive protocol

- A standard immunosuppressive protocol consists of *induction* and *maintenance* immunosuppression. All kidney transplant recipients also receive prophylactic therapy with an antibiotic, antiviral, and antifungal agents, and a nondihydropyridine calcium channel blocker to boost CNI or mTOR inhibitor levels (Table 9.8). The use of diltiazem or verapamil may permit CNI dose reductions up to 40% and 30% to 50%, respectively.

Table 9.8 Components of a standard immunosuppressive protocol (immunosuppressive and nonimmunosuppressive agents)

Immunosuppressive Agents	Options
Induction	Lymphocyte-depleting or nonlymphocyte-depleting agent
Standard triple maintenance immunosuppression 1. Calcineurin inhibitor 2. Adjunctive agent 3. Corticosteroid	1. Cyclosporine or tacrolimus 2. Mycophenolic acid derivatives, sirolimus (or everolimus), or azathioprine 3. Maintenance dose: prednisone 5 mg daily
Nonimmunosuppressive Agents	**Options**
Supplementary agents	Nondihydropyridine calcium channel blockers
Infection prophylaxis	*Pneumocystis jirovecii* (trimethoprim and sulfamethoxazole, atovaquone, dapsone) Cytomegalovirus (acyclovir, valganciclovir) Antifungals (nystatin, fluconazole)

- *Induction therapy* is used to rapidly create a therapeutic net state of immunosuppression in the first few days or week after transplantation in order to prevent rejection.
  - Induction therapy can be classified into lymphocyte-depleting and nonlymphocyte-depleting agents.
    - Lymphocyte-depleting agents: thymoglobulin (antithymocyte globulin [ATG]), alemtuzumab

- Nonlymphocyte-depleting agent: basiliximab (anti–IL-2-receptor antibody)

- The choice of one induction agent over the other is generally based on each individual immunologic risk factors or anticipated delayed graft function (DGF) or both (Table 9.9).

Table 9.9 Induction therapy: lymphocyte-depleting versus nonlymphocyte-depleting agents

Lymphocyte-Depleting Agents[a]	Nonlymphocyte-Depleting Agents	Comments
Thymoglobulin (antithymocyte globulin [Rabbit])	Basiliximab	Thymoglobulin vs. basiliximab induction • Thymoglobulin: commonly used in high immunologic risk patients (e.g., highly sensitized or re-allograft transplant recipient, donor-specific antibody positive, high cPRA[b]) or anticipated delayed graft function to avoid early exposure to cyclosporine or tacrolimus (nephrotoxic) • Basiliximab: commonly used in low-to-moderate immunologic risk transplant recipients
Alemtuzumab		Alemtuzumab is used at a small number of transplant centers in the United States

[a]Lymphocyte-depleting agents can cause first-dose reaction or cytokine-release syndrome, including chills, fever, arthralgia, and, rarely, serum sickness.
[b]cPRA is discussed in **Chapter 8 Transplant Immunobiology**.
Abbreviation: cPRA, calculated panel reactive antibody.

  - In the presence of anticipated DGF due to donor acute tubular injury (aka acute tubular necrosis), it is important to maintain adequate immunosuppression. It has been suggested that endothelial injury upregulates and exposes donor histocompatibility antigens, adhesion molecules, and costimulatory molecules, heightening the risk of acute rejection. Induction therapy with lymphocyte-depleting agent and delayed introduction of CNI may avoid the additive injury associated with CNI nephrotoxicity (due to afferent arteriolar vasoconstriction) while reducing the risk of allograft rejection at the time of heightened immunogenicity.

- *Maintenance immunosuppression* is used to sustain a therapeutic net state of immunosuppression in order to prevent rejection.
  - A standard immunosuppressive regimen consists of triple-drug therapy:

CNI (cyclosporine or tacrolimus) + adjunctive agent + corticosteroid.

- CNI: The choice of tacrolimus over cyclosporine A (CSA) or vice versa is generally based on the potential adverse effects of these agents. The side-effect profile of cyclosporine and tacrolimus are summarized in Table 9.10.

Table 9.10 Side-effect profiles of cyclosporine and tacrolimus

Cyclosporine	Tacrolimus	Comments
Nephrotoxicity	Nephrotoxicity	CSA > Tac
Hypertension and sodium retention	Hypertension and sodium retention	CSA > Tac
Hyperlipidemia	Hyperlipidemia	CSA > Tac
Diabetes mellitus	Diabetes mellitus	Tac > CSA
Neurotoxicity (headache, tremors, confusion, paresthesia)	Neurotoxicity (headache, tremors, confusion, paresthesia, insomnia)	Tac > CSA
Thrombotic microangiopathy	Thrombotic microangiopathy	
Gastrointestinal side effects (hepatotoxicity approximately 4% first month, dose related)	Gastrointestinal side effects (diarrhea, abdominal pain, nausea, vomiting, decreased appetite)	
Hyperkalemia	Hyperkalemia	
Hypomagnesemia	Hypomagnesemia	
Hyperchloremic metabolic acidosis	Hyperchloremic metabolic acidosis	
Hyperuricemia, gout	Hyperuricemia, gout	CSA > Tac
Others: Hirsutism, gingival hyperplasia	Others: Alopecia, pancreatitis	

Abbreviations: CSA, cyclosporine A; Tac, tacrolimus.

- Adjunctive agents:
  - MMF, mycophenolate sodium, sirolimus, everolimus, AZA
  - MMF or mycophenolate sodium is the most commonly used adjunctive agent. The side-effect profiles of MMF and mycophenolate sodium are summarized in Table 9.11.

Table 9.11 Side-effect profiles of mycophenolate mofetil and mycophenolate sodium

Mycophenolate Mofetil (Cellcept)	Mycophenolate Sodium (Myfortic) (enteric-coated mycophenolic acid derivative formulation)
Diarrhea, nausea, vomiting, abdominal pain, flatulence, dyspepsia	Potentially less gastrointestinal toxicity compared with Cellcept
Hematologic effects: leukopenia, leukocytosis	Hematologic effects: leukopenia, leukocytosis

(less commonly seen than leukopenia), anemia, thrombocytopenia	(less commonly seen than leukopenia), anemia, thrombocytopenia
Comments: More than 2 g/d is usually not well tolerated	Comments: Myfortic 180 mg = Cellcept 250 mg (similar efficacy)

- **Note**: MMF (or mycophenolate sodium) and sirolimus (or everolimus) must be discontinued in anticipation of pregnancy. MPA derivative use in pregnancy has been shown to be associated with first-trimester pregnancy loss and congenital malformation, whereas mTOR inhibitor use in pregnancy has been reported to be associated with fetal mortality, decreased fetal weight, and delayed ossification of skeletal structure.
- AZA, sirolimus, or everolimus is generally used in place of MMF for special indications:
  - Azathioprine (AZA):
    - AZA use is safe in pregnancy.
    - Avoid use with allopurinol (a xanthine oxidase inhibitor) because of the inhibition of AZA metabolism by xanthine oxidase inhibitors.
    - Febuxostat is a nonpurine selective inhibitor of xanthine oxidase. Hence, it should be avoided (or use with caution) in patients taking AZA.
  - Sirolimus or everolimus (mTOR inhibitors)
    - Potential beneficial effect in patients with history of malignancy, particularly skin cancers, renal cell carcinoma (RCC), or Kaposi sarcoma. Its use in posttransplantation lymphoproliferative disorder (PTLD) has inconsistently been shown to be beneficial.
    - Not recommended in the early postoperative period (may impair wound healing and delayed recovery of acute tubular injury)
    - The side-effect profiles of sirolimus and everolimus are summarized in Table 9.12.

Table 9.12 Side-effect profiles of mammalian target of rapamycin inhibitors (sirolimus or

everolimus)	
Potential Side Effects	**Comments**
Delayed recovery of acute tubular injury (acute tubular necrosis)	Not recommended in the early postoperative period Not recommended in patients with preexisting proteinuria ≥ 500 mg/d or at the discretion of the clinician (practice may differ among centers) Calcineurin inhibitor target level should be lowered when used in combination with mammalian target of rapamycin (mTOR) inhibitors mTOR inhibitor use is associated with the worst lipid profile compared to cyclosporine and tacrolimus
Impaired wound healing	
Increased risk of lymphocele formation	
May potentiate calcineurin inhibitor nephrotoxicity	
Oral ulcers	
Diabetogenic	
Proteinuria	
Dyslipidemia (increased cholesterol; may significantly increase triglyceride levels)	
Peripheral edema	
Pulmonary toxicity	
Thrombotic microangiopathy	
Others: acne, rash, anemia, thrombocytopenia, decreased testosterone	

Steroid- or CNI-free maintenance immunosuppressive protocol

- Must be individualized based on immunologic risk
- *Steroid withdrawal (CNI + MPA derivatives dual therapy)*
  - Safe in low immunologic risk patients at short-term follow-up (long-term graft function and the risk of chronic rejection have not been thoroughly evaluated)

- The 2016 Cochrane review suggests that steroid avoidance and withdrawal after kidney transplantation significantly increase the risk of acute rejection. There is no difference in patient mortality or graft loss up to 5 years after transplantation. However, long-term consequences of steroid avoidance and withdrawal remain unclear due to the lack of prospective long-term studies.

- *Belatacept in CNI-free protocol*
  - Clinicians must be familiar with its use.
  - May be considered in low immunologic risk patients with biopsy-documented CNI toxicity or CNI-induced thrombotic microangiopathy (TMA) and absence of acute rejection
  - Potential replacement for CNI in CNI-based immunosuppressive protocols
  - Typically used in combination with basiliximab induction, MPA derivatives, and corticosteroids: belatacept + MPA derivatives + corticosteroid
  - US FDA black box warning: Belatacept is contraindicated in Epstein–Barr virus (EBV)–naïve kidney transplant recipients due to increased risk of PTLD predominantly involving the central nervous system (CNS).

Drug–Drug Interaction

- Important drug–drug and drug–food interactions are summarized in Table 9.13.

Table 9.13 Drug–drug and drug–food interactions[a]

Drugs That Increase CNI Level by Inhibition of CYP3A or by Competition for Its Pathways	
Calcium channel blockers: diltiazem, verapamil > nicardipine	• Changing the dose of these drugs is equivalent to changing CNI dosage. • Brand vs. generic names and immediate vs. delayed-release formulations of diltiazem may have different effects on CNI levels.
The "azole" antifungals: fluconazole, ketoconazole, itraconazole, voriconazole, posaconazole, isavuconazole	• The "azole" antifungals markedly increase CNI levels. Great care must

	be taken when starting and stopping these drugs. • The absorption of ketoconazole and itraconazole requires acidic gastric contents. The use of proton-pump inhibitors/H2 blockers may reduce CNI-absorption, hence blood levels.
Antibiotics: erythromycin > other macrolide antibiotics (clarithromycin, josamycin, ponsinomycin)	• Azithromycin (conflicting reports): A short course can generally be given without the need for CNI level monitoring.
Antiretroviral agents: essentially all currently available protease inhibitors (e.g., ritonavir, ritonavir/lopinavir combination therapy, i.e., Kaletra, darunavir, indinavir/ritonavir, saquinavir, atazanavir, amprenavir)	• Immunosuppressive management in HIV patients requires close collaboration with infectious disease specialist due to multiple drug–drug interactions.
Hepatitis C protease inhibitors: telaprevir/boceprevir (no longer available in the United States)	
Others (less well established): amiodarone, carvedilol, allopurinol, bromocriptine, chloroquine	
Drugs that decrease CNI level by induction of CYP3A activity	
Antituberculous drugs: rifampin > rifabutin	• Rifampin markedly reduces CNI levels, and its use should be avoided if possible. • Pyrazinamide and ethambutol may reduce drug levels. Their use requires drug monitoring. • Isoniazid (INH) can be used with careful drug level monitoring.
Anticonvulsants: barbiturates > phenytoin > carbamazepine	• Oxcarbazepine (Trileptal) may decrease cyclosporine level. • Gabapentin (Neurontin) and levetiracetam (Keppra) and other drugs in this category do not appear to have significant drug interactions.
Corticosteroids	• Discontinuation of steroid therapy may result in an increase in tacrolimus level by up to 25%
Antidepressants herbal preparation: *Hypericum perforatum* (St. John wort)	
Others (less well-established/case reports): nafcillin, IV trimethoprim, IV sulfadimidine, imipenem,	

cephalosporins, terbinafine, ciprofloxacin	
Drugs or food that increase the absorption of CNIs	
Grapefruit, pomegranate, star fruit (also inhibits CYP3A) • Metoclopramide	• The effect of grapefruit juice may vary widely among brands and is concentration, dose, and preparation dependent.
Drugs or food that decrease the absorption of CNIs	
GoLYTELY, sevelamer, olestra, cholestyramine	
Nephrotoxic drugs or drugs that may potentiate CNI toxicity	
mTOR inhibitors, NSAIDs, tenofovir, amphotericin, aminoglycosides, ACE inhibitors, ARBs	• CNI target levels should be lowered when used in combination therapy with mTOR inhibitors. • Amphotericin and aminoglycoside-associated nephrotoxicity may occur earlier than anticipated when used with CNI therapy.
Commonly used herbals that may have an immune-stimulating effect	
Ginseng, licorice, alfalfa sprouts, astragalus	
Cholesterol-lowering agents	
Cyclosporine has an inhibitory effect on CYP3A and P-glycoprotein. The concomitant use of cyclosporine and statins can result in a several-fold increase in statin blood level and an increased risk for myopathy and rhabdomyolysis and acute kidney injury.	• All statins should be started at low dose. Any increase in dose requires close monitoring. Maximal dose should be avoided. • Rhabdomyolysis associated with tacrolimus and statin use is generally seen in patients on concomitant diltiazem therapy. • Concomitant lovastatin (or simvastatin) and gemfibrozil therapy increases the risk of rhabdomyolysis and should be avoided.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CNI, calcineurin inhibitor; IV, intravenous; mTOR, mammalian target of rapamycin; NSAIDs, nonsteroidal anti-inflammatory drugs.

Allograft Rejection: Types and Treatment Strategies

- Allograft rejection can be classified into hyperacute, acute, and chronic rejection.
- The 2017 Banff classification of renal allograft pathology is discussed in a later section. Hyperacute rejection is not classified under Banff categories.

Hyperacute rejection

- Pathogenesis
  - Caused by preformed antidonor HLA antibodies
  - Preformed antidonor HLA antibodies bind to graft endothelial antigens and activate complement, leading to severe vascular injury, thrombosis, coagulative necrosis, and obliteration of the graft vasculature
- With the current cytotoxic crossmatch and the advent of the single-antigen bead-based Luminex assays, hyperacute rejection has become virtually nonexistent.
- Hyperacute rejection can occur immediately following vascular anastomosis or within minutes to hours after graft revascularization.
- Hyperacute rejection uniformly results in graft loss, requiring allograft nephrectomy.

Acute rejection

- Acute rejection can be classified into acute T-cell–mediated rejection (TCMR) or acute antibody-mediated rejection (ABMR). Diagnosis requires allograft biopsy.
  - Acute TCMR:
    - Generally occurs after the first posttransplantation week and most commonly within the first 3 to 6 months after transplantation
    - In unsensitized patients with low levels of preformed anti-HLA antibodies, TCMR rarely occurs in the first week.
    - Acute TCMR has been suggested to be a risk factor for the development of de novo DSAs and subsequent ABMR.
    - Clinical manifestations: Most patients present with asymptomatic acute rise in serum creatinine. In the era of potent immunosuppression, fever, malaise, oliguria, and graft tenderness are usually absent unless immunosuppression is completely discontinued.
    - Pathogenesis: caused by T cells reacting to donor histocompatibility antigens expressed in the tubules, interstitium, vessels, and glomeruli to various extent
  - Acute ABMR:

- Clinical manifestations: Allograft dysfunction frequently more severe than that of TCMR.
- ABMR with concomitant features of TCMR may be seen.
- ABMR is a risk factor for chronic rejection.
- Pathogenesis: generally caused by DSA against HLA. Although uncommon, non-HLA DSAs have also been implicated in ABMR (e.g., anti-MHC class I–related chain A [MICA] and MHC class I–related chain B [MICB] antibodies, antiendothelial antibodies, or angiotensin-receptor 1 antibodies).

- *Treatment of acute TCMR based on Banff classification* (summarized in Table 9.14)

Table 9.14 T-cell–mediated rejection treatment strategies

Suspicious for Acute TCMR	Type 1 Acute TCMR	Type 2 Acute TCMR	Type 3 Acute TCMR	Chronic Active TCMR
Observe and follow creatinine trend vs. oral or IV steroid pulse per risk (such as degree of acute kidney injury, history of medical nonadherence, and immunologic risk)	Banff 1A: IV steroid pulse (5 mg/kg body weight) Banff 1B: IV steroid pulse or antithymocyte globulin (such as Thymoglobulin) per risk	Banff 2A: Antithymocyte globulin Banff 2B: Antithymocyte globulin	Antithymocyte globulin	There is no standardized protocol for the treatment of chronic active TCMR. Consider maximizing antimetabolite therapy if applicable.

Abbreviations: IV, intravenous; TCMR, T-cell–mediated rejection.

- Suspicious for rejection
  - Decision to treat with corticosteroid pulse is generally based on clinical history such as severity of acute kidney injury (AKI), immunologic risk, history of medical nonadherence, and/or subtherapeutic CNI levels.
- Banff grade 1A
  - High-dose intravenous (IV) corticosteroid, usually referred to as “pulse steroid” or “SoluMedrol pulse” (methylprednisolone pulse) at 5 mg/kg body weight for 3 days. Higher dose such as 500 to 1,000 mg for 3 days does not appear to be more effective. The dose of prednisone can be continued at its previous level after completion of

the pulse steroid. Some centers may elect to follow various oral steroid tapering protocols.
        - Antithymocyte globulin (ATG) should be considered in TCMR refractory to corticosteroid therapy (refractory can be arbitrarily defined as failure of serum creatinine to improve or deterioration of graft function despite three "daily methylprednisolone pulse"). Note that there may be a delay in serum creatinine improvement by 2 to 5 days following completion of steroid pulse. Clinical judgment is required.
    - Banff grade 1B
        - Choice of high-dose IV corticosteroid versus ATG such as thymoglobulin generally requires clinical correlation. ATG is generally employed in patients with moderately severe to severe AKI or in those who develop acute TCMR in the early posttransplantation period. ATG should also be considered in those who fail to respond to pulse corticosteroid (particularly when there is rapid deterioration of renal function).
    - Banff grade 2A or 2B
        - ATG (e.g., thymoglobulin)
    - Banff grade 3
        - ATG
- *Treatment of acute ABMR*
    - Standard of care: plasmapheresis and intravenous immunoglobulin (IVIG)
        - The DSA mean fluorescence intensity threshold to initiate plasmapheresis differs among centers and clinicians.
        - Standard IVIG dose: 2 g/kg body weight total dose (usually given in two divided doses)
        - Some centers also advocate steroid pulse therapy x 3-5 days
    - Other treatment modalities (clinicians must be familiar with its use):
        - Agents targeting B cells: rituximab
        - Agents targeting plasma cells: bortezomib
            - Limited efficacy data. Significant adverse effects have been

reported.

- Agents targeting the complement system: eculizumab
  - Prophylactic measures to reduce meningococcal disease risk: Meningococcal vaccination recommended at least 2 weeks prior to eculizumab therapy. If vaccination is given < 2 weeks prior to first dose, must start antibiotic prophylaxis × 2 weeks (see package insert).
  - Efficacy and safety remains to be determined.
- Other agents: anti–IL-6-receptor monoclonal antibody, C1-esterase inhibitor, anti-C1s monoclonal antibody. Discussion is beyond the scope of this chapter.

- Table 9.15 summarizes the potential mechanisms of action of various treatment modalities.

Table 9.15 Potential mechanisms of action of various treatment modalities used in the treatment of acute ABMR

Treatment Modalities	Potential Mechanism(s) of Action	Comments/Clinical Use
Plasmapheresis	Removes circulating alloantibodies	May stimulate rebound immunoglobulin production
Intravenous immunoglobulin (IVIG)	Anti-idiotypic antibodies (inhibits anti-HLA antibody) Produce long-term suppression or elimination of anti-HLA reactive T and B cells Induce apoptosis of B cells Downregulate antibody production by plasma cells Inhibit complement-mediated damage Inhibit cytokine signaling pathway and alloimmunization via blockade of the T-cell receptor Immune modulation	Removed by plasma exchange (must give after plasmapheresis)
Agent targeting B cells: Rituximab	Anti-CD20 monoclonal antibodies May induce naïve and memory B-cell depletion Plasma cells lack CD20 and are unaffected by rituximab	• Treat ABMR • Use as part of a conditioning regimen in patients with preformed anti-HLA antibodies or ABO incompatibility
Agent targeting plasma cells: Bortezomib	Proteasome inhibitor; induce plasma cell apoptosis Reduce donor-specific antibody (DSA) production by plasma cells	• Rescue therapy for ABMR refractory to IVIG and/or rituximab (based on small studies)

		• Limited efficacy data and significant adverse effects
Agents targeting the complement system: • Eculizumab • C1 esterase inhibitor (C1-INH) • BIVV009	*Eculizumab:* terminal complement inhibitor (binds to C5, preventing cleavage of C5 into C5a and C5b and the formation of C5b and membrane attack complex) Protects endothelium from injury caused by existing antibodies *C1-INH:* inhibits multiple enzymes, including inhibition of complement activation by interruption of assembly of C1s and C1r in the classic pathway *BIVV009:* selectively targets the serine protease C1s In vitro studies showed that it prevents activation of the classic complement pathway and reduces downstream deposition of complement fragments and generation of anaphylatoxins	*Eculizumab* • Preventive or rescue therapy (based on small studies) • Treatment of ABMR (based on case reports) • **NCT01895127**[a]: Phase 2 open-labeled randomized trial comparing the efficacy and safety of eculizumab vs. plasmapheresis and IVIG in kidney transplant recipients with biopsy-documented ABMR was terminated after 11 subjects were enrolled due to lack of efficacy • **NCT01399593**[b]: Results of phase 2 trial suggests a beneficial effect of eculizumab in preventing ABMR compared with standard of care in highly sensitized living donor transplant recipients requiring pretransplant desensitization *C1-INH* • Further studies are needed *B1VV009* • Further studies are needed

Anti–interleukin-6 (IL-6) receptor monoclonal antibody: Tocilizumab	The proinflammatory cytokine IL-6 may play an important role in the development of DSA and chronic active ABMR. Limited data demonstrated that IL-6 neutralization delayed onset of acute cell–mediated rejection and prolonged graft survival	Rescue therapy for DSA-positive chronic active ABMR and evidence of transplant glomerulopathy not responsive to standard-of-care treatment with IVIG and rituximab with or without plasmapheresis (based on small case series)

[a]ClinicalTrials.gov Identifier: NCT01895127.

[b]Marks WH, Mamode N, Montgomery RA, et al. Safety and efficacy of eculizumab in the prevention of antibody-mediated rejection in living-donor kidney transplant recipients requiring desensitization therapy: a randomized trial. *Am J Transplant*. 2019;19(10):2876–2888.

Abbreviations: ABMR, antibody-mediated rejection; HLA, human leukocyte antigen.

- *Manipulation of maintenance immunosuppression following treatment of acute TCMR and/or acute ABMR*
  - Increase maintenance immunosuppressive drug target levels (tacrolimus or cyclosporine).
  - In patients who are on cyclosporine-based immunosuppression, may also consider cyclosporine to tacrolimus switch.
  - Maximize antimetabolite therapy as tolerated (if patient is not already on maximum dose of MMF or mycophenolate sodium).

Chronic rejection

- Graft deterioration in the late posttransplantation period can be due to alloimmune or nonalloimmune causes or both. Diagnosis requires allograft biopsy.
- Chronic rejection is an alloimmune-dependent process associated with T-cell–mediated and/or antibody-mediated injury.
- Risk factors: prior acute rejection episodes (TCMR or ABMR or both). Poor HLA matching, prior sensitization or posttransplantation development of HLA antibodies (de novo or anamnestic response), underimmunosuppression, or medical nonadherence
- Clinical manifestations: Patient generally present with gradual deterioration in kidney allograft function with or without various degrees of proteinuria.

- Chronic rejection of the kidney transplant is the most common cause of graft loss in the late posttransplantation period.
- Pathogenesis:
  - Chronic ABMR is a process in which donor-specific anti-HLA antibodies develop, followed by immune-mediated injury to the kidney allograft. Continuous antibody-mediated injury can lead to separation of the endothelial cells from the underlying basement membrane. These cells will, in turn, lay down new basement membrane matrix, resulting in the so-called basement membrane duplication and the histologic appearance of transplant glomerulopathy (TG).
  - Interstitial inflammation in the areas of interstitial fibrosis and tubular atrophy (i-IFTA) is considered a potential lesion of chronic active TCMR. However, the pathogenesis of i-IFTA and to what extent this represents a manifestation of TCMR remain to be studied.
- Treatment:
  - Chronic active TCMR
    - The optimal management of chronic active TCMR remains to be defined. Table 9.14 summarizes the treatment strategies for acute TCMR and chronic active TCMR (opinion based).
  - Chronic active ABMR
    - There is currently no effective therapy for chronic active ABMR. Consider maximizing antimetabolite therapy as tolerated if applicable (i.e., MMF 1,000 mg twice a day or mycophenolate sodium 720 mg twice a day).
    - The presence of chronic TG portends poor graft prognosis, particularly when associated with positive C4d staining. The use of tocilizumab or other anti-IL-6 receptor monoclonal antibody in the treatment of DSA-positive chronic active ABMR is an area of intense clinical research.

KIDNEY ALLOGRAFT BIOPSY

Histopathologic Terminologies

- Acute tubular injury (also known as, acute tubular necrosis) (**Fig. 9.2**):

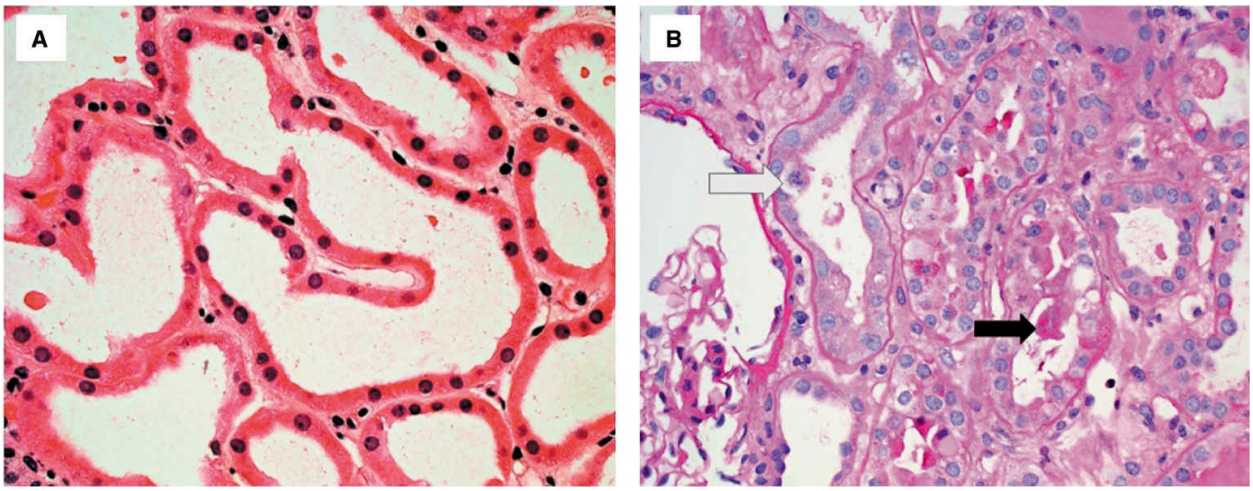

FIGURE 9.2 Acute tubular injury. **A.** Tubular cells are flattened and have lost brush borders (hematoxylin and eosin stain, ×400). **B.** Severe tubular injury with epithelial cell necrosis and sloughing into tubular lumina (*black arrow*). A tubular mitotic figures is present (*white arrow*) (periodic acid–Schiff stain, ×400).

- Proximal tubule epithelial cell flattening, loss of brush border staining, cellular degeneration or necrosis, mildly dilated lumina, and/or sloughed epithelial cells

- Tubulitis (**Fig. 9.3**):

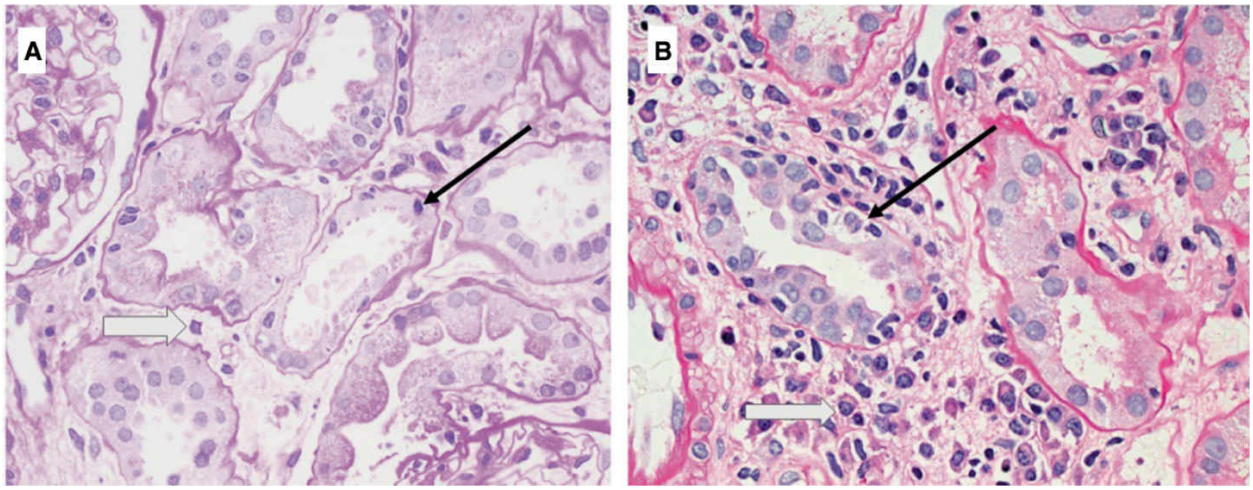

FIGURE 9.3 Interstitial inflammation and tubulitis are the histologic features of acute T-cell–mediated rejection (TCMR). **A.** Acute TCMR grade 1A. Moderate tubulitis represented by 5 to 10 lymphocytes within a tubular cross section (*black arrow*). Interstitial inflammatory cells (lymphocytes) between tubules (*white arrow*). **B.** Acute TCMR grade 1B. Severe tubulitis represented by >10 lymphocytes within a tubular cross section (*black arrow*). Dense interstitial inflammatory cells (lymphocytes and plasma cells) between tubules (*white arrow*) (periodic acid–Schiff stain, ×400).

- Mononuclear cells within tubular walls between epithelial cells

- Interstitial inflammation (**Fig. 9.3**):
  - Inflammatory cells between tubules in interstitial spaces and can include lymphocytes, plasma cells, macrophages, eosinophils, and/or rare neutrophils may be seen
- Intimal arteritis (i.e., endarteritis or endotheliitis) (**Fig. 9.4A**):

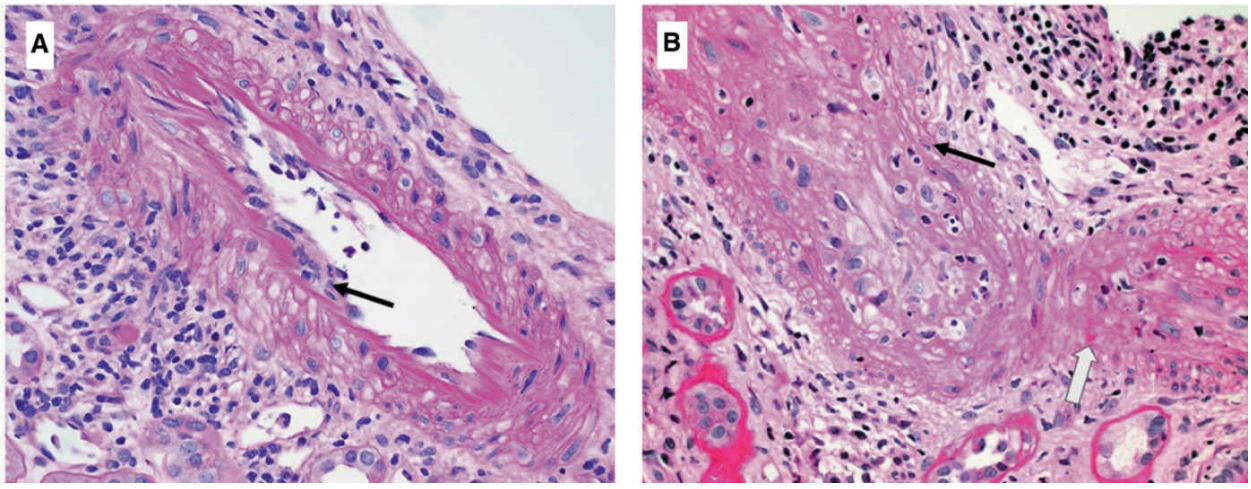

FIGURE 9.4 Vascular inflammation is a histologic features of severe acute T-cell–mediated rejection (TCMR). These changes can also be seen with active antibody-mediated rejection. **A.** Acute TCMR grade 2A. Mild intimal arteritis (<25% luminal obstruction) represented by leukocytes directly beneath the artery endothelial cells within the intimal layer only (*black arrow*). **B.** Acute TCMR grade 3. Transmural arteritis (*black arrow*) with fibrinoid necrosis (*white arrow*) (periodic acid–Schiff stain, ×400).

  - Lymphocytes underneath the endothelium in the arterial intima
- Arterial transmural inflammation (transmural arteritis) and fibrinoid change (**Fig. 9.4B**):
  - Inflammation extending into arterial medial layer with smooth muscle cell necrosis and fibrin deposition
- Glomerulitis (**Fig. 9.5A**):

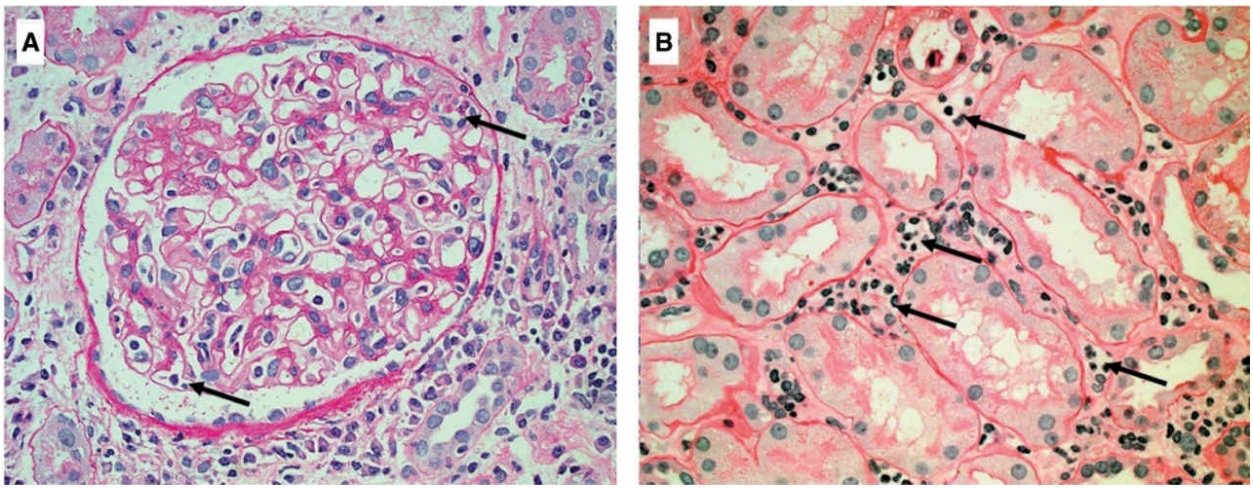

FIGURE 9.5 Microvascular inflammation is a histologic feature of active antibody-mediated rejection. **A.** Glomerulus involved by glomerulitis represented by increased endocapillary leukocytes and swollen endothelial cells (*arrows*). **B.** Peritubular capillaritis represented by increased peritubular capillary leukocytes (*arrows*) (periodic acid–Schiff stain, ×400).

  - Leukocytes and swollen endothelial cells within glomerular capillary lumens
- Peritubular capillaritis (**Fig. 9.5B**):
  - Leukocytes within peritubular capillary lumens
- Transplant glomerulopathy (TG) (**Fig. 9.6**):

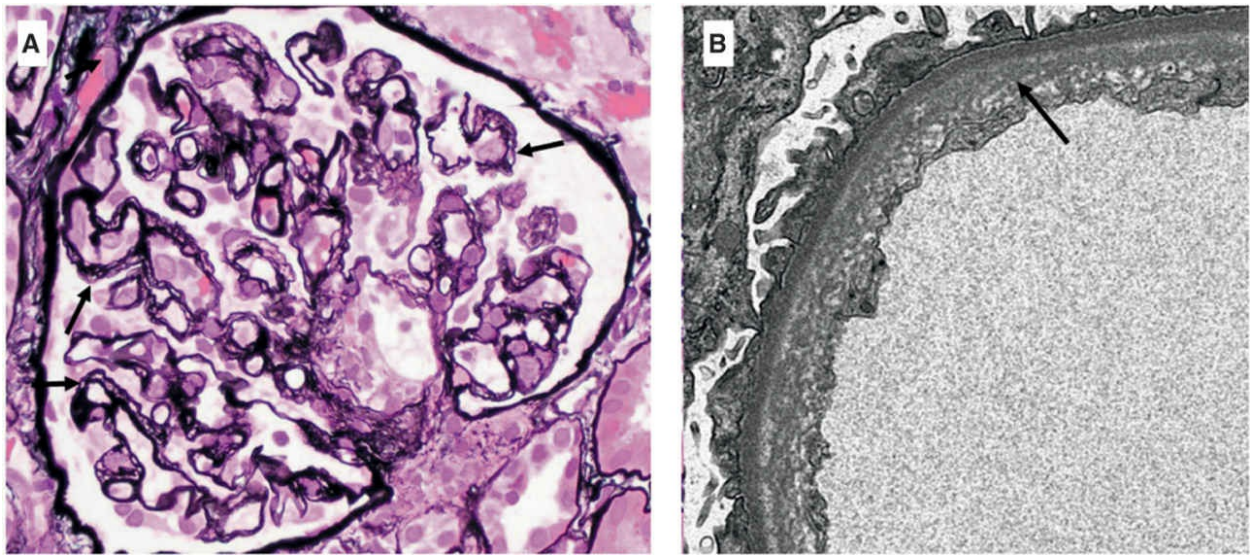

FIGURE 9.6 Transplant glomerulopathy is a feature of chronic antibody-mediated rejection. **A.** Glomerulus with double contours on light microscopy (*arrows*) (Jones Silver stain, ×400). **B.** Electron micrograph demonstrating multilayered capillary loop glomerular basement membrane duplication (×6,300).

- Glomerular capillary double contours composed of subendothelial lucencies with deposition of new subendothelial basement membrane

- Chronic transplant arteriopathy: expansion of arterial intimal spaces by fibrosis admixed with mononuclear cells with or without foam cells (**Fig. 9.7A**)

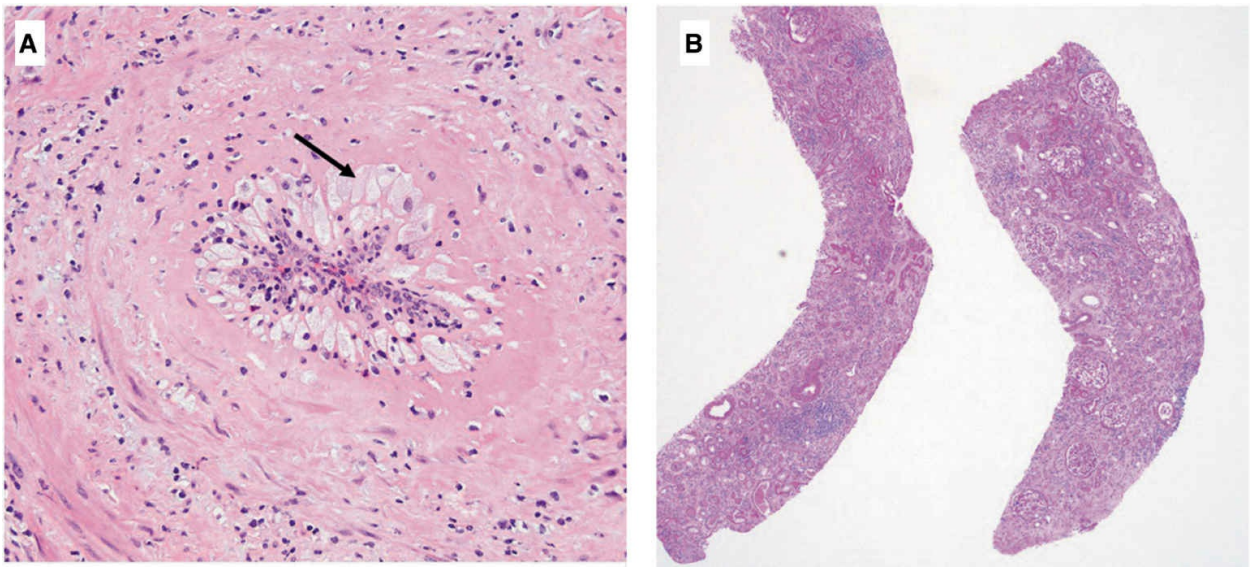

FIGURE 9.7 Chronic active T-cell–mediated rejection (TCMR). **A.** Chronic allograft arteriopathy (chronic active TCMR II). Arterial intimal fibrosis admixed with lymphocytes and foam cells (*arrow*) (hematoxylin and eosin stain, ×400). **B.** Inflammation and tubulitis in areas of cortical scar can be features of chronic active (TCMR) (periodic acid–Schiff stain, ×400).

- Thrombotic microangiopathy (TMA) (**Fig. 9.8**):

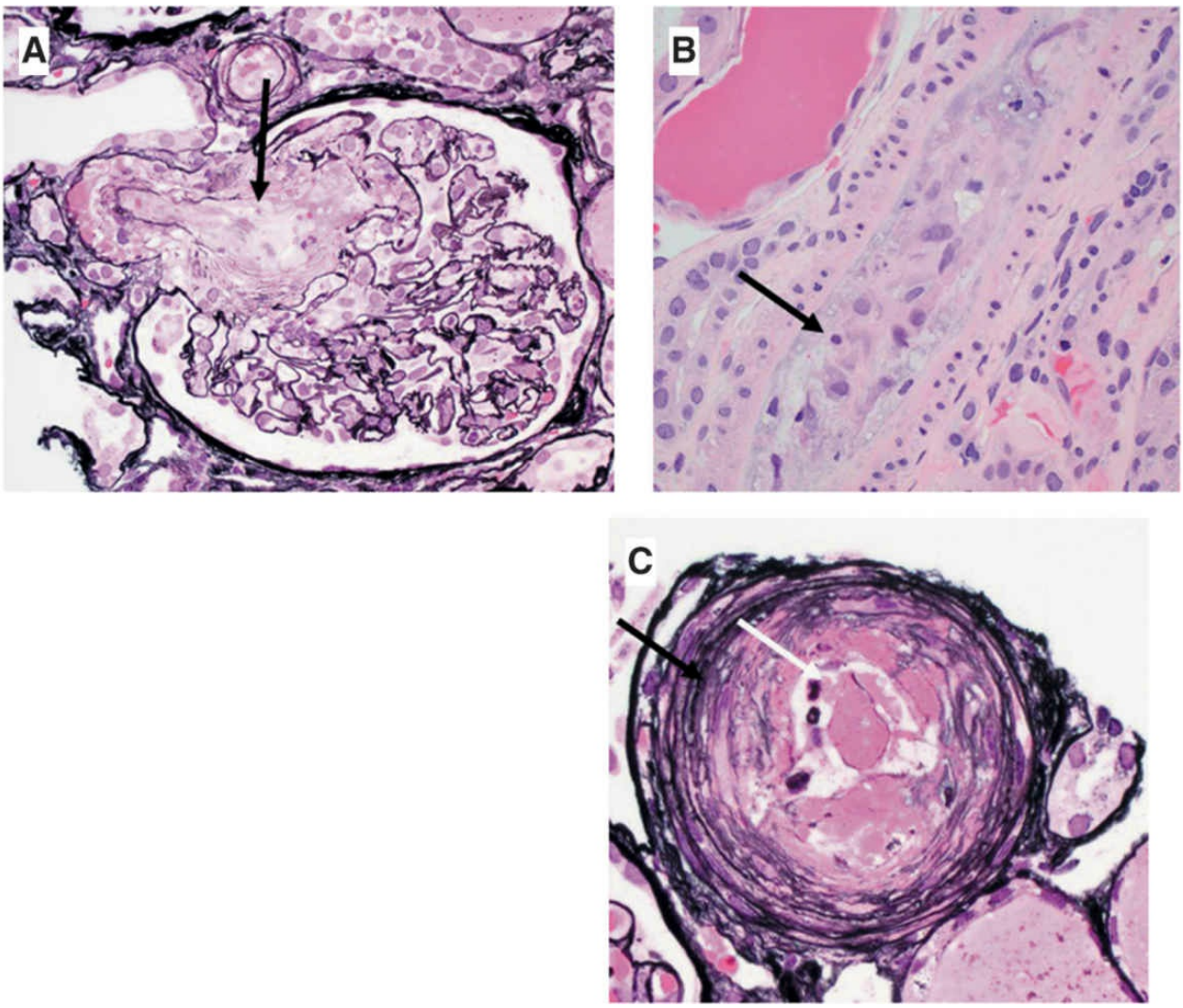

FIGURE 9.8 Thrombotic microangiopathy can be associated with antibody-mediated rejection, calcineurin inhibitor therapy, and wide variety of conditions including thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, autoimmune disorders, viral infections, and other drug toxicities. Distinguishing specific etiology on biopsy is not possible. **A.** Glomerular thrombosis (*arrow*) with early capillary loop double contours (Jones Silver stain, ×400). **B.** Artery with mucoid intimal edema (*arrow*) (hematoxylin and eosin stain, ×400). **C.** Arterial luminal thrombus (*white arrow*) with early "onion-skin change" (*black arrow*) (Jones Silver stain, ×400).

  - Luminal aggregates of platelets and/or fibrin within arterial or glomerular capillary lumens and/or subendothelial edema (mucoid intimal edema) within arteries/arterioles
  - Chronic TMA can mimic TG and shows "onion-skin" change in arteries/arterioles.
- C4d staining (**Fig. 9.9**):

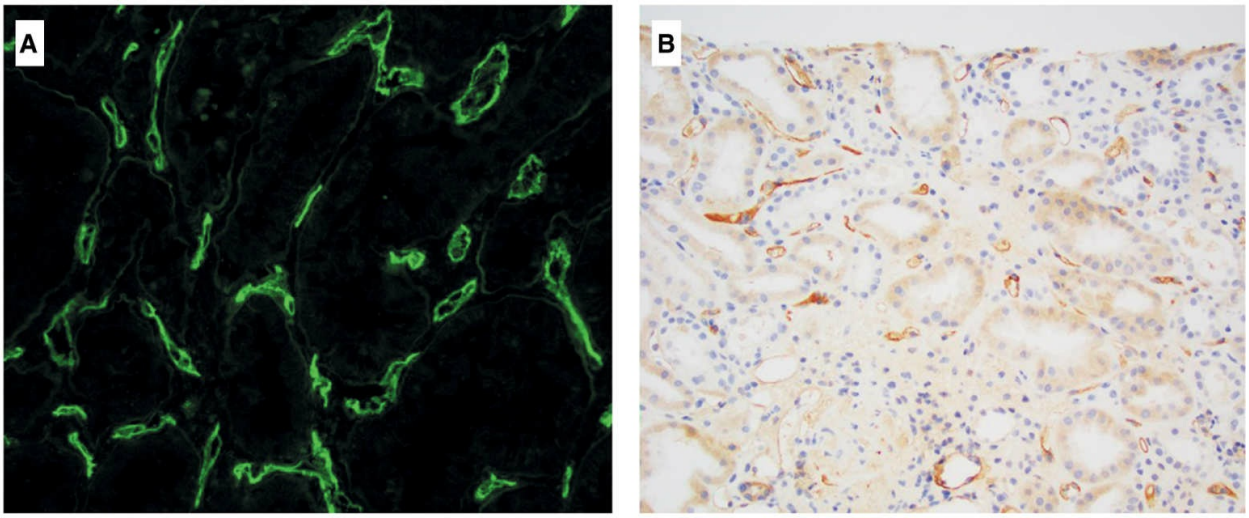

FIGURE 9.9 C4d staining of peritubular capillaries is a marker of antibody-mediated rejection. **A.** Immunofluorescence staining for C4d is more sensitive. **B.** Immunohistochemical staining for C4d is more specific (images at ×400).

- Component of the classic complement cascade that is covalently linked to tissue
- Surrogate marker of antibody endothelial cell interaction
- Staining is evaluated in peritubular capillaries (cortex or medulla).
- Glomerular staining not specific and is not scored.

- Proximal tubule isometric vacuolization (**Fig. 9.10A**):

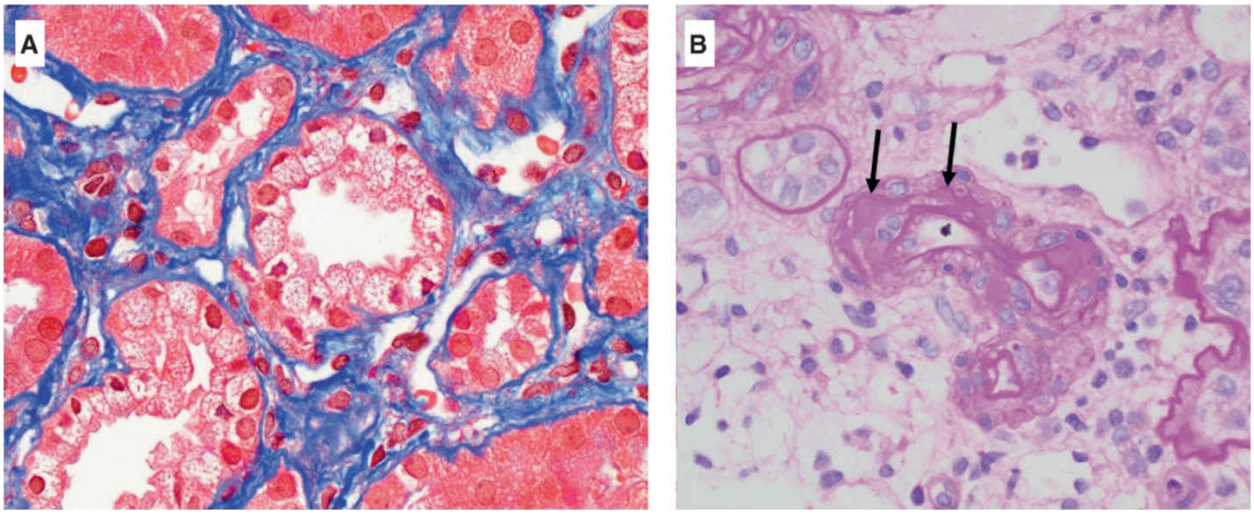

FIGURE 9.10 Acute and chronic sequelae of calcineurin inhibitors. **A.** Isometric vacuolization of proximal tubules cells is frequently associated with acute calcineurin inhibitor toxicity (Trichrome stain, ×400). **B.** Nodular medial hyalinosis (*arrows*) is associated with chronic calcineurin inhibitor effect.

- Focal proximal tubule cells with uniform cytoplasmic vacuolization often with small shrunken (pyknotic) nuclei, usually S3 segment of proximal tubule

- Nodular medial hyalinosis (**Fig. 9.10B**):
  - Nodular hyaline accumulation within the walls of arterioles
  - Presumed to result from degeneration of the arteriolar smooth muscle cells
- Arteriosclerosis (**Fig. 9.11A**):

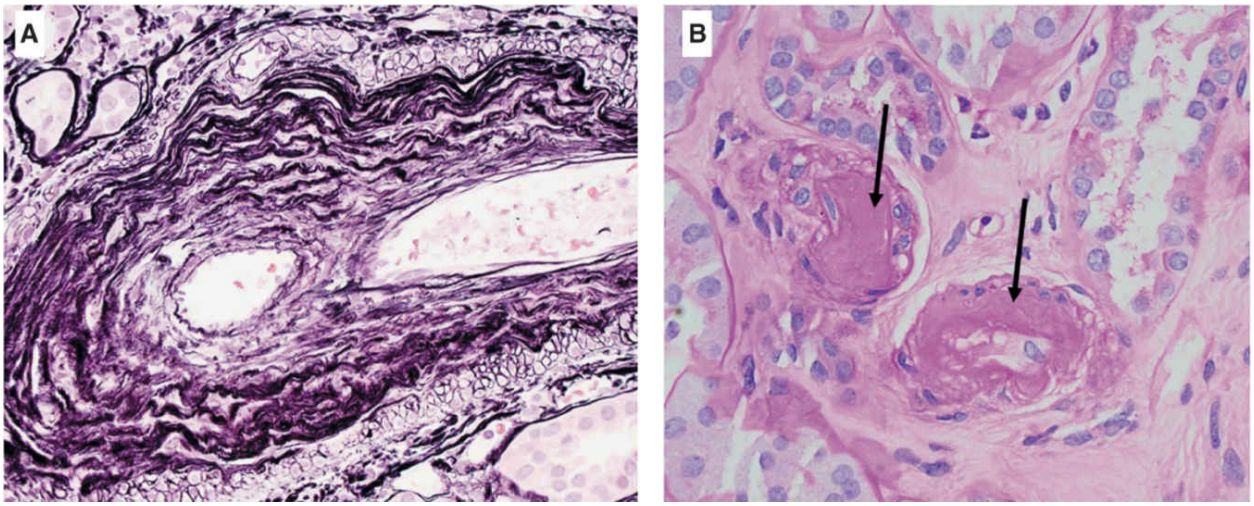

FIGURE 9.11 Chronic noninflammatory vascular changes usually related to age or chronic hypertension. **A.** Arteriosclerosis—expansion of the arterial intima by fibrosis with concentric duplication of the internal elastic lamina. **B.** Arteriolosclerosis—subintimal accumulation of hyaline insudate beneath arteriolar endothelial cells (*arrows*).

  - Intimal fibrosis of arteries without inflammation
- Arteriolosclerosis (**Fig. 9.11B**):
  - Hypertrophy of medial layer of arterioles with or without intimal hyalinization

Banff Classification

- Most widely accepted classification system for allograft biopsy diagnostic changes, specifically for alloimmune-related graft injury—rejection
- A working classification that is updated every 2 years
- The 2017 Banff classification is categorized into six broad categories

based on the presence or absence of the histopathologic features described above.

- *Banff categories 1 to 5:* predominantly refers to categories of transplant rejection (summarized in Tables 9.16 and 9.17)

Table 9.16 Banff Categories 1 to 5

Category 1	Category 2	Category 3	Category 4	Category 5
Normal biopsy or nonspecific changes	Antibody-mediated changes	Suspicious or borderline changes for acute TCMR	TCMR	IFTA
	See **Table 9.17**	• Up to 25% interstitial inflammation with any degree of tubulitis • >25% interstitial inflammation and up to one to four lymphocytes per tubular cross section	**Acute TCMR** Banff 1A: • >25% unscarred interstitial inflammation • Tubulitis with 5–10 lymphocytes Banff 1B: • >25% unscarred interstitial inflammation • Tubulitis with >10 lymphocytes or any degree of tubulitis with tubular rupture Banff 2A: • Subendothelial artery inflammation[a] with 25% vascular luminal occlusion • Any degree of interstitial or tubular inflammation banff 2b: • subendothelial artery inflammation[a] with ≥25% vascular luminal occlusion • Any degree of interstitial or tubular inflammation Banff 3: • Mononuclear arterial inflammation that is transmural and/or with smooth muscle fibrinoid	**Grade 1:** • 25% cortical ifta (mild ifta) **Grade 2:** • 26%–50% cortical IFTA (moderate IFTA) **Grade 3:** • >50% cortical IFTA (severe IFTA)

			necrosis • Any degree of interstitial or tubular inflammation • May reflect ABMR **Chronic active TCMR** Banff 1A: • >25% IFTA with inflammation (i-IFTA) without other known cause of inflamed fibrosis[b] • >25% inflamed total cortical interstitial area • Tubulitis with 5–10 lymphocytes in preserved to moderately atrophic tubules Banff 1B: • Changes similar to Banff 1A but tubulitis with >10 lymphocytes in preserved to moderately atrophic tubules Banff 2: • Artery with mononuclear inflammation in intimal fibrosis (chronic allograft arteriopathy)	

[a]Endarteritis, intimal arteritis, endotheliitis.

[b]Such as chronic pyelonephritis or chronic BK virus infection.

Abbreviations: ABMR, antibody-mediated rejection; IFTA, interstitial fibrosis and tubular atrophy; TCMR, T-cell–mediated rejection.

Table 9.17 Banff category 2 (antibody-mediated changes)

Antibody-Mediated Changes	Histologic and Other Features
Active ABMR (all three criteria must be present) 1. One or more histologic features of active antibody-mediated injury[a] 2. Evidence of antibody-mediated vascular injury[a] 3. Evidence of DSA[a]	**Histologic features of active antibody-mediated injury** • Microvascular inflammation (glomerulitis or peritubular capillaritis) • Arterial inflammation • Thrombotic microangiopathy without other causes • Acute tubular injury without other causes
Chronic active ABMR (all three criteria must be present) 1. Histologic features of chronic antibody-	**Histologic features of chronic antibody-mediated injury** • Transplant glomerulopathy (TG); glomerular

mediated injury[a] 2. Evidence of antibody-mediated vascular injury[a] 3. Evidence of DSA[a]	capillary double contours with new layers of subendothelial basement membrane material • Identified by light microscopy or EM only • Multilayered peritubular capillary basement membranes (seen by EM) • New-onset arterial intimal fibrosis without other cause
Chronic ABMR (both criteria must be present) 1. Histologic features of chronic antibody-mediated injury[a] 2. Prior documented active or chronic active ABMR or prior documented DSA	**Evidence of antibody-mediated vascular injury** • Peritubular capillary C4d staining in >10% by IF or >0% by immunohistochemistry • Expression of ABMR-associated gene transcripts in renal tissue • Moderate glomerulitis and/or peritubular capillaritis
C4d staining without evidence of rejection (criteria 1–3 must be present. Criterion 4 must be present if done)[b] 1. Positive C4d stain 2. No histologic features of active or chronic active ABMR 3. No histologic features of T-cell–mediated rejection or borderline lesions 4. No expression of validated ABMR-associated gene transcripts	**Evidence of DSA** • Serologic evidence of DSA to HLA or non-HLA antigens (such as anti-AT1R antibodies or MICA) • C4d positive • Expression of ABM-associated gene transcripts in renal tissue

[a]See right column for detailed criteria.

[b]In ABO-incompatible transplant, this may represent accommodation.

Abbreviations: DSA, donor-specific antibody; EM, electron microscopy; IF, immunofluorescence; MICA, MHC class-I–related chain A.

- The histopathologic features of Banff categories 2 and 4 are shown in **Figures 9.3 to 9.9**.
  - T-cell–mediated rejection (TCMR):
    - Acute TCMR: Banff grades 1A, 1B, 2A, 2B, 3 (**Figs. 9.3 and 9.4**)
    - Chronic active TCMR: Banff grades 1A, 1B, 2 (**Fig. 9.7**)
  - Antibody-mediated changes
    - Acute ABMR, chronic active ABMR, chronic ABMR (**Figs. 9.5, 9.6, and 9.9**)
- Banff category 6: Histopathologic changes not considered to be caused by acute or chronic rejection:

- Acute tubular injury (also known as acute tubular necrosis) (**Fig. 9.2**)
- Polyomavirus nephropathy, usually BK virus (BKV) (rarely JC virus) (**Fig. 9.12**)

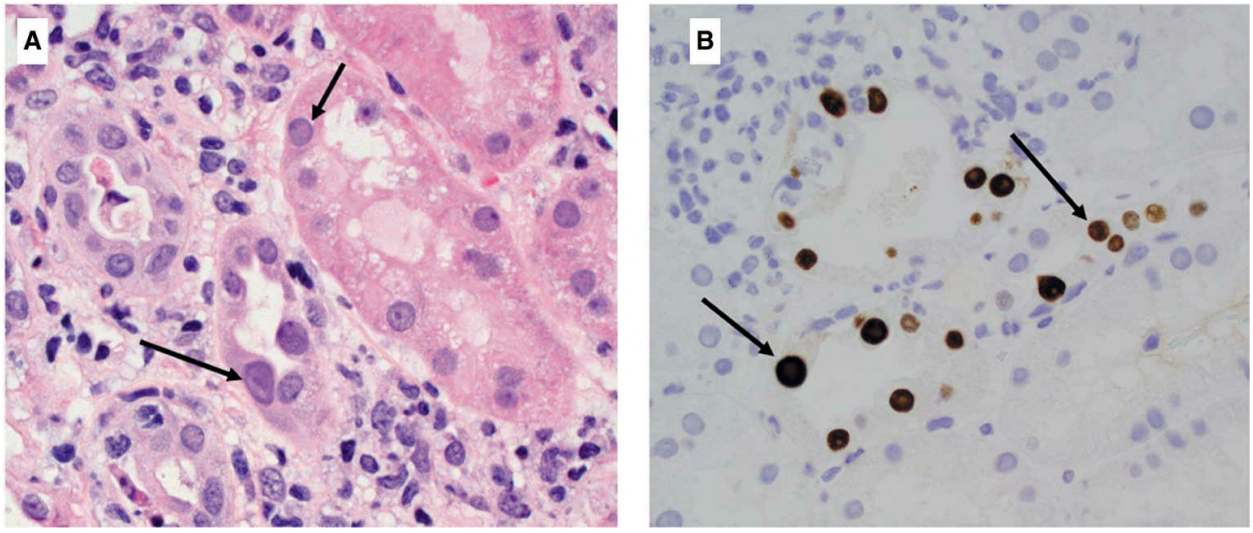

FIGURE 9.12 Polyoma (BK) virus nephropathy. **A.** Tubular epithelial cells with viral inclusions (*arrow*) (hematoxylin and eosin, ×400). **B.** SV40 immunostain demonstrates strong nuclear staining (*arrow*) and is confirmatory of polyomavirus infection (×400).

  - Most common infection identified on allograft biopsy
  - Ascending infection from infected urothelial cells of the bladder
  - Tubulointerstitial inflammation often with prominent plasma cells
  - Confirmed with SV40 immunostain and/or the presence of viral inclusion
  - Histologic changes may be identical to acute TCMR.
- CNI nephrotoxicity (**Fig. 9.10**)
- Pyelonephritis (**Fig. 9.13**)

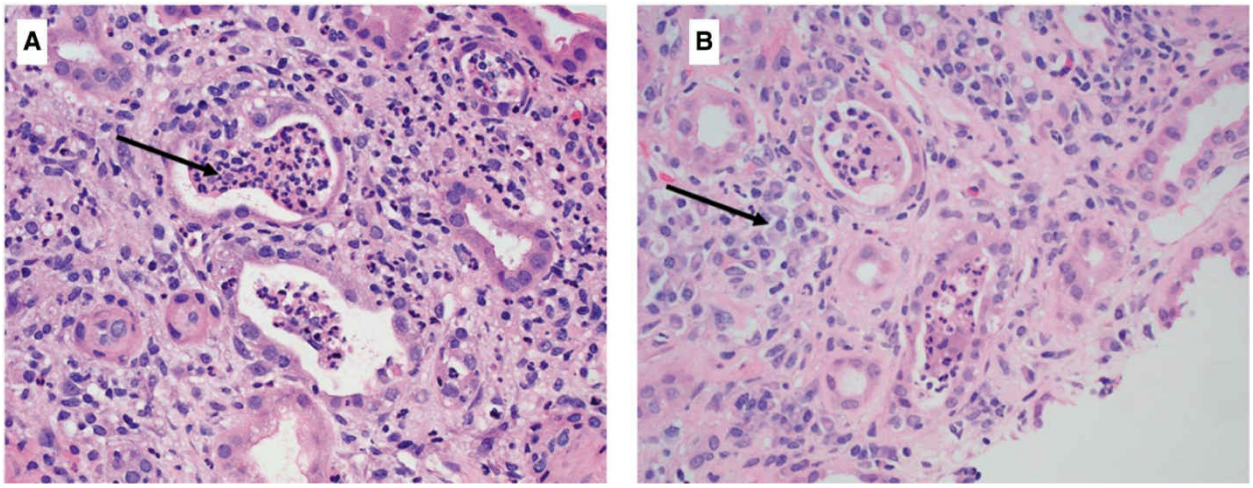

FIGURE 9.13 Pyelonephritis results from ascending bacterial infections. **A.** Neutrophilic intraluminal tubular cast (*arrow*) and adjacent neutrophilic interstitial inflammation are features of acute pyelonephritis. **B.** Chronic pyelonephritis typically shows increased plasma cells (*arrow*) and interstitial fibrosis.

- Drug-induced interstitial nephritis
- Posttransplant lymphoproliferative disorders (**Fig. 9.14**)

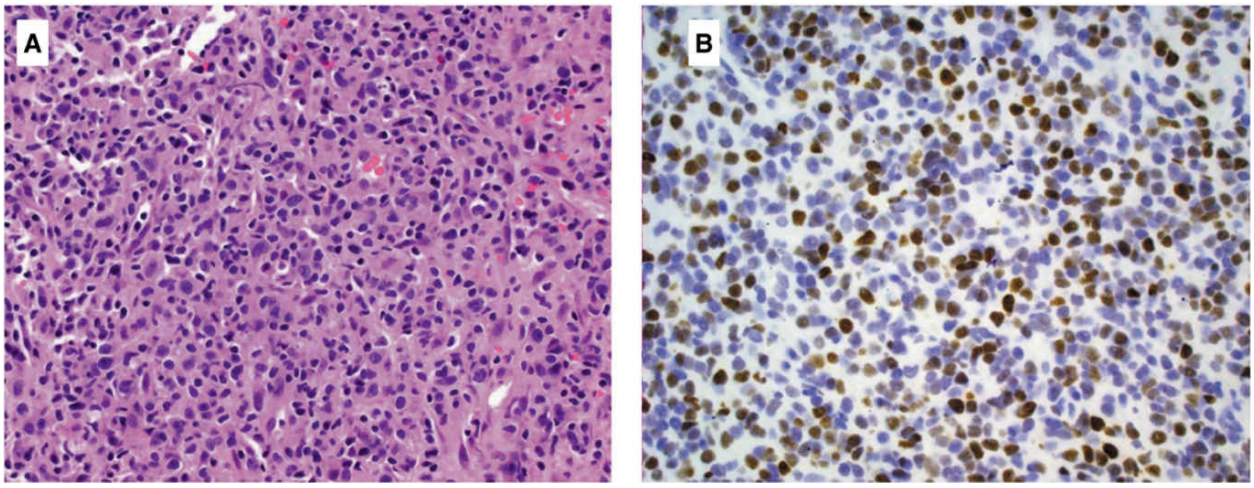

FIGURE 9.14 Posttransplant lymphoproliferative disorder (PTLD). **A.** Diffuse large B-cell lymphoma (hematoxylin and eosin, ×400). **B.** Epstein–Barr virus (EBV) is present in the majority of cases of PTLD. (EBV-encoded small RNAs in situ hybridization, ×400.)

- Recurrent disease (**Fig. 9.15**)

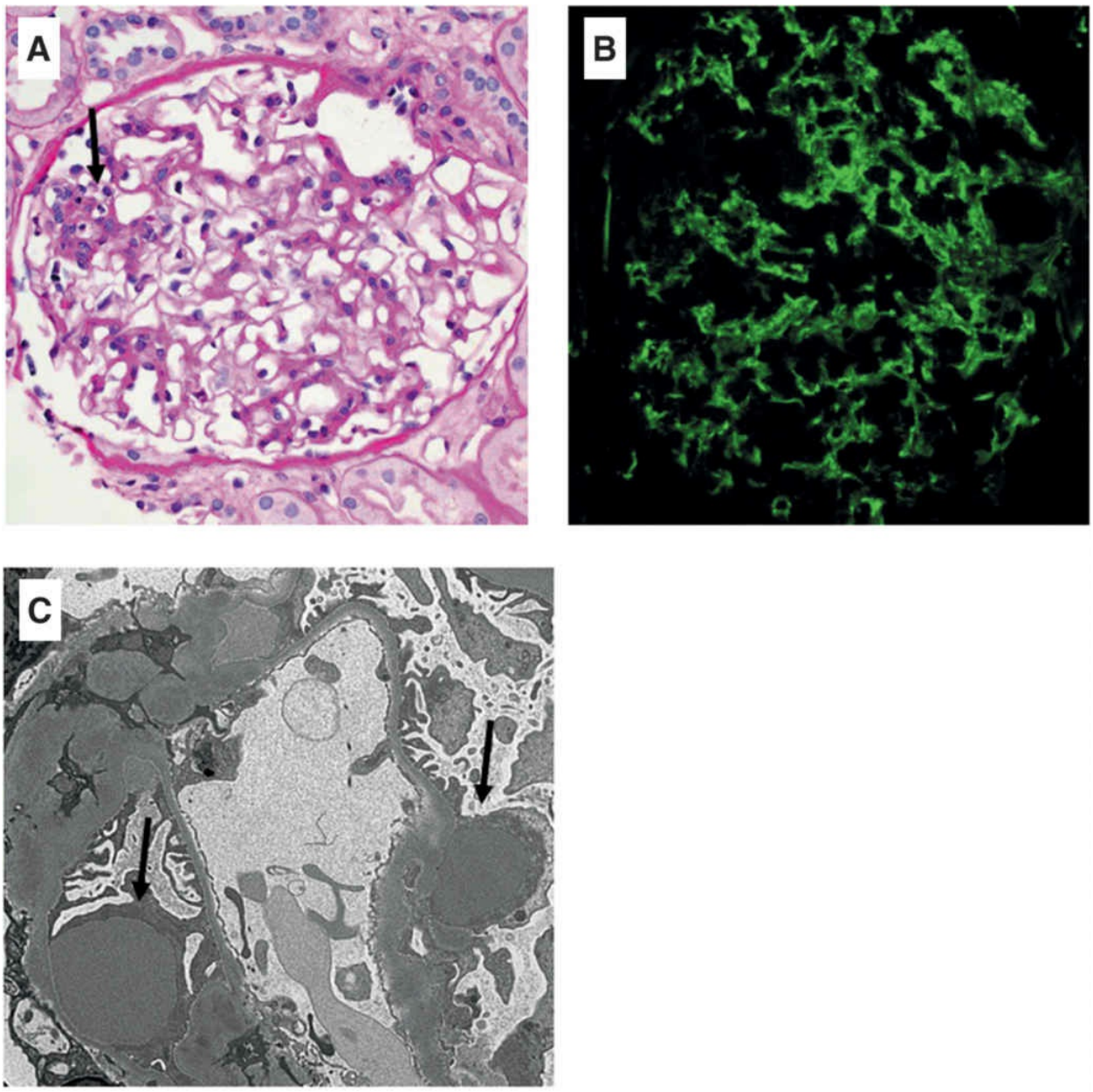

FIGURE 9.15 C3 glomerulonephritis nearly always recurs in the kidney allograft with a generally indolent course. **A.** Acute proliferative glomerulonephritis represented by segmental endocapillary neutrophils (*arrow*). **B.** Bright C3 immunofluorescence staining (×400). **C.** Subepithelial "hump-like" deposits (*arrows*) present on electron microscopy (×4,000).

- Disease that commonly recur include:
  - C3 glomerulopathy
  - Idiopathic/primary FSGS
  - Immunoglobulin A (IgA) nephropathy
  - Membranous nephropathy

- De novo glomerular disease (**Fig. 9.16**)

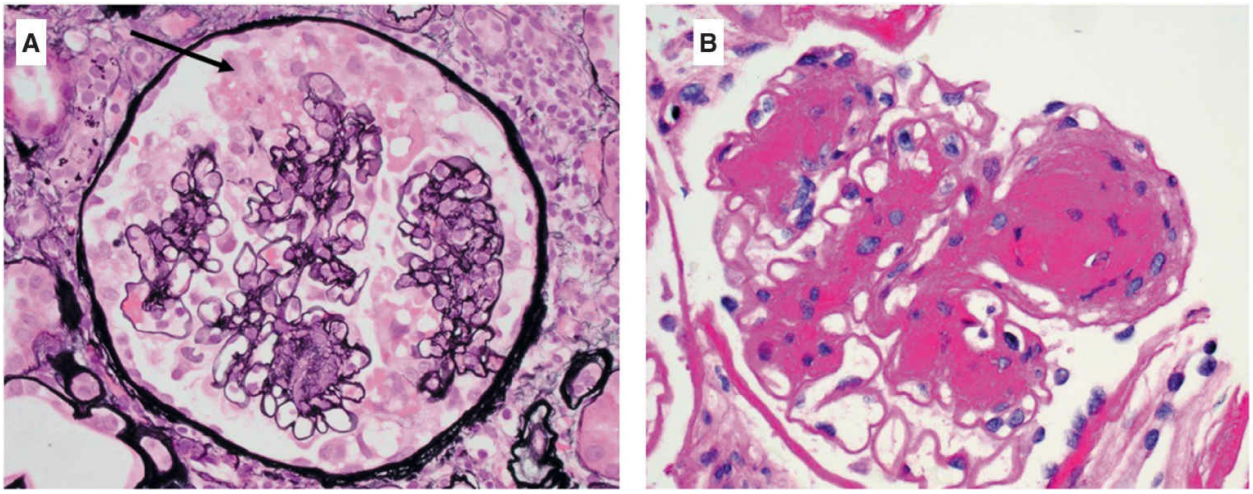

FIGURE 9.16 Examples of de novo glomerular disease in the renal allograft. **A.** Collapsing glomerulopathy (collapsing variant segmental glomerulosclerosis) represented by marked podocyte hypertrophy (*arrow*) and collapse of the underlying capillary loops (Jones Stain, ×400). **B.** Nodular diabetic nephropathy can develop de novo in a transplant kidney (periodic acid–Schiff stain, ×400).

Other Transplant Histopathology (Not Classified Under Banff Categories)

- Hyperacute rejection (**Fig. 9.17**):

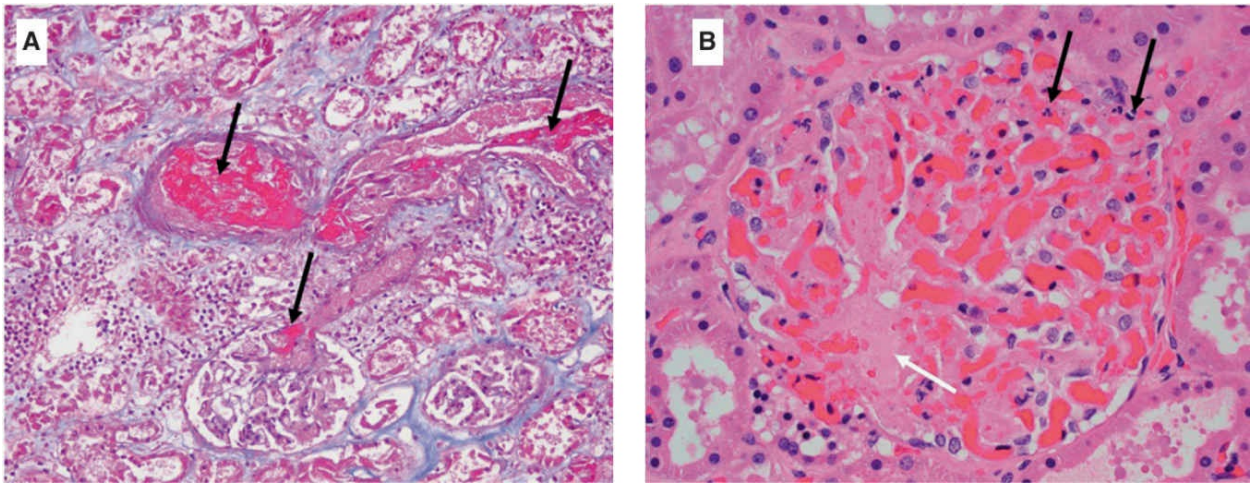

FIGURE 9.17 Hyperacute rejection is unusual in the modern transplant era. **A.** Hyperacute rejection with diffuse large thrombi filling arterial and arteriolar lumens (*arrows*) with adjacent cortical necrosis (Trichrome stain, ×200). **B.** Marked glomerular vascular congestion with associated small luminal thrombus (*white arrow*) and neutrophilic endocapillary inflammation (*black arrows*) (hematoxylin and eosin, ×400).

- Caused by preformed antidonor HLA antibodies

- Occurs immediately following or within minutes to hours of vascular anastomosis
- Exceedingly rare in the modern transplant era
- Histopathology:
  - Thrombosed arteries, arterioles, and glomerular capillaries, often with neutrophils incorporated into the thrombi
  - Ischemic acute tubular injury
  - Minimal interstitial or tubular inflammation

- CMV nephropathy:
  - Rare infectious complication
  - Tubulointerstitial inflammation often with prominent plasma cells
  - Nuclear and/or cytoplasmic inclusions in tubular epithelium. Endothelial cells and, to a lesser extent, in monocyte/macrophages
  - Immunohistochemistry needed for confirmation
- Chronic vascular changes attributable to age, HTN, or chronic vascular injury (nonrejection) (**Fig. 9.11**):
  - Arteriosclerosis/arteriolosclerosis
  - May be donor derived
  - Intimal fibrosis of arteries without inflammation
  - Hyalinization of arterioles other than an outer nodular pattern
  - Similar changes can be seen in diabetic patients.

POSTTRANSPLANTATION INFECTIOUS COMPLICATIONS AND VACCINATIONS

Vaccinations

- General considerations:
  - All kidney transplant candidates should receive vaccinations for hepatitis B, pneumococcus, and other standard vaccinations appropriate for age and presence of ESKD.
  - Household members, close contacts, and health care workers should also be fully immunized.
  - Vaccinations using inactivated or killed microorganisms, components,

and recombinant moieties are safe for transplant recipients.
  - Live vaccines are contraindicated posttransplantation.
  - Seasonal influenza vaccine (injectable) is safe and effective; both quadrivalent and high-dose trivalent can be used.
  - Ensuring adequate response to hepatitis B vaccination is important to prevent transmission of donor-derived infection (from organ or blood donors).
- Timing of vaccinations:
  - Vaccinations should be administered ≥ 4 weeks before transplant to achieve optimal response and to minimize the possibility of live vaccine–derived infection in the posttransplant period.
  - Vaccinations during the first 3 months after transplantation may result in suboptimal response and protection because of heavy immunosuppression. Most centers restart vaccinations 6 to 12 months after transplantation, 3 months posttransplantation for influenza during outbreaks.

Recommended vaccinations before and after transplantation are listed in Table 9.18.

Table 9.18 Recommended vaccinations before and after transplant

Vaccines	Before Transplant	After Transplant[a] ≥ 3 mo Posttransplant	Comments[b]
Measles–mumps–rubella	Yes	No	Should be administered ≥4 wk prior to transplant/onset of immunosuppression
Diphtheria–tetanus–pertussis	Yes	See comments	Diphtheria and tetanus: booster every 10 y
Varicella live (Varivax)	Yes	No	Should be administered ≥4 wk prior to transplant if nonimmune
Poliovirus	Yes	Inactivated polio	For travelers to endemic areas (e.g., some parts of Asia, Africa)
Haemophilus influenza type b	Yes	Yes	Especially important for patients who have undergone splenectomy
Inactivated influenza vaccine	Yes	Yes	Annually All patients who are >3 mo posttransplant should receive seasonal influenza vaccine

			May be administered in the immediate posttransplant period during an outbreak
Pneumococcal conjugate PCV13	Yes	Yes	For those who have not received either pneumococcus vaccine, PCV13 should be administered first, followed 8 wk later by PPSV23.
Pneumococcal polysaccharide PPSV23	Yes	Yes	Recommend posttransplant if not administered pretransplant Patients who have already received one dose of PPSV23 should receive an additional dose 5 y after the first dose of PPSV23.
Hepatitis A	Yes	Yes	Recommend posttransplant if not administered pretransplant For travelers to endemic areas, men who have sex with men, other risk factors
Hepatitis B	Yes	Yes	Recommend posttransplant if not administered pretransplant. High dose often more effective than standard dose; can accelerate series if needed before transplant. Monitor titers for response to vaccination and repeat vaccination series if needed
Human papillomavirus	Yes	Yes	Nonpregnant female candidates aged 11–26, males aged 11–21 y
Neisseria meningitides (both quadrivalent and group B vaccines)	Yes	Yes	Recommended for patients before/after splenectomy, those with functional asplenia, with properdin terminal component deficiencies or receiving eculizumab therapy Others: military members, travelers to high-risk areas, college freshman living on campus
Zoster-nonlive viral particle (Shingrix)	Yes	Yes	Recommend over Zostavax; limited safety data in patients posttransplant, contains adjuvant, moderately reactogenic
Zoster-live (Zostavax)	Yes	No	Should be administered ≥4 wk prior to transplant[c]/onset of immunosuppression

[a]Live vaccines are contraindicated posttransplant.

[b]Vaccinations <3 mo posttransplant may result in suboptimal response and protection.

[c]If inadvertently given within 4 weeks before transplant, consult infectious disease specialist and administer acyclovir to prevent reaction of vaccine-strain virus.

Abbreviations: PCV13, pneumococcal conjugate vaccine, PPSV23, pneumococcal polysaccharide vaccine.

Risk Factors for Posttransplant Infectious Complications

- Donor-derived infections

- Recipient-related risks:
  - Net state of immunosuppression: intensity and duration of immunosuppression
  - Surgical instrumentation, wound, abdominal fluid collections
  - Underlying medical risks (e.g., diabetes mellitus, uremia)
  - Increased patient age
  - Hypogammaglobulinemia: Although prospective controlled trials are lacking, currently available literature suggests that posttransplant monitoring of IgG levels and immunoglobulin replacement therapy may reduce infection rates in patients with hypogammaglobulinemia (especially IgG < 400 mg/dl).
  - Neutropenia and leukopenia:
    - Drug induced: thymoglobulin, MMF, AZA, sirolimus, valganciclovir, trimethoprim–sulfamethoxazole, dapsone, or possible idiosyncratic drug–drug reaction
    - The use of granulocyte colony-stimulating factor (G-CSF) is considered safe and effective in kidney transplant recipients.
  - Infections with immunomodulating viruses
- Environmental exposures: nosocomial, immediate living surrounding, endemic/epidemic, colonization, travel

Timetable of Posttransplant Infectious Complications

Infection follows CVD as the second most common cause of death with a functioning graft in kidney transplant recipients. Both the type and occurrence of infections in the immunocompromised transplant recipient follow a timetable pattern (Table 9.19). However, the timing of infections may be altered by intensity of immune suppression, use of antimicrobial prophylaxis, and patient exposures. All transplant recipients should be counseled to minimize environmental exposure (primarily avoidance of pigeon droppings and areas of active building construction).

Table 9.19 Timetable of infections

Time After Transplant	Infectious Agents	Comments/Preventive Measures

Month 1	**Bacterial (sites and sources)** Urinary tract Respiratory Bacteremia Surgical wound or intra-abdominal sources (lymphoceles, hematomas, urine leak) Vascular access or instrumentation (catheters, drains, urinary stents) Anatomic or functional genitourinary tract abnormalities (ureteral stricture, vesicoureteric reflux, neurogenic bladder) *Clostridium difficile* or center-specific multidrug-resistant species **Viral** Uncommon, except for HSV **Fungal** *Candida* species predominate (recipient pretransplant colonization or donor derived) Organisms transmitted with donor organ	Common nosocomial bacterial pathogens and *Candida* species predominate. Risk can be mitigated by appropriate prophylaxis (see **Tables 9.20 and 9.21**). Minimize or avoid environmental exposure at all time after transplant (primarily avoidance of pigeons and areas of active building construction).
Month 1–6	**Viral** CMV, HSV, VZV, EBV, HBV, HCV,[a] BK virus (exogenous infection or reactivation of latent disease due to immunosuppression) Others: HHV-6, HHV-7, influenza, parainfluenza, RSV, adenovirus **Fungal** *Aspergillus* species, *Cryptococcus*, agents of mucormycosis **Bacterial** Recurrent urinary tract infections or pyelonephritis *Nocardia*, *Listeria*, *Mycobacterium* species (tuberculous and nontuberculous), *Legionella* **Parasitic** *Pneumocystis jirovecii*, *Toxoplasma*, and *Strongyloides* species	Unconventional or opportunistic infections due to immunosuppression Risk can be mitigated by appropriate prophylaxis (see **Tables 9.20 and 9.21**). Minimize or avoid environmental exposure (primarily avoidance of pigeons and areas of active building construction).
More than 6 mo posttransplant	**Stable patients on low-dose immunosuppressants** Community-acquired respiratory and GI viral pathogens **History of multiple rejection episodes requiring intensification of immunosuppression** Viral infections (invasive CMV such as CMV colitis or pneumonitis, VZV, parvovirus B19), late opportunistic infections (*Pneumocystis*, *Cryptococcus*, *Listeria*, nocardiosis), tuberculosis **Persistent infections:** HBV, HCV,[a]	Infection risks associated with duration and intensity of immunosuppression and epidemiologic exposures Minimize or avoid environmental exposure (noted above).

	papillomavirus, BK virus **Geographically restricted** (e.g., coccidioidomycosis. histoplasmosis, blastomycosis, paracoccidioidomycosis) **Deep-seated infections** (e.g., osteomyelitis, paravertebral abscess). Predisposing risk factors: chronic skin infections, long-standing poorly controlled diabetes, peripheral vascular disease **Associated with malignancies:** EBV (PTLD), papilloma (squamous cell carcinoma), HSV (cervical cancer), HHV-8 (Kaposi sarcoma)	

[a]Incidence should decrease with the use of interferon-free and ribavirin-free direct-acting antiviral agent combination therapy.

Abbreviations: CMV, cytomegalovirus; EBV, Epstein–Barr virus; GI, gastrointestinal; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV-6, human herpes virus 6; HHV-7, human herpes virus 7; HHV-8, human herpes virus 8; HSV, herpes simplex virus; PTLD, posttransplantation lymphoproliferative disorder; RSV, respiratory syncytial virus; VZV, varicella-zoster virus.

- Month 1 after transplantation
  - Donor- and recipient-derived infections with common nosocomial bacterial microorganisms and *Candida* species predominate.
  - Most bacterial infections involve wounds, catheters, and drainage sites.
  - Aspiration pneumonia and urinary tract infections (UTIs) are common.
  - UTI preventive measures: early urethral catheter removal and antibiotic prophylaxis
  - Infections caused by multidrug-resistant bacteria are center specific.
- Month 1 to 6 after transplantation
  - Unconventional or opportunistic infections secondary to immunosuppression are most common.
  - Viral infections:
    - Common viral infections including CMV, herpes simplex virus (HSV), varicella-zoster virus (VZV), EBV, HBV, and HCV may occur de novo or reactivation of latent disease.
    - Community-acquired respiratory viruses are a common hazard.
    - Viral infections may further impair immunity and increase the risk for additional opportunistic infections.
    - BKV infection is an important cause of allograft loss (discussed in

BK Polyomavirus section).

- Fungal infections:
  - Repeated courses of antibiotics and corticosteroid therapy increase the risk of fungal infections.

- After 6 months:
  - Patients can be arbitrarily divided into three categories in terms of infection risks.
    - **Category 1** (70% to 80% of patients) consists of patients with satisfactory or good allograft function, on relatively low doses of immunosuppressants, and no history of chronic viral infection.
      - The risk of infection is similar to that of the general population.
      - Community-acquired respiratory viruses constitute the major infective agents.
      - Opportunistic infections are unusual unless environmental exposure has occurred.
    - **Category 2** (~10% of patients) consists of those with chronic viral infection (e.g., HBV, HCV, CMV, EBV, BKV, papillomavirus).
      - In the setting of immunosuppression, chronic viral infections may accelerate disease progression or give rise to associated complications, such as liver cirrhosis with HBV and HCV, BK nephropathy (BKN), posttransplant lymphoproliferative disease (EBV), or squamous cell carcinoma (SCC) (papillomavirus). The advent of the direct-acting anti-HCV antiviral agents should result in a decrease in the incidence of chronic HCV infection and cirrhosis.
    - **Category 3** (~10% of patients) consists of those who experience multiple rejection episodes requiring repeated exposure to potent immunosuppression.
      - These patients are the most likely to develop chronic viral infections and superinfection with opportunistic infections.
  - Other considerations:
    - New infections occurring after 6 months often reflect recent exposures (e.g., *Listeria monocytogenes* [dietary exposure], Lyme

disease [tick exposure], and malaria [travelers to endemic areas]).

- Suggested antimicrobial prophylactic therapy in kidney transplant recipients is summarized in Table 9.20.

Table 9.20 Posttransplantation antimicrobial prophylaxis

Prophylaxis	Regimen	Comments
Pneumocystis jirovecii	**First line:** trimethoprim–sulfamethoxazole (TMP-SMX)[a] × 6–12 mo (lifelong in some, especially thoracic organs) **Second line** (sulfa allergies)[b]: atovaquone, dapsone, or aerosolized pentamidine	TMP-SMX also reduces the incidence of *Toxoplasma gondii*, *Listeria monocytogenes*, and *Nocardia asteroides* and reduces the incidence of UTI in kidney transplant recipients. Check glucose-6-phosphate dehydrogenase prior to initiation of dapsone. Be aware of the risk of methemoglobinemia on dapsone.
Fungal	Nystatin S&S or fluconazole[c]	Fluconazole recommended in high-risk recipients (e.g., simultaneous pancreas-kidney or simultaneous liver-kidney transplant recipients, history of coccidioidomycosis, or patients who live in endemic areas)
CMV	Acyclovir, valganciclovir, ganciclovir (see Table 9.21)	Acyclovir for HSV and VZV prophylaxis for patients not on CMV prophylaxis

[a]Restart trimethoprim–sulfamethoxazole (TMP-SMX) prophylaxis × 3 months after any SoluMedrol pulse or antibody treatment (duration of prophylactic therapy may vary among centers).

[b]Listed in order of preference. Consider adding fluoroquinolones or other agents for antibacterial activity for higher risk recipients.

[c]The authors advocate lifelong therapy in patients with history of coccidioidomycosis or in those who live in endemic areas.

Abbreviations: CMV, cytomegalovirus; HSV, herpes simplex virus; UTI, urinary tract infection; VZV, varicella-zoster virus.

Screening and Management of Common Posttransplant Viral Infections

Cytomegalovirus

- CMV infection generally refers to asymptomatic CMV seroconversion detected during CMV surveillance.
- CMV infection categorization:
  - Primary infection: donor seropositive (D+), recipient seronegative (R−)
  - Reactivation of endogenous latent virus: D+/R+ or D−/R+
  - Superinfection with a new virus in a seropositive recipient: D+/R+
- Clinical presentations:

- Primary CMV infection is usually more severe than reactivated infection or superinfection.
- CMV disease refers to acute symptomatic CMV infection associated with various signs and symptoms, including:
  - CMV syndrome (fever, fatigue, leukopenia, and/or thrombocytopenia and evidence of CMV viremia)
  - Invasive CMV disease involving various organ systems, including the liver, gastrointestinal (GI) tract, lung, or the kidney allograft. Clinically, patients may present with hepatitis, esophagitis, colitis, pneumonitis, pancreatitis, or AKI.

- CMV diagnosis:
  - Screening for CMV is best performed using PCR-based methods for CMV DNA. Whole blood may result in higher CMV DNA results than plasma. It is best to use one specimen type for comparison.
  - CMV DNA assay is highly specific and sensitive for the detection of CMV viremia, whereas pp65 antigenemia is a semiquantitative fluorescent assay in which circulating neutrophils are stained for nonspecific uptake of CMV early antigen (pp65). With the widespread availability of nucleic acid testing (NAT), antigen-based method has largely been replaced by CMV DNA testing.
  - PCR results may vary significantly among laboratories. CMV quantitative NAT (QNAT) calibration based on the WHO International Reference Standard is recommended.
  - Serum quantitative CMV assays in patients with invasive colitis and gastritis or neurologic disease including chorioretinitis are often negative. Patients suspected to have tissue-invasive CMV disease but with negative QNAT or pp65 antigenemia should have tissue biopsy and histopathology to confirm the clinical suspicion of CMV disease.
- CMV prevention can be achieved by prophylaxis or preemptive therapy.
  - Prophylactic therapy involves antiviral beginning in the immediate postoperative period and continuing for a finite period (i.e., 3 to 6 months).
  - Preemptive therapy entails close CMV surveillance weekly for 12 weeks

after transplant and initiation of treatment only in patients who are found to reach a certain threshold of positive CMV DNA by PCR (threshold to treat may differ among centers).

- Both approaches are recommended in the 2018 International Consensus Guidelines for at-risk kidney transplant recipients.
- Suggested CMV prophylaxis protocol is provided in Table 9.21.

Table 9.21 Suggested cytomegalovirus prophylaxis protocol[a]

For CMV (−) recipient of a CMV (+) organ donor (D+/R−)
• After antibody induction: valganciclovir 900 mg orally once a day × 6 mo
• If no antibody induction: valganciclovir 900 mg orally once a day × 3 mo
• After the end of prophylaxis, consider CMV DNA weekly × 3 mo
For CMV (+) recipient of a CMV (−) organ donor (D−/R+) or a CMV (+) organ donor (D+/R+)
• Valganciclovir 900 mg orally once a day × 3–6 mo
• Lung transplant, composite tissue: valganciclovir 900 mg orally once a day × 6 mo
For CMV (−) recipient of a CMV (−) organ donor (D−/R−)
• Acyclovir 400 mg twice a day[b] (for herpes prophylaxis) × 3 mo
• CMV DNA screening when clinically indicated (or if exposure to high volume of blood product)

[a]Acyclovir, valganciclovir, ganciclovir, famciclovir, valacyclovir: Dose adjustment for renal function necessary.
[b]May use acyclovir, famciclovir, or valacyclovir (center dependent).
Abbreviations: CMV, cytomegalovirus; D, donor; R, recipient.

- Management of CMV:
  - For mild clinical symptoms: oral valganciclovir 900 mg twice daily (adjusted for GFR)
  - For severe disease, high viral load, significant GI disease, or life-threatening disease or in those intolerant to oral medication, IV ganciclovir 5 mg/kg every 12 hours, adjusted for GFR should be used (2018 International Consensus guidelines).
  - Treatment duration (2013 AST Infectious Diseases Community of Practice Guidelines): Therapy should be continued until clearance of viremia. Generally, CMV disease should be monitored once weekly using CMV QNAT (or pp65 antigenemia) to assess virologic response.
  - Patients with CMV disease should remain on full therapeutic dose of antiviral therapy until CMV DNA load (or antigenemia) is undetectable

(or very low, with ultrasensitive diagnostics). **After completion of full-dose treatment**, consider continuing weekly monitoring for CMV DNA for 8 to 12 weeks, primarily in those at higher risk for relapse.

- Other considerations in the management of CMV disease:
  - Cautious reduction of immunosuppression should be considered in moderate-to-severe disease, in slow or nonresponders, and in those with high viral load or leukopenia.
  - Monitor graft function closely during CMV disease. Late-onset CMV disease occurring > 2 years after transplant has been shown to be associated with poor transplant outcome.
  - The beneficial effect of adding IVIG or CMV Ig to existing antiviral therapy is unclear but may be considered for patients with life-threatening disease, CMV pneumonitis, resistant virus, or other severe forms of disease.
  - Ganciclovir-resistant strains: Consider high-dose ganciclovir or foscarnet (potential for nephrotoxicity and synergistic nephrotoxic effect with CNIs). Obtain genotypic resistance testing (*UL97* or *UL54* gene mutation).
  - Measuring anti-CMV cell–mediated immunity (using QuantiFERON-CMV or T-SPOT.CMV assays to measure the level of T-cell IFN-γ production after CMV antigen exposure) to assess the risk of CMV infection or disease and to guide therapeutic duration/management is a subject of ongoing clinical research.

BK polyomavirus

- BKV is a ubiquitous human polyomavirus with a seroprevalence rate of > 80% to 90% among the adult population worldwide.
- After primary infection, BKV preferentially establishes latency within the genitourinary tract and frequently reactivates in the setting of immunosuppression.
- BK-associated clinical syndromes: asymptomatic viruria with or without BK viremia (BK DNAemia), BK allograft nephropathy (BKN), and, less commonly, interstitial nephritis, and ureteral stenosis and obstruction. BK viremia and BK DNAemia will be herein used interchangeably.

- BK viruria generally precedes BK viremia by a median of 4 weeks; BK viremia commonly precedes BKN by a median of 8 weeks.
- BK nephropathy (BKN):
  - BKN is an important cause of allograft dysfunction and graft loss.
  - BKN most commonly presents with an asymptomatic rise in serum creatinine between 2 and 24 months after transplantation (median 9 months).
  - Urinalysis is usually unremarkable but may reveal pyuria, hematuria, and/or cellular casts, consisting of renal tubular cells and inflammatory cells.
  - A definitive diagnosis of BKN requires allograft biopsy.
  - Histopathologic findings of BKN (**Fig. 9.12**):
    - BK viral inclusions in renal tubular cell nuclei and occasionally in glomerular parietal epithelium
    - Interstitial mononuclear inflammation, often with many plasma cells, degenerative changes in tubules, and focal tubulitis (may mimic acute rejection)
    - BK infection and acute rejection may occur simultaneously. Distinguishing between BKN and acute rejection or the presence of both can be a diagnostic challenge.
    - The 2017 Banff Working Group on BKN proposed using interstitial fibrosis and intrarenal BK load levels to diagnose "definitive BKN." BKN can be further categorized into three classes based on the percentage of tubules/ducts with evidence of viral replication, as well as Banff scores of interstitial inflammation and tubulitis. Class 1 denotes early-stage BKN with favorable outcome. Class 2 and class 3 have more pronounced adverse impact on graft function, with graft failure rate reaching 50% in class 3.
- Posttransplant BK screening:
  - **2009 KDIGO clinical practice guidelines**:
    - QNAT plasma screening should be performed (1) monthly for the first 3 to 6 months after transplant and then every 3 months until the end of the first posttransplant year, or (2) whenever there is an

unexplained rise in serum creatinine, or (3) after treatment of acute rejection.

- Reduce immunosuppression when plasma BKV DNA is persistently $>10^4$ copies/mL.

- **2019 AST Infectious Diseases Community of Practice guidelines:**
  - All kidney transplant recipients should be screened for BK DNAemia monthly until month 9 and then every 3 months until 2 years posttransplant. Extended screening after 2 years may be considered in pediatric kidney transplant recipients.
  - Stepwise immunosuppression reduction is recommended for patients with plasma BK DNAemia of >1,000 copies/mL sustained for 3 weeks or increasing to >10,000 copies/mL, reflecting “probable” and “presumptive” BKN, respectively.
  - Reducing immunosuppression is also the primary intervention for biopsy-proven BKN.
  - Allograft biopsy is not required for treating BK DNAemic patients with baseline renal function.
  - Despite virologic rationales, proper randomized clinical trials are lacking to generally recommend treatment by switching from tacrolimus to CSA, from mycophenolate to mTOR inhibitors or leflunomide, or by the adjunct use of IVIGs, leflunomide, or cidofovir.
  - Fluoroquinolones are not recommended for prophylaxis or therapy.
  - Retransplantation after allograft loss due to BKN can be successful if BK DNAemia is definitively cleared, independent of failed allograft nephrectomy.
- **Note:**
  - BK PCR assays are not standardized across centers, and the sensitivity and specificity of the assays may vary.
  - Optimal reduction of immunosuppressive therapy may allow sufficient reconstitution of BKV-specific T cells to control BKV replication, while maintaining adequate immunosuppression to prevent allograft rejection.

- Although immunosuppression reduction may improve BK viremia and subsequent development of BKN, it may increase the risk of de novo DSA development, underscoring the need for routine DSA surveillance. Treatment should best be individualized based on patient's immunologic risk.
- Reduction in immunosuppression is not universally effective, suggesting that the balance between viral replication and virus-specific immune surveillance determines the clinical course of BK-associated clinical syndromes. Nonetheless, routine BK screening and early intervention (i.e., reduction in immunosuppression) may prevent the development of BKN.

- Future directions (detailed discussion is beyond the scope of this book):
  - Monitoring BKV-specific T-cell response might prove useful in guiding therapeutic intervention.
  - Monitoring BKV genotype-specific neutralizing antibodies as a potential novel predictive marker of BKV replication.
  - Development of BKV-specific T cell for adoptive transfer or antibody-based vaccines against BKV is a subject of ongoing research.

Herpes simplex virus 1, 2

- Results primarily from reactivation of endogenous latent virus, causing clinical infection within the first few months after transplantation (without prophylaxis)
- The routine use of acyclovir prophylaxis in the early posttransplantation period is recommended (see Table 9.21) (also covered by valganciclovir for those on CMV prophylaxis).
- Clinical manifestations: oral mucocutaneous lesions or gingivostomatitis with or without odynophagia and dysphagia
- Treatment (2009 KDIGO guidelines):
  - Superficial HSV 1, 2 infection: Oral antiviral agent (e.g., acyclovir, valacyclovir, or famciclovir) until all lesions are crusted.
  - Systemic HSV 1, 2 infection: IV acyclovir and reduction in immunosuppression. IV acyclovir should be continued until the patient

has a clinical response, then switch to an appropriate oral antiviral agent to complete a total treatment duration of 14 to 21 days.
    - In patients with frequent recurrences of HSV 1, 2 infection, prophylactic antiviral agent is recommended.

Varicella-zoster (2009 KDIGO guidelines)

- Primary VZV infection (chickenpox): IV or oral acyclovir or valacyclovir and temporary reduction in immunosuppression. Treatment should be continued until all lesions have crusted.
- Uncomplicated herpes zoster (shingles): Oral acyclovir or valacyclovir (better bioavailability) until all lesions have crusted.
- Disseminated or invasive herpes zoster should be treated with IV acyclovir and temporary reduction in immunosuppression until all lesions have crusted.
- Prevention of primary varicella-zoster should be instituted to varicella-susceptible patients after exposure to individuals with active varicella infection.
    - If the transplant recipient is already immune to varicella/chickenpox by either history of disease, vaccination, or serology positive for varicella IgG, there is no need for concern or additional measures.
    - If nonimmune, consider a course of acyclovir 400 mg daily three times × 2 to 3 weeks or varicella immunoglobulin (VARIZIG). The latter can be expensive and difficult to obtain.

Adenovirus

- Occurs in 4% to 5% of kidney transplant recipients
- Risk factors: Intensity of immunosuppression. Supporting evidence:
    - Higher incidence in the first 3 months after transplantation
    - Infection occurs in association with treatment of acute rejection.
    - Resolution of the infection with immunosuppression reduction
- Clinical manifestations:
    - Vary with the transplanted organ, with the allograft itself being the most frequent organ involved
    - Kidney transplant recipients frequently present with hemorrhagic

cystitis, fever, dysuria, frequency, urgency, and gross hematuria.
    - Hemorrhagic cystitis is frequently accompanied by graft dysfunction, and kidney function generally returns to baseline after resolution of the adenovirus disease.
- Treatment:
    - Reduction of immunosuppression is the mainstay of therapy.
    - Cidofovir is used for the treatment of adenovirus disease by some centers, although its use is not supported by any prospective randomized clinical trials. Additionally, routinely suggested dosing may not achieve therapeutic levels against adenovirus.

Hepatitis B

- Recipients who are hepatitis B core total antibody positive should be monitored after transplant by periodic HBV viral load testing (or given antiviral prophylaxis if they receive ATG or rituximab).
- Evidence of posttransplant HBV reactivation should be treated with entecavir or tenofovir (see **Chapter 10 Pharmacology** for HBV therapy and antiviral drug-resistance).
- The authors advocate antiviral prophylactic therapy in all HBsAg-positive candidates at the time of transplantation.

Hepatitis C

- Kidneys from hepatitis C–positive donors may be offered to hepatitis C–positive transplant candidates (who are viremic) who have consented to receive such kidney.
- Active viral replication at the time of transplant has been shown to be associated with a higher incidence of long-term clinical liver disease and worse allograft function and survival compared with HCV-positive recipients with persistently negative viremia.
- Patients who are not viremic at the time of transplant but become viremic posttransplant have inferior outcomes compared with those who remain free of viral replication.
- Treatment:
    - Stable kidney transplant recipients with HCV viremia detected by PCR

are routinely referred to hepatology for treatment.

- Currently available fixed-dose combination DAAs that have been approved for use in kidney transplant recipients:
  - Ledipasvir (90 mg) and sofosbuvir (400 mg) combination therapy is approved for the treatment of HCV genotype 1 or 4 infection.
  - Glecaprevir (300 mg) and pibrentasvir (120 mg) combination therapy is approved for the treatment of HCV genotypes 1 through 6 infections.
  - Sofosbuvir (400 mg) and daclatasvir (60 mg) plus a low initial dose of ribavirin (600 mg)
  - Elbasvir/grazoprevir or glecaprevir/pibrentasvir: recommended drug regimens for severe renal impairment (sustained viral response rates > 90%)
- The introduction of DAA may improve outcomes in hepatitis C–positive transplant recipients; some programs are using these agents to treat HCV-negative transplant recipient of HCV-positive donor kidney (discussion is beyond the scope of this chapter).
- Interferon (IFN)-based therapy increases the risk of allograft rejection. However, with the advent of DAA, INF-based therapy has become obsolete.

Pneumocystis jirovecii (Previously Known as *Pneumocystis carinii*)

- *Pneumocystis jirovecii pneumonia* (PJP) commonly occurs 2 to 6 months after transplantation or following augmentation of immunosuppression.
- *P. jirovecii* outbreaks and person-to-person spread have been reported to occur > 6 to 12 months after transplant.
- Common clinical presentation and radiographic findings: nonproductive cough, fever, arteriolar–alveolar mismatching, and diffuse interstitial infiltrate or focal airspace consolidation
- *PJP* prophylactic therapy (see Table 9.20)
- Prophylactic therapy should be reinstituted following intensification of immunosuppression (e.g., pulse steroid or ATG to treat rejection).
- All exposed susceptible individuals should receive PJP prophylaxis.

Posttransplantation Diarrhea and Common GI Infections

- Posttransplantation diarrhea is common and can be noninfectious (commonly drug related) or infectious in etiology.
  - Drug-related diarrhea
    - MMF is the most common cause of diarrhea in the early posttransplant period. Other GI side effects include nausea, vomiting, dyspepsia, anorexia, and flatulence.
    - Dose reduction or transient discontinuation of the drug often ameliorates or resolves GI symptoms.
    - Mycophenolate sodium (Myfortic, the enteric-coated formulation of MPA) has not been consistently shown to be better than the original formulation in ameliorating GI symptoms. Nonetheless, MMF to enteric-coated mycophenolate sodium conversion therapy can be considered in patients with GI intolerance associated with MMF use.
    - Sirolimus, tacrolimus, and cyclosporine have all been suggested to cause diarrhea to variable extent.
    - Diarrhea may cause elevation in tacrolimus levels due to reduced presystemic metabolism in gut wall via P-glycoproteins and CYP 3A4/5 (see **Chapter 10 Pharmacology**).
  - Infectious causes of diarrhea
    - Most commonly encountered bacterial pathogen: *Clostridium difficile*
      - Diagnostic testing: stool toxin or PCR
      - Treatment: *First episode*: oral vancomycin 125 mg four times a day for 10 to 14 days or fidaxomicin 200 mg twice a day for 10 days. *First relapse*: treatment same as for first episode. *Second relapse*: oral vancomycin. *Third or more relapses*: prolonged oral vancomycin taper (125 mg four times per day for 10 to 14 days, two times per day for a week, once per day for a week, and then every 2 or 3 days for 2 to 8 weeks). May consider fecal microbiota transplantation or the monoclonal antibody bezlotoxumab. **Note:** Metronidazole is no longer considered a first-line regimen due to risk of recurrence after treatment.

- Most commonly encountered viral pathogen: CMV
  - Diagnostic testing: plasma CMV PCR; colonoscopy may be required for diagnosis.
  - Treatment (see **Cytomegalovirus** section)
- Norovirus is increasingly recognized as a cause of diarrhea after solid organ transplantation.
  - Can cause both acute and chronic diarrhea in solid organ transplant recipients
  - Diagnostic testing: norovirus PCR
  - Treatment: supportive (volume repletion, antimotility agents), reduction in immunosuppression (inconclusive evidence), nitazoxanide or IVIG in conjunction with immunosuppression reduction (anecdotal case reports)
  - Other pathogens: bacterial (*Salmonella*, *Campylobacter*); parasitic infections (*Giardia*, *Cryptosporidium*, *Strongyloides*)
    - Detected by stool culture, bacterial PCR panel, parasite-specific antigen testing, or ova and parasite examination
    - *Cryptosporidium* may result in very high tacrolimus levels.

- Posttransplant infections of the GI tract may be viral, fungal, or bacterial in etiology.
  - Common viral infections: CMV, HSV
  - Common opportunistic fungal infection: *Candida*
  - Common bacterial pathogens: *C. difficile*, *Helicobacter pylori*
    - *H. pylori*
      - Clinical disease spectrum of *H. pylori* includes chronic gastritis, duodenal and gastric ulcers, mucosa-associated lymphatic tissue (MALT) lymphoma, and gastric carcinoma.
      - Treatment includes a triple-drug regimen consisting of two antibiotics and an acid-suppressive agent such as an H2-blocker or a PPI.
      - In kidney transplant recipients infected with *H. pylori*, MALT lymphoma may be less aggressive than other lymphomas, and the disorder may be cured by eradication of *H. pylori*.

Routine Donor Screening for Infectious Disease

- Deceased donor testing:
  - Blood and urine cultures
  - HIV-1/2 antigen/antibody fourth generation with reflex confirmation
  - HBsAg, HBcAb, and anti-HCV or HCV NAT
  - CMV antibody (anti-CMV IgG)
  - Epstein–Barr virus antibody (anti-EBV)
  - Syphilis screening
  - Donor screening in endemic settings: TB, strongyloides, West Niles virus
  - If a donor is identified as being at increased risk for HIV, HBV, and HCV transmission according to the US Public Health Service (PHS) guidelines, testing must also include HIV RNA by NAT or HIV-1/2 antigen/antibody fourth generation with reflex confirmation.
  - The infectious window period reduced by NAT is presented in Table 9.22.

Table 9.22 Infectious window period reduced by nucleic acid testing

Etiologic Agent	Standard Serology (d)	Fourth Generation or Combination Tests (d)	Nucleic Acid Testing (d)
HIV	17–22	~7–16	5–9
HCV	~70	~40–50	3–7
HBV	35–44	NA	20–22

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NA, not applicable.

- Living donor testing (discussed under **Living Donor Evaluation**)

Posttransplantation Serology Monitoring for Recipients Accepting PHS Increased Risk Organs

- **PHS increased risk organs:** Donors who meet one or more of the following criteria should be identified as being at increased risk for recent HIV, HBV, and HCV infections.
  - Persons who have had sexual contact with persons known or suspected to have HIV, HBV, or HCV infections in the preceding 12 months

(through percutaneous inoculation, open wound, nonintact skin, or mucous membranes)

- Male homosexual contact in the preceding 12 months
- Women who have had sex with a man with a history of male homosexual contact in the preceding 12 months
- Promiscuous sexual relations in exchange for money or drugs in the preceding 12 months
- Persons who have had sexual contact with persons who had injected drugs by IV, intramuscular, or subcutaneous route for nonmedical reasons in the preceding 12 months
- A child who is <18 months of age and born to a mother known to be infected with or at increased risk for hiv, hbv, or hcv infections
- A child who has been breastfed within the preceding 12 months, and the mother is known to be infected with or at increased risk for HIV infection (birth mother, if available, should be interviewed about behaviors that may have placed her at risk for HIV, HBV, or HCV infection)
- Nonmedical IV, intramuscular, or subcutaneous use of drugs in the preceding 12 months
- Inmates of correctional systems for more than 72 hours in the preceding 12 months
- Persons with newly diagnosed with or have been treated for syphilis, gonorrhea, Chlamydia, or genital ulcers in the preceding 12 months
- Persons who are hemodiluted as per the OPTN/UNOS policy
- Donors who have been on hemodialysis in the preceding 12 months should be identified as being at increased risk for recent HCV infection only.

- Informed consent must be obtained prior to transplantation of PHS increased risk organs.
- Protocol surveillance for PHS increased risk donor kidney recipients is presented in Table 9.23. Additional testing may be performed based on patient’s clinical characteristics, symptoms, immunosuppression, or at the discretion of the transplant team.

Table 9.23 Protocol surveillance for PHS increased risk donor kidney recipient

Pretransplant	Posttransplant
At baseline • HIV RNA • HBsAg, HBV DNA quantitative PCR • HCV RNA quantitative PCR	At 6 wk posttransplant • HIV RNA quantitative PCR • HBsAg, HBV DNA quantitative PCR • HCV RNA quantitative PCR At 12 mo posttransplant • HBsAg or HBV NAT, anti-HBsAb, and anti-HBcAb

Abbreviations: NAT, nucleic acid testing; PCR, polymerase chain reaction.

- In the event a recipient seroconverts, a treatment plan will be developed by the transplant team in conjunction with transplant infectious disease consultation.

NONINFECTIOUS COMPLICATIONS AFTER KIDNEY TRANSPLANT

Surgical Complications (Usually Occur Early After Transplantation)

- Wound infections:
  - Obese transplant recipients are at increased risk.
  - mTOR inhibitors may delay wound healing and increase the incidence of lymphocele formation. Its use should be avoided in the early posttransplantation period.
- Perinephric fluid collections:
  - Lymphoceles:
    - Most common type of peritransplant fluid collection
    - Usually occur several weeks to months after surgery
    - Incidence higher with mTOR inhibitors
    - Small lymphoceles are usually asymptomatic (conservative management), but larger lymphoceles can cause obstruction (management include percutaneous drainage or surgical repair).
  - Hematomas:
    - Usually occur in the immediate postoperative period
    - May be external or subcapsular, usually resolve spontaneously
    - May occur after allograft biopsy

- Urinomas (urine leak)
  - Clinical manifestations:
    - Patients may present with pain over the allograft or abdominal pain (often severe), with or without scrotal pain or swelling, increasing wound drainage (clear fluid), decreasing urine output.
    - If a surgical drain is present, rising serous output may indicate a urine leak.
  - Diagnosis:
    - Measure both creatinine concentration in drain fluid (or fluid drained from the incision) and serum creatinine: Surgical drain fluid with creatinine concentration of at least 1 to 2 mg/dL greater than that measured for serum is suggestive of a urine leak, although drain fluid values are often >20 mg/dL in brisk urine leaks.
    - Diagnosis may be confirmed with a computed tomography (CT) cystogram, plain film cystogram, or voiding cystourethrogram (VCUG) demonstrating urine extravasation.
  - Management:
    - A Foley catheter should be immediately placed if there is a clinical suspicion of a urine leak. The catheter reduces intravesical pressure and may occasionally reduce or stop the leakage.
    - Low-volume urine leaks (low drain output, minimal extravasation on cystogram) may be successfully managed with prolonged ureteral stenting and Foley catheter drainage (typically 1 to 3 weeks). A repeat cystogram should be performed to confirm resolution of the leak prior to catheter removal.
    - High-volume leaks should be explored, and a ureteral reimplantation or other urinary reconstruction performed.
- Obstructive uropathy: Etiologies: ureteral blood clots, stones, ureteral kinking, neurogenic bladder, benign prostatic hypertrophy causing bladder outlet obstruction, ureteral strictures due to ischemia or BK infection

Medical Complications (May Occur Early or Late After

Transplantation)

- Posttransplantation CVD is the most frequent cause of death with a functioning graft:
  - Conventional risk factors: family history, pretransplant diabetes, male gender, age, white race, HTN, dyslipidemia, obesity, smoking
  - Unconventional or transplant-related risk factors: Posttransplantation diabetes mellitus (PTDM), anemia, proteinuria, impaired graft function, low albumin, hyperuricemia, left ventricular hypertrophy
  - Selected risk factors are discussed below.

Posttransplantation HTN

- Recipient-related risk factors: preexisting HTN, high BMI or excess weight gain, sodium intake after transplantation, corticosteroids, cyclosporine, and, to a lesser degree, tacrolimus. Excess renin output from the native kidneys may play a contributory role in some patients.
- Donor-related factors: donor age, HTN, and donor family history of HTN. Donor factors associated with reduced graft function may indirectly increase posttransplantation HTN risk (e.g., donor *APOL-1* or *CYP3A5* gene variants. The former is associated with early graft failure and the latter with CNI nephrotoxicity).
- Kidney allograft-related factors: DGF, chronic allograft injury, acute rejection episodes, recurrent or de novo glomerulonephritis, transplant renal artery stenosis
- Management of posttransplantation HTN
  - The KDIGO guidelines suggest a blood pressure goal of < 130/80 mm hg for kidney transplant recipients, irrespective of the level of albuminuria (recommendations based solely on epidemiologic data).
  - A blood pressure goal <125/75 mm hg for patients with proteinuria is of uncertain benefit.
  - Currently available literature shows no conclusive evidence to suggest that one class of antihypertensive agent is superior to another in the transplant setting. Treatment should be individualized based on efficacy, tolerability, concomitant comorbidity, and drug–drug interactions with immunosuppressive agents. Nondihydropyridine calcium channel

blockers increase CNI blood levels and permit CNI dose reduction.

- Potential advantages and disadvantages of different classes of antihypertensive agents in kidney transplant recipients are summarized in Table 9.24.

Table 9.24 Potential advantages and disadvantages of different classes of antihypertensive agents

Classes of Drugs	Advantages/Beneficial Effects	Disadvantages/Adverse Effects
Angiotensin-converting enzyme inhibitors Angiotensin-receptor blockers	Beneficial in patients with proteinuria, DM, LVH Renoprotective and cardioprotective Beneficial in posttransplantation erythrocytosis	Potential worsening anemia, hyperkalemia
Aldosterone-receptor blockers (e.g., spironolactone, eplerenone)	May improve outcome in patients with HFrEF May improve blood pressure control in difficult-to-treat hypertension	Severe hyperkalemia when used in combination with ACEI or ARB, particularly in patients with poor kidney function
α-Blockers (e.g., prazosin, doxazosin)	Beneficial in patients with benign prostatic hypertrophy, neurogenic bladder, or orthostatic hypertension	Orthostatic hypotension
β-Blockers (e.g., carvedilol, metoprolol, bisoprolol)	Beneficial in patients with CAD or ischemic heart disease	Blunting of hypoglycemic unawareness, erectile dysfunction, hyperlipidemia, bronchospasm, hyperkalemia (nonselective > selective β1-blockers)
Calcium channel blockers: dihydropyridine (e.g., amlodipine, nifedipine)	Amlodipine may be used in patients with HFrEF	Nifedipine, amlodipine (peripheral edema) Nifedipine (reflex tachycardia)
Calcium channel blockers: nondihydropyridine (e.g., diltiazem verapamil)	Ameliorate CNI-induced vasoconstriction Increase CNI level, allowing CNI dose reduction: Diltiazem may permit CNI dose reduction by up to 40% and verapamil by 30%–50%	Increased risk of bradycardia when used with β-blockers (verapamil > diltiazem)
Central α-agonist (e.g., Clonidine, methyldopa)	Beneficial in patients with diabetic autonomic dysfunction	Depression
Diuretics (e.g., loop, thiazide, thiazide-like diuretics)	Beneficial in patients who are volume expanded Thiazide may improve hyperkalemia commonly seen in CNI-treated patients. Its use may also increase BMD and decrease fracture risk (beneficial in	Hyperuricemia, gout Thiazides may remain effective for some patients with eGFR 30 mL/min/1.73 m^2

	osteoporosis)	
Direct vasodilators (e.g., hydralazine, minoxidil)	Minoxidil: may be beneficial in difficult-to-treat hypertension Hydralazine/isosorbide dinitrate combination: may be beneficial in HFrEF among African Americans	Minoxidil (peripheral edema, reflex tachycardia, hirsutism) Hydralazine (lupus syndrome and antineutrophil cytoplasmic antibody vasculitis)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BMD, bone marrow density; CAD, coronary artery disease; CNI, calcineurin inhibitor; DM, diabetes mellitus; GFR, glomerular filtration rate; HFrEF, heart failure with reduce dejection fraction; LVH, left ventricular hypertrophy.

Posttransplantation dyslipidemia

- Common after transplantation
- Risk factors:
  - Immunosuppressive agents: corticosteroids, cyclosporine and, to a lesser extent, tacrolimus, and the mTOR inhibitors sirolimus and everolimus. Of all immunosuppressive agents, mTOR inhibitors are associated with the worst lipid profiles. Severe hypertriglyceridemia may occur with the use of sirolimus and everolimus due to decreased catabolism of apoB-100–containing lipoproteins (dose dependent, generally reversible upon discontinuation of mTOR inhibitors).
  - Others: age, diet, rapid weight gain, hyperinsulinemia, preexisting hypercholesterolemia, allograft dysfunction, proteinuria, genetic predisposition, β-blockers, diuretics

PTDM, also known as new-onset diabetes after transplantation

- In 2014, the International Expert Panel recommended changing the terminology New-Onset Diabetes After Transplantation (NODAT) back to PTDM, excluding transient posttransplantation hyperglycemia (transient is defined as posttransplant day 0 to 45).
- The diagnostic criteria for PTDM and prediabetes should follow those set forth by the American Diabetes Association expert panel (Table 9.25).

Table 9.25 The American Diabetes Association diagnostic criteria for prediabetes and diabetes

Diagnostic Test/Criteria	Normoglycemia (mg/dL)	Prediabetes IFG or IGT (mg/dL)	Diabetes (mg/dL)
Casual plasma glucose with diabetic symptoms[a]			>200

Fasting plasma glucose	100	100–125[b]	≥126
Oral glucose tolerance test	140	140–199[b]	≥200
HbA1C		5.7–6.4%[b]	≥6.5%

[a]Diabetic symptoms defined as polyuria, polydipsia, weight loss. In the absence of unequivocal hyperglycemia, diagnosis should be confirmed by repeat testing on a different day.
[b]The risk is continuous and becomes disproportionately greater at higher glucose or A1C levels.
Abbreviations: IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

- Risk factors:
  - PTDM may arise from both transplant-related and traditional risk factors.
  - Diabetogenic immunosuppressive agents: corticosteroids, CNIs (tacrolimus > cyclosporine), mTOR inhibitors
  - Nondiabetogenic agents:
    - The antimetabolites AZA and MPA derivatives (MMF, mycophenolate sodium)
    - Belatacept use in kidney transplant recipients has not been shown to increase PTDM risk.
  - Risk factors for PTDM are summarized in Table 9.26. They may be loosely categorized into those that are nonmodifiable, potentially modifiable, and modifiable.

Table 9.26 Risk factors for posttransplantation diabetes mellitus

Nonmodifiable	Potentially Modifiable	Modifiable
• African American, Hispanics • Age > 40–45 y • Recipient male gender • Family history of diabetes mellitus • HLA-A30, HLA-B27, HLA-B42 • HLA mismatches • Acute rejection history • Deceased donor • Male donor • Polycystic kidney disease[c]	• Hepatitis C[a] • CMV infection[b] • Pretransplant IFG/IGT • Hypomagnesemia • Proteinuria[c]	• Manipulation of immunosuppression (clinicians must be familiar with patient's immune history) • Obesity or other component of the metabolic syndrome • Vitamin D deficiency

• Genetic polymorphisms (e.g., TCF7L2rs7903146)		

[a]The advent of direct-acting antiviral agents (DAAs) may improve outcomes.
[b]Suggested posttransplant CMV prophylactic therapy (see Table 9.21).
[c]The association between proteinuria (and polycystic kidney disease) and PTDM has not been consistently observed.
Abbreviations: CMV, cytomegalovirus; HLA, human leukocyte antigen; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

- Both preexisting diabetes and PTDM have an adverse impact on patient survival.

Anemia

- Perioperative or early postoperative period: dilutional anemia due to aggressive volume expansion, surgical postoperative bleeding
- Mild anemia is common in the early postoperative period when erythropoietin (EPO)-stimulating agent (ESA) is discontinued but usually improves within several weeks.
- Drug induced: MMF, sirolimus, everolimus, AZA, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), dapsone
- Sirolimus inhibits erythropoiesis at the level of the EPO receptor.
- Other etiologic factors: iron deficiency, impaired graft function, acute rejection episodes, and parvovirus B19 infection. Treatment of the latter includes IVIG and lowering of immunosuppression to facilitate viral clearance

Posttransplantation erythrocytosis

- Defined as persistently elevated hematocrit (Hct) to > 51% or hemoglobin (Hb) > 17 g/dL after transplant
- Hct and Hb thresholds to define posttransplantation erythrocytosis (PTE) may differ among centers due to differences in institutional reference range (and age- and gender-adjusted Hct and Hb levels).
- ACEIs and ARBs are used to treat PTE.
- Incidence appears to have decreased to <10%, ascribed to more frequent use of aceis and arbs.
- May develop within the first 2 years posttransplant (usually between 8 and

24 months) and generally affects those with good allograft function

- Spontaneous remission within 2 years of onset is observed in one-fourth of patients and may persist for several years in others.
- Persistent PTE or PTE occurring late after transplant warrants further evaluation to exclude:
  - EPO-producing neoplasms:
    - RCC in the native or transplanted kidneys, hepatocellular carcinoma, cerebellar hemangioblastoma
    - Imaging studies of the allograft and native kidneys should be performed particularly when RCC risk factors are present (e.g., pretransplant increased dialysis duration or known acquired cystic kidney disease).
  - EPO-producing kidney disease/disorder: autosomal dominant PKD, renal artery stenosis
  - Hypoxemia-associated increased EPO production: sleep apnea, high altitude, chronic pulmonary disease
  - Drug related: use of androgen, anabolic steroids, or surreptitious exogenous ESA
  - Hemoconcentration associated with diuretic use
  - Risk factors: presence of native kidneys, male gender, absence of rejection episodes, high baseline Hb before transplant, HTN, PKD, and glomerulonephritis as the cause of ESKD. Transplant renal artery stenosis has not consistently been shown to be a risk factor for PTE.
- Treatment:
  - The Hb/Hct threshold for treatment may vary depending on gender and institutional reference range. Generally, treatment is recommended for Hb levels exceeding 17 to 18 g/dL or Hct levels greater than 51% to 54% because of the associated risk of thromboembolic complications, HTN, and headaches.
  - Treatment with ACEIs or ARBs is often sufficient. Relapse is common and often necessitates long-term ACEI or ARB treatment.
  - Phlebotomy may be considered in severe PTE after optimization/treatment of any associated hypoxia-driven PTE.

- Low-dose aspirin 81 mg daily may be considered if there is no contraindication.

Posttransplantation proteinuria

- Occurs in 9% to 40% of kidney transplant recipients with a functioning graft (wide range reported due, in part, to the threshold use to define proteinuria and time after transplantation)
- Proteinuria from native kidneys typically decreases rapidly after transplantation and resolves within 3 months (generally within the first month) after transplant.
- Urine protein-to-creatinine (UPC) ratio and urine albumin-to-creatinine ratio are reasonable screening tests. Significant proteinuria warrants confirmation with 24-hour urine collection (although seldom performed in clinical practice).
- Persistent or worsening proteinuria is usually indicative of allograft pathology.
- Monitoring UPC ratio at each clinic visit and allograft biopsy should be performed in kidney transplant recipients with persistent or worsening proteinuria and in those whose primary kidney disease is FSGS to monitor for disease recurrence.
- Etiologies of posttransplantation proteinuria: recurrent disease particularly primary FSGS, secondary FSGS, TG, acute allograft rejection (proteinuria usually < 500 mg/dl, but higher levels may be seen), mtor inhibitor use (with or without association with fsgs), and chronic cni nephrotoxicity. proteinuria has also been reported to be associated with de novo dsa detection.
- As in the nontransplant setting, posttransplantation proteinuria increases the risk of cardiovascular events, graft loss, mortality, and PTDM.
- mTOR inhibitor–induced proteinuria:
  - The effect of mTOR-induced proteinuria on CVD risk is currently not known.
  - Although proteinuria generally increases the risk of cardiovascular events, mTOR inhibitor use has also been shown to have antiproliferative and cardioprotective effects. Hence, the independent

effect of mTOR inhibitor–induced proteinuria on CVD risk is difficult to delineate and remains to be studied.

- The use of ACEI or ARB:
  - The favorable effect of ACEI or ARB on patient and graft survival has not been consistently demonstrated. Nonetheless, ACEI or ARB should be considered in transplant recipients with proteinuria because of their well-established antiproteinuric and cardioprotective effects.

Chronic allograft injury

- Both immunologic and nonimmunologic factors have been suggested to play an interactive role in the development of chronic allograft injury and graft loss. These may include:
  - Chronic ABMR or chronic cell–mediated rejection or both
  - Recurrent glomerular disease
  - BKN
  - PTLD
  - Chronic CNI nephrotoxicity, among others
  - Suggested immunologic and nonimmunologic causes of chronic allograft injury are listed in Table 9.27.

Table 9.27 Alloimmune and nonalloimmune causes of chronic allograft dysfunction

Alloimmune Causes	Nonalloimmune Causes Include, But Not Limited to, the Following Factors
Chronic antibody-mediated rejection	Chronic CNI toxicity
Chronic T-cell–mediated rejection	Chronic hypertension
Mixed chronic antibody-mediated and T-cell–mediated rejection	Hyperlipidemia
	Viral infection (BK, CMV)
	Chronic bacterial pyelonephritis
	Recurrent or de novo diabetic changes
	Recurrent or de novo glomerular disease
	Posttransplantation lymphoproliferative disorder
	Marginal donor kidneys (e.g., preimplantation glomerulosclerosis and IFTA, long cold and/or warm ischemia times with suboptimal renal

	function recovery after transplant)

Abbreviations: CMV, cytomegalovirus; CNI, calcineurin inhibitor; IFTA, interstitial fibrosis and tubular atrophy.

Recurrent diseases

- Clinicians *must* remain vigilant for the possibility of glomerular disease recurrence after transplantation.
- Patients should be counseled on the risk of disease recurrence and the risk of graft loss associated with disease recurrence.
- Specific glomerular disease recurrence and suggested treatment (when applicable) are summarized in Table 9.28. Recurrent disease in patients with ESKD associated with primary hyperoxaluria type 1 is discussed below. For a more comprehensive review of glomerular disease recurrence after transplantation, interested readers are referred to reference 5.

Table 9.28 Risk for recurrent disease after transplant and graft loss from disease recurrence

Glomerular Disease	Recurrence Rates or Incidence	Risk of Graft Loss	Comments/Treatments
RECURRENT DISEASE			
Primary glomerular disease			
Dense deposit disease	70%–100%	10%–25%	
Primary FSGS **Note:** Secondary FSGS does not recur if the underlying etiology leading to FSGS has been modified.	17%–50%	10%–50%	May recur immediately or months to years after transplant. Risk factors for recurrence: Younger age at diagnosis, rapid progression to ESKD (3 y), white race, high level of proteinuria (60% recurrence), up to 80% recurrence in subsequent grafts if prior graft lost to FSGS. With the exception of podocin mutations (NPHS2), genetic forms of FSGS including those with the high-risk APOL1 genotype have a very low risk of recurrence Treatment: Plasmapheresis (standard of care) Others (less well defined): rituximab, adrenocorticotropic hormone analog gel, abatacept, cyclophosphamide, galactose infusion therapy[a]
Collapsing FSGS	NA	Up to 100%	
IgA nephropathy	10%–60% (histologic)	2%–16%	Clinical recurrence is 10%–25% (increases with longer duration of follow up)
Immune-complex–	25%–65%	10%–	Recurrence risk varies depending on underlying

mediated MPGN		33%	etiology
Fibrillary glomerulonephritis	50%	50%	
Membranous nephropathy (MN)	3%–50%	5%–30%	Often anti-PLA2R positive, IgG4 dominant Disappearance of anti-PLA2R at time of transplant (10% recurrence) Persistent anti-PLA2R antibody at time of transplant (50% recurrence) MN without ever having anti-PLA2R antibody in either serum or kidney biopsy (30% recurrence) Treatment: Rituximab regardless of anti- PLA2R levels (recommended by some experts as first-line therapy)
C3 glomerulonephritis	> 50%		
Associated with systemic disease			
Atypical HUS	25%–80%	40%–60%	May be triggered by: allograft rejection, endothelial injury, ischemia–reperfusion injury, infections (e.g., CMV, influenza, parvovirus B19, BK virus, upper respiratory or GI infections) Very high risk of recurrence in patients with mutations involving circulating factors (particularly complement factor H and factor I). Mutation in membrane cofactor protein has low risk of recurrence unless it is associated with other mutations Treatment: Eculizumab[b]
Cryoglobulinemia	50%	NA	
Monoclonal immunoglobulin deposition disease	50%	NA	
ANCA-associated crescentic glomerulonephritis	9%–50%	Rare	Less recurrence if in sustained remission before transplantation (sustained remission defined as at least 1 y before transplantation) Recurrence rates have decreased in recent years, thought to be due to the use of more potent immunosuppressive agents
Diabetic glomerulosclerosis	40%	17%–40%	
IgA vasculitis (Henoch–Schonlein purpura)	15%–60%	10%	
Lupus nephritis	2%–30%	5%	May recur as nonspecific immune complex disease
Anti-GBM antibody nephritis	Clinical recurrence is low	50%	De novo anti-GBM may develop after transplant in patients whose primary disease is Alport syndrome (particularly males with X-linked COL5A large deletional mutations).
Fabry disease	5%		

Shiga-toxin–associated HUS	0%–10%		
Amyloidosis	20%–30%		**Secondary or AA amyloidosis** • Recurrence risk varies depending on whether the underlying cause of chronic inflammation can be controlled or eradicated. • Familial Mediterranean fever (FMF): Recurrence of amyloid deposition in the allograft is common. Colchicine may prevent the development of proteinuria. **Primary or AL amyloidosis** • Recurrence is likely if patient is not in complete hematologic response at transplant (Hematology/Oncology consultation is strongly recommended).

[a]Galactose infusion binds and clears FSGS permeability factor from the circulation

[b]In patients with high risk of recurrence, prophylactic eculizumab therapy is recommended

Abbreviations: ABMR, antibody-mediated rejection; ANCA, antineutrophil cytoplasmic antibodies; DM, diabetes mellitus; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; HCV, hepatitis C virus; HUS, hemolytic uremia syndrome; IgA, immunoglobulin A; IgG1, immunoglobulin G1; IgG4, immunoglobulin G4; MPGN, membranoproliferative glomerulonephritis; NA, not available; PLA2R, phospholipase A2 receptor.

Primary hyperoxaluria type 1

Lack of liver enzyme-specific peroxisomal enzyme alanine-glyoxylate aminotransferase in patients with primary hyperoxaluria type 1 (PH1) results in decreased transamination of glyoxylate to glycine and increased production of oxalate and glycolate. Because oxalate is eliminated unaltered by renal excretion, isolated kidney transplantation can result in rapid deposition of oxalate in the allograft and subsequent stone formation, nephrocalcinosis, and graft failure. Liver transplantation corrects the underlying hepatic-based metabolic disorder. Hence, in patients with ESKD due to PH1, simultaneous liver-kidney transplant is recommended.

De novo glomerular diseases after transplantation (see Appendix A)

POSTTRANSPLANTATION BONE AND MINERAL DISORDER

Hypophosphatemia

- Hypophosphatemia can be seen in 40% to 90% of patients after transplant. The majority of cases are mild to moderate (serum phosphorous >1.5 to <2.3 mg/dl).
- Hypophosphatemia is most pronounced within the first 3 months posttransplant and generally recovers to normal levels by 1 year.
- Concomitant hypercalcemia suggests posttransplantation hyperparathyroidism.
- In the absence of hypercalcemia, renal phosphate wasting syndrome or malnutrition should be considered.
- Etiologies of posttransplantation hypophosphatemia:
  - Renal phosphate wasting due to high serum levels of the bone-derived phosphaturic hormone FGF23 and hyperparathyroidism. FGF23 levels gradually decrease in the first few months after transplant in response to low phosphorous levels, resulting in decreased phosphaturia and improvement in serum phosphate.
  - Elevated parathyroid hormone (PTH) levels can persist beyond improved serum phosphorus, making it appear that FGF23 may be the more important factor in causing hypophosphatemia; elevated FGF23 levels more strongly correlate with hypophosphatemia than PTH.
  - Reduced intestinal phosphate absorption due to reduced calcitriol related to elevated FGF23 level (see Chapter 3 Calcium, Phosphorous, Magnesium, Stones)
  - Other contributors to hypophosphatemia:
    - Metabolic acidosis stimulates phosphaturia.
    - Glucocorticoids inhibit intestinal sodium-phosphate transporter activity.
    - mTOR inhibitors (sirolimus, everolimus) inhibit renal tubular phosphate reabsorption by a not well-defined mechanism.
    - Early after transplantation, hypophosphatemia has been attributed to a massive initial diuresis, defective renal phosphate reabsorption due to ischemic injury, glucosuria (due to hyperglycemia-induced osmotic diuresis), and corticosteroid use (by inhibiting proximal tubular reabsorption of phosphate).

- Treatment:
  - Mild-to-moderate hypophosphatemia is not likely to be associated with significant adverse symptoms and does not need to be treated.
  - More pronounced hypophosphatemia may be associated with symptoms of muscle weakness.
  - Serum phosphate level of 1.5 mg/dL (~0.5 mmol/L) has been suggested as the lower limit to consider initiation of oral phosphate replacement, because symptoms can develop below this level.
  - Potential adverse effects of aggressive phosphorous supplementation: worsening existing hyperparathyroidism and elevated FGF23 levels, vascular and kidney allograft calcifications

Calcium

- Serum calcium levels may follow a biphasic pattern with significant decline in the first 1 to 2 weeks posttransplant followed by a significant increase during the first 3 to 6 months after transplantation.
- Hypercalcemia:
  - Hypercalcemia is common after transplantation and is generally due to persistent secondary hyperparathyroidism. Total calcium may underestimate diagnosis of hypercalcemia compared to ionized calcium due to concurrent metabolic acidosis.
  - The concomitant presence of severe hypophosphatemia particularly in patients with excellent graft function may exacerbate hypercalcemia through stimulation of renal proximal tubular 1α-hydroxylase.
  - Resolution of soft-tissue calcifications and immobilization are potential contributing factors.
  - Hypercalcemia is generally moderate, with total calcium ranging between 10.5 and 11.5 mg/dL. Severe hypercalcemia (total calcium level > 12 mg/dL) is uncommon.
  - Hypercalcemia prevalence decreases over time. However, hypercalcemia can persist in as much as 15% of patients at 1 year after transplantation but generally ranges between 0.5% and 5.6%.
  - In kidney transplant recipients with hypercalcemic hyperparathyroidism,

treatment with the calcimimetic cinacalcet can reduce serum calcium and PTH levels and improve hypophosphatemia.

- Severe hypercalcemia or persistent hypercalcemia (≥12 months) requires further evaluation.
  - Initial assessment should include an intact PTH level.
  - Neck ultrasound or preferably parathyroid technetium 99mTc-sestamibi scan is required to determine whether the clinically observed hyperparathyroidism arises from parathyroid adenoma or parathyroid gland hyperplasia, or hyperplastic nodular formation of the parathyroid glands.

- Hypocalcemia:
  - Early posttransplant low calcium levels are associated with lower pretransplant parathyroid levels and may be associated with low bone turnover, but may also be impacted by postsurgical early hypoalbuminemia and volume expansion.

Hyperparathyroidism

- Secondary hyperparathyroidism improves after kidney transplantation with good allograft function, with progressive decrease in PTH levels in the first 3 to 6 months.
- Involution of parathyroid hyperplasia occurs very slowly and is associated with persistent hyperparathyroidism.
  - 50% of recipients continue to have elevated PTH levels at 1-year posttransplant; longer term follow-up has shown that only approximately 25% of recipients have normal PTH levels and 25% continue to have elevated PTH levels > two times normal at 5 years after transplantation.
- Risk factors for persistent posttransplantation hyperparathyroidism:
  - Time on dialysis > 6 years, calcium-phosphate product >55 mg/dL, cinacalcet use prior to transplant
  - Others: higher pretransplant PTH levels, larger gland size and presence of multinodular hyperplasia, persistent elevation of alkaline phosphatase
- Adverse effects associated with persistent hyperparathyroidism:

hypercalcemia, development or exacerbation of osteopenia/osteoporosis, fractures, allograft dysfunction, renal calcinosis, vascular calcifications, increased risk of cardiovascular event

- Treatment:
  - Clinically significant hypercalcemia due to persistent (tertiary) hyperparathyroidism after transplantation may be managed medically (calcium-sensing receptor agonist) or surgically (parathyroidectomy).
  - The use of cinacalcet for the treatment of hypercalcemia after transplant is off label and has not been approved for this indication by the FDA.
  - Parathyroidectomy: Observational studies of parathyroidectomy in kidney transplant recipients for persistent (tertiary) hyperparathyroidism show high success rates in resolving hyperparathyroidism with subtotal parathyroidectomy or total parathyroidectomy with autotransplantation. Limited glandular resection (of only one or two macroscopically enlarged glands) is associated with significant risk of recurrence of hyperparathyroidism.
  - Choice of therapy (medical vs. surgical): No specific guidelines dictating timing or goals of treatment exists due to lack of evidence supporting specific recommendations. Comparison of treatment outcomes and advantages and disadvantages of cinacalcet versus parathyroidectomy is summarized in Table 9.29.

Table 9.29 Cinacalcet versus parathyroidectomy for hypercalcemia after transplant

	Cinacalcet	Parathyroidectomy
Control of hypercalcemia	80% of patients	90%–100% of patients
PTH normalization	Minority	Nearly all
Effect on BMD	No effect	Improved BMD
Potential adverse effects	Possible hypercalciuria Nephrocalcinosis and renal stones have been reported	Surgical risks Recurrent laryngeal nerve injury Early and long-term hypocalcemia Irreversible low bone turnover
Costs	Open-ended costs of therapy for indefinite duration	Cost equals to approximately 14 mo of cinacalcet therapy

Abbreviations: BMD, bone marrow density; PTH, parathyroid hormone.

- Opinion-based recommendations or considerations that may guide therapy based on available evidence and/or clinical situation include:
  - Delaying treatment beyond 6 to 9 months after transplant because hypercalcemia and associated hyperparathyroidism may continue to abate during this time frame.
  - Age and medical infirmity, as well as patient preference, may favor medical versus surgical treatment due to potential surgical risks.
  - Hypercalcemia that is not controlled with calcimimetics may require parathyroidectomy.
  - Symptomatic/progressive hypercalcemia:
    - Nephrolithiasis
    - Persistent metabolic bone disease
    - Calcium-related allograft dysfunction
    - Progressive vascular calcification
    - Calciphylaxis
  - Cost of calcimimetics may impact treatment decisions.
  - Treatment goal of improving low bone density may favor parathyroidectomy (beneficial effect on complications of vascular calcification complications unclear).
  - Presence of multiple risk factors prior to transplant that significantly decrease the likelihood of avoiding complications of persistent hyperparathyroidism after transplant

Vitamin D Insufficiency or Deficiency

- Calcidiol [25(OH)D] deficiency is common in transplant recipients and can persist for more than 1 year after transplantation.
  - Approximately 80% are insufficient with levels <30 ng/ml.
  - Up to 30% are deficient with levels <20 ng/ml.
  - Factors associated with calcidiol deficiency can include:
    - Female sex, ethnicity (African Americans have high incidence of deficiency, but this is associated with lower binding protein; active unbound form may be sufficient)
    - Malabsorption or malnutrition

        - Seasonal variation
        - Proteinuria and hypoalbuminemia can decrease the levels of binding protein and lower total levels.
        - Increased catabolism of calcidiol due to corticosteroids
        - Reduced production from sterol precursors due to recommendations to reduce ultraviolet (UV) light exposure to reduce skin cancer risk after transplantation
    - Low calcidiol levels in transplant recipients may be associated with:
        - Increased risk of chronic allograft nephropathy
        - Increased risk of CVD
        - Increased risk of malignancy
        - Increased risk of PTDM
        - Elevated PTH levels and metabolic bone disease after transplant
- Calcitriol [$1,25(OH)_2D$] levels improve after transplantation and normalize in the majority of recipients by 3 to 6 months after transplantation. The increase in calcitriol levels are associated with:
    - 1-alpha-hydroxylase activation related to elevated PTH levels
    - Fall in FGF-23 levels after a successful transplant
- KDIGO suggests correcting vitamin D deficiency in transplant recipients using treatment strategies recommended for the general population, and transplant recipients with advanced CKD and low bone marrow density (BMD) be managed according to nontransplant CKD recommendations.

Posttransplantation Bone Disease

- Osteopenia/osteoporosis: Posttransplant decline in BMD is most pronounced in the first 6 months and correlates with higher corticosteroid exposure. **Note:** Osteopenia on bone density does not predict osteoporosis on bone biopsy.
- The early rapid decrease in BMD is usually followed by a slower rate of bone loss.
- Avascular necrosis:
    - Most commonly affects the femoral head and neck but may affect other joints, including knees, shoulders, ankles, elbows, and wrists

    - Risk factors: greater exposure to IV corticosteroid pulse therapy, low bone mass, increasing dialysis duration, excessive weight gain, dyslipidemia, microvascular thrombosis, and history of local trauma
    - Early steroid withdrawal has been shown to reduce fracture risk.
- Other bone disease: adynamic bone disease, osteomalacia, and mixed bone disease
- Prevention of bone complications:
    - Goal: To reduce fracture risks. However, randomized studies of therapy for metabolic bone disease have shown benefit in terms of improved bone density but failed to show reduction in fracture risk endpoint.
    - Vitamin D has been suggested to improve bone density.
    - Bisphosphonate should be used with caution in patients with impaired kidney function and avoided in CKD stages 4 to 5.
    - Pamidronate use has been reported to be associated with collapsing FSGS, noncollapsing FSGS, and minimal change disease.
    - Denosumab is a humanized monoclonal antibody that binds to and prevents RANKL (receptor activator of nuclear factor-β ligand) from activating its receptor (RANK) on the surface of osteoclast and their precursors. Denosumab has been shown to increase BMD.
- The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines:
    - *First 3 months posttransplant, eGFR > 30 mL/min/1.73 m^2:* Measuring BMD is suggested if patients receive corticosteroids or have risk factors for osteoporosis as in the general population **(2D)**.
    - *First 12 months posttransplant, eGFR > 30 mL/min/1.73 m^2, and low BMD:* Treatment with vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents may be considered.
    - *After the first 12 months:* There are insufficient data to guide treatment **(2D)**.
    - *Other suggestions:* Treatment choices may be influenced by the presence of CKD-mineral and bone disorder, as indicated by abnormal levels of calcium, phosphate, PTH, alkaline phosphatase, and 25(OH)D **(2C)**. It is reasonable to consider a bone biopsy to guide treatment **(not graded)**.

- **Note:** KDIGO guideline recommendation ratings: level 1 “we recommend”; level 2 “we suggest”; grade A: Quality of evidence is high; grade B: Quality of evidence is moderate; grade C: Quality of evidence is low; grade D: Quality of evidence is very low.

POSTTRANSPLANTATION MALIGNANCY

Malignancy After Solid Organ Transplantation

- Recipients of organ transplants are at increased risk for developing certain neoplasms compared with the general population.
- Posttransplant malignancy is an important cause of death in long-term kidney transplant recipients.
- The overall incidence of de novo malignancies is two- to fourfold greater in solid organ transplant recipients compared with that of the general population.
- Compared with the general population, kidney transplant recipients have a substantially higher risk for:
  - Nonmelanoma skin cancers
  - Kaposi sarcoma
  - PTLD
  - **Note**: Nonmelanoma skin cancers (particularly squamous cell carcinoma) have the highest “standardized incidence ratios” (ratio of observed number of cases to the expected number of cases) in transplant recipients.
- Common cancers in the general population, including the breast, colon, prostate, lung, bladder, stomach, and pancreas, were found to occur more frequently in kidney transplant recipients in some, but not all, studies.
- Suggested risk factors:
  - Duration and intensity of immunosuppressive agents due to their presumed ability to promote replication of oncogenic viruses
  - Infection-associated cancers:
    - Kaposi sarcoma and human herpes type 8
    - Non–Hodgkin lymphoma and EBV

Well-described viral-associated cancers are summarized in Table 9.30.

Table 9.30 Viral-associated cancers

Oncogenic Viruses	Specific Viral-Associated Cancers
Epstein–Barr virus	Posttransplant lymphoproliferative disorder, non–Hodgkin lymphomas, Hodgkin lymphoma, and plasma cell neoplasms
Human herpes virus 8	Kaposi sarcoma
Hepatitis B and hepatitis C	Hepatocellular carcinoma
Human papillomaviruses (HPV)	Vulva, vagina, cervix, penis, anus, oral cavity, and pharynx
Possibly HPV related	Nonmelanocytic-related skin cancer

- The precise cause of increased risk of lip cancer has not been well defined. The Transplant Center Match Study database demonstrated a strong association of lip cancer with white race and prior history of skin cancer, suggesting that UV radiation exposure is an important risk factor. A higher incidence of lip cancer was also found among transplant recipients receiving cyclosporine/AZA compared with tacrolimus/MMF maintenance immunosuppression. The contributory role of cyclosporine and AZA was thought to be due to their photosensitizing or DNA-damaging effects.
- Although melanoma has no known infectious etiology, a causal relationship between immunosuppression and its development in recipients of kidney transplants has been suggested.
- Others: older age, male gender, Caucasian race, pretransplant dialysis duration, smoking history, deceased donor organ, cumulative exposure to radiation from repeated medical imaging studies, antecedent use of immunosuppressive agents to treat primary kidney diseases

Skin Cancers

- Most common de novo posttransplant malignancy in the adult transplant population

- Incidence of squamous cell carcinoma (SCC) >> basal cell carcinoma (BCC)
- SCC in organ transplant recipients:
  - Most common cutaneous malignancies in solid organ transplant recipients, with a 65- to 100-fold greater incidence compared with the general population
  - More clinically aggressive disease and worse tumor histology compared with that of the general population
- Risk factors for skin cancers:
  - Pretransplant history of SCC
  - Actinic keratoses and viral warts (increased risk for keratinocyte carcinoma)
  - Duration of follow-up after transplant
  - Light-skin color (easily sunburnt)
  - Intensity of sun (UV radiation) exposure (e.g., high-altitude residence)
  - Older age at transplant
  - Patients who develop SCC after transplantation are at increased risk for subsequent SCC, whereas those with a first posttransplant BCC are at risk for subsequent BCC.
  - AZA-based immunosuppression was found to be associated with a significantly increased risk for subsequent SCC, but not for subsequent BCC.
  - **Note:** Voriconazole (a commonly used antifungal agent to treat invasive fungal infection in organ transplantation) use is associated with increased cutaneous SCC risk in organ transplant recipients, particularly in recipients of lung transplants. Voriconazole's increased risk of skin malignancy has been suggested to be due to increased skin photosensitivity.
- mTOR inhibitor in posttransplant cutaneous malignancies:
  - The mTOR inhibitors sirolimus and everolimus have antiproliferative and antitumoral effects.
  - The Sirolimus Renal Conversion Trial (CONVERT) in which patients were randomized to sirolimus conversion or CNI continuation

demonstrated that:

- Sirolimus-based, CNI-free immunosuppression was associated with a significant reduction in nonmelanoma skin cancers at 2 years postconversion (1.2 vs. 4.3, $p < 0.001$).
- Sirolimus-treated patients had a significantly lower incidence of melanoma, although the incidence of melanoma was low (1.1% in the CNI continuation group and 0% in the sirolimus conversion group, $p = 0.06$).
- There was a nonstatistically significant lower rate of all other cancers (1.0 vs. 2.1, $p = 0.058$).

- Both "de novo" mTOR inhibitor use and CNI to mTOR inhibitor "conversion therapy" were found to be associated with decreased nonmelanoma skin cancer risks. Its use is effective in both primary and secondary skin cancer prevention. Furthermore, the earlier the conversion after an initial diagnosis of cutaneous SCC, the greater the efficacy.
- Meta-analyses and randomized trials evaluating mTOR inhibitor use in secondary prevention of SCC showed a reduction in cumulative tumor load, suggesting that most benefit is gained by early conversion to an mTOR inhibitor–based maintenance regimen.
- It is suggested that the protective effect of mTOR inhibitors against skin cancer is a result of its inhibition of several UV-induced mechanisms involved in skin carcinogenesis.

- Dermatology surveillance (guidelines drawn from evidence-based skin cancer surveillance program, UK):
  - High risk (age >55 years at transplant and light-skin color): annually for the first 2 years and then every 6 months thereafter
  - Low risk (Asian or Black): every 2 years
  - Increased surveillance recommended after first cancer

Posttransplantation Lymphoproliferative Disorder

- PTLD encompasses a wide spectrum of lymphoid proliferations ranging from reactive polyclonal lesions to frank malignant monoclonal

lymphomas.

- The WHO histologic classification of PTLD can be divided into four subtypes based on morphology, clonality, and molecular criteria:
  - Early lesions
  - Polymorphic PTLD
  - Monomorphic PTLD
  - Classic Hodgkin lymphoma–type PTLD
- Most common type of posttransplantation malignancy in children
- Second or third most common posttransplantation malignancy in adults (follows only nonmelanoma skin cancers and Kaposi sarcoma)
- Incidence: varies with the type of organ transplanted
  - Kidney (1% to 2%); liver (1% to 4%); simultaneous kidney pancreas (2% to 3%); heart, lung, and heart-lung transplants (2% to 10%); small bowel and multivisceral transplantation (up to 33%)
  - The high incidence of PTLD in intestinal and multiorgan transplants has been attributed to the use of more intensive immunosuppression and the amount of donor-derived lymphoid tissue transferred at organ transplantation.
- The majority of PTLD are non–Hodgkin lymphoma of B-cell origin and are CD20 positive.
- Although PTLD was originally thought to be uniformly linked to EBV infection, an increased incidence of EBV-negative PTLD has been reported. In some series, EBV-negative PTLD may occur in up to 30% to 50% of cases. EBV-associated PTLD appears to vary with PTLD subtypes (Table 9.31).

Table 9.31 Incidence of EBV-associated PTLD by PTLD subtypes and time of onset after transplant

PLD Subtypes	EBV Association	Onset After Transplant
Early lesions	Almost 100% EBV positive	Most early PTLD
Polymorphic PTLD	>90% EBV positive	Variable
Monomorphic PTLD	Both EBV positive and EBV negative	• EBV positive: Most occur within the first 3 y after transplantation • EBV negative: late-occurring PTLD (>5 y

		after transplant)
Hodgkin lymphoma–like PTLD	>90%	

Abbreviations: EBV, Epstein–Barr virus; PTLD, posttransplant lymphoproliferative disorder.

- EBV-positive versus EBV-negative PTLD:
  - Pathogenesis:
    - Immunosuppression-related decrease in T-cell immune surveillance has been suggested to play a major contributory role in EBV-positive PTLD. In immunocompetent hosts, EBV-specific $CD8^+$ effector and memory T cells are responsible for controlling EBV-infected B cells from uncontrolled proliferation and transformation.
    - The pathogenesis of EBV-negative PTLD remains speculative. Proposed hypotheses include: hit-and-run EBV infection (disappearance of EBV following an initial infection that leads to PTLD), viral infection other than EBV (e.g., CMV), persistent antigen stimulation by the graft, and long-term immunosuppression.
  - Molecular-genomic studies revealed that EBV-negative PTLD shares many genomic and transcriptomic features with diffuse large B-cell lymphoma (DLBCL) in immunocompetent patients, whereas EBV-positive PTLD has fewer genomic abnormalities.
  - Although the molecular genetic separation between EBV-positive and EBV-negative PTLD is well defined, EBV status is not prognostic or predictive with respect to treatment response. In a subset of patients, reduction in immunosuppression alone is effective, regardless of EBV status.
- EBV-positive PTLD is typically considered to result from EBV infection of recipient B cells, but may be of donor origin.
- PTLD may also develop in donor organs (allograft PTLD).
  - Generally occurs in the first 2 years after transplant
  - Suggested pathogenic mechanisms: development of lymphoproliferations from donor passenger lymphocytes, chronic antigenic stimulation, EBV proliferation
- Mortality is greater with PTLD than with lymphomas in the general population.

- Risk factors:
  - EBV donor–recipient mismatch (donor seropositive, recipient seronegative at transplant):
    - EBV donor–recipient mismatch is the most well-established risk factor.
  - Extreme of age (children and advanced age). The increased incidence of PTLD in children is attributed to their pretransplant EBV-naïve status.
  - Immunosuppression:
    - Induction with T-cell–depleting antibodies or the degree of T-cell immunosuppression. (**Note:** Studies showed no consistent association between PTLD and any individual immunosuppressive agent, suggesting that the overall degree of immunosuppression may play a more important role than any individual agent.)
    - Clinical trials showed an increase in the incidence of PTLD with CNS involvement among EBV-seronegative transplant recipients who received belatacept. Its use is contraindicated in recipients with pretransplant EBV-naïve or unknown status.
  - Higher degree of HLA mismatches and individual recipient HLA type (e.g., recipient HLA-B38 has been shown to be associated with a 1.48-fold increased risk of DLBCL. In contrast, recipients HLA-B58 and HLA-DR13 have been reported to be associated with reduced DLBCL risk)
  - Other risks: white compared with African American race, male gender, pretransplant malignancy, infections with HHV-8 and simian virus 40, CMV seronegative status at transplant (conflicting data), CMV disease (conflicting data), recipient with monoclonal gammopathy of undetermined significance
- Clinical manifestation:
  - Time of occurrence after transplant:
    - PTLD occurs at a median of 18 months posttransplant.
    - Most EBV (+) PTLD occur within the first 3 years after transplant.
    - Bimodal distribution with time after transplant has been reported: The first peak occurs in the first year posttransplant, and the second

peak 5 to 15 years posttransplant.

- Registry studies and the UNOS/OPTN database demonstrated that EBV-negative PTLD generally presents later after transplant (>5 years) and has been suggested to account for the bimodal distribution pattern of PTLD occurrence, with early cases being predominantly EBV positive and late cases being EBV negative. A French registry study suggests that late-occurring PTLD (between 8 and 10 years) is less likely to be due to EBV lymphoproliferation and more likely to be a consequence of aging and duration of immunosuppression exposure.
- An increasing number of very late cases occurring >20 years has been reported.

- Clinical presentation:
  - Clinical manifestation spectrum spans from incidental asymptomatic findings or constitutional symptoms (e.g., fevers, night sweats, malaise, weight loss) to symptomatic organ involvement and spontaneous tumor lysis.
  - Localized symptoms may involve the respiratory tract (e.g., infection, mass, tonsillitis, or even gingival involvement), GI tract (e.g., diarrhea, pain, perforation, bleeding, mass), or CNS (e.g., headache, seizure, or confusion).
  - Extranodal involvement is common, and multiple sites are often involved. GI tract involvement has been reported to occur in 20% to 30% of cases, solid graft organs in 10% to 15%, and the CNS in 5% to 20%.
  - Others: symptoms related to allograft dysfunction or compression of surrounding structures
  - Clinical presentation of PTLD based on the German multicenter pediatric PTLD registry:
    - Early PTLD (<1 year) development was associated with younger age, extranodal disease, and graft organ involvement and was often of b-cell lymphoma histology and tended to be ebv positive.
    - Burkitt lymphoma and Hodgkin disease were only observed in late

PTLD (>1 year) and were more likely to be associated with nodal disease.

- Treatment:
  - Treatment strategies include immunosuppression reduction or discontinuation, surgical resection with or without local radiation for localized disease, rituximab, and chemotherapy. Adoptive immunotherapy using EBV-specific cytotoxic T cells has been reported to be effective in relapsed or refractory PTLD. However, such therapy requires specialized techniques and is not readily available (discussion is beyond the scope of this chapter). For PTLD involving the CNS, whole-brain radiation is a therapeutic option for those who cannot undergo chemotherapy due to specific contraindications.
  - **Reduction or discontinuation of immunosuppression:**
    - Immunosuppression reduction to restore EBV-specific cellular immunity should be the first line of treatment.
    - The antimetabolites AZA or MPA derivatives are generally discontinued, although their use has not been consistently demonstrated to increase PTLD risk. A lower or no increased risk has been observed. Nonetheless, it is common practice to discontinue the antimetabolites because of the theoretical risk of net protumor effect of overimmunosuppression.
    - CNI dose reduction by 50% to 75% at the discretion of the clinician. Prednisone can be continued to prevent allograft rejection. For critically ill patients, those with monoclonal tumors or extensive disease, immunosuppression should be drastically reduced or discontinued.
    - Patients with polyclonality are most likely to respond to immunosuppression reduction.
    - EBV negative is less responsive to immunosuppression reduction alone than EBV-positive disease.
    - Suggested factors predictive of a poor response to reduction in immunosuppression alone include:
      - Elevated lactate dehydrogenase, organ dysfunction at diagnosis,

multiple organ involvement, bulky disease (largest tumor deposit > 7 cm in diameter), advanced stage (Ann Arbor stage III or IV), and older age (>50 years)

- Other poor prognostic factors include: WHO performance status score of 3 or 4 (a score of 3 is defined as confined to bed or a chair for >50% of waking hours, and a score of 4 as completely disabled), late onset of disease (>1 year after transplant), CNS disease, severe organ dysfunction, AKI at diagnosis, and T-cell disease

- Restaging should be performed 2 to 4 weeks after immunosuppression reduction.

- **Failure to respond to immunosuppression reduction alone:**
  - Rituximab, a chimeric monoclonal antibody targeting CD20 on the surface of B cells, is currently considered standard therapy for CD20-positive PTLD that fails to respond to manipulation of immunosuppression alone (recommended dose: rituximab at 375 mg/m^2 body surface area weekly for 4 weeks. Extended treatment with four additional doses may increase complete response rate).
  - Chemotherapy:
    - Indicated in patients refractory to reduction in immunosuppression and/or rituximab, in those with aggressive disease at presentation, and in those not amenable to surgery
    - Other indications: peripheral T-cell lymphoma, Hodgkin lymphoma, Burkitt lymphoma, primary CNS lymphoma, and other uncommon lymphoma. All CD20-positive subtypes should also receive rituximab.
    - **C**yclophosphamide, **H**ydroxydaunorubicin or doxorubicin, **O**ncovin or vincristine, **P**rednisone **(CHOP)**–based chemotherapy is the most widely used regimen. Currently reduced immunosuppression and risk-stratified sequential treatment with rituximab followed by CHOP (i.e., R-CHOP) are considered standard of care for polymorphic and monomorphic DLBCL-like PTLD, irrespective of EBV status (rituximab at 375 mg/m^2 weekly

for 4 weeks, followed by CHOP every 3 weeks with granulocyte-stimulating factor support).

- **Antiviral therapy:**
  - The use of acyclovir and ganciclovir is of unproven benefit because their activity is dependent on intracellular phosphorylation by virally coded thymidine kinase. EBV-driven lymphomas do not express thymidine kinase.
- **mTOR inhibitors**
  - Although sirolimus has antiproliferative effects, there are insufficient data to recommend or refute its use in the treatment of PTLD. Although a direct antitumor effect cannot be excluded, it is speculated that the beneficial effect of conversion to sirolimus monotherapy (or sirolimus and prednisone dual therapy) may be due to a reduction in overall immunosuppression.
- PTLD treatment modalities are summarized in Table 9.32.

Table 9.32 PTLD treatment modalities[a]

Treatment	Indications	Comments
Immunosuppression reduction	Mainstay of therapy in all PTLD subtypes	
Rituximab	First-line treatment for CD20-positive PTLD not responsive to IS reduction alone	
Chemotherapy	• For those who fail to achieve complete remission despite IS reduction and rituximab therapy • Currently, IS reduction and risk-stratified sequential treatment with rituximab followed by CHOP (i.e., R-CHOP) are considered standard of care for polymorphic and monomorphic diffuse large B-cell lymphoma. • Other indications: aggressive disease at presentation, lesions not amenable to surgery among others	CHOP-based therapy is the most widely used regimen.Increased infectious riskG-CSF use may decrease morbidity and mortality.
Surgery	• For localized disease in conjunction with IS reduction • Palliative care (symptomatic relief)	

Radiation therapy	• For localized disease in conjunction with surgery and IS reduction • Palliative care (symptomatic relief)	
Antiviral therapy	Acyclovir and ganciclovir are of unproven benefit because their activity is dependent on intracellular phosphorylation by virally coded thymidine kinase. EBV-driven lymphomas do not express thymidine kinase.	Some centers continue to use antiviral therapy based on limited studies, suggesting that lytic viral DNA (not just latent viral DNA) is also present in established PTLD.
mTOR inhibitors	Insufficient data to recommend or refute its use in the treatment of PTLD	
Adoptive immunotherapy (adoptive transfer of EBV-specific cytotoxic T cells)	• Relapsed or refractory PTLD • Preemptive therapy	EBV-positive PTLD onlyExpensive, not readily available, time-consuming
Retransplantation	Should be disease free for at least 1–2 y prior to retransplantation. Consultation with hematology/oncology recommended	

[a]Detailed discussion is beyond the scope of this chapter. Interested readers are referred to Pham and Pham (2020).

Abbreviations: CHOP, **C**yclophosphamide, **H**ydroxydaunorubicin or doxorubicin, **O**ncovin or vincristine, **P**rednisone; G-CSF, granulocyte colony-stimulating factor; IS, immunosuppression; mTOR, mammalian target of rapamycin; PTLD, posttransplantation lymphoproliferative disorder.

- Retransplantation after PTLD
  - Re-allograft transplant candidates should be disease free for at least 1 to 2 years prior to retransplantation. Consultation with hematology/oncology is recommended.

MULTIORGAN TRANSPLANTATION

- Kidney and pancreas transplant options for patients with type 1 diabetes:
  - Simultaneous pancreas-kidney (SPK) transplantation:
    - Pancreas transplantation performed simultaneously with kidney transplantation from the same deceased donor (most common surgical procedures done)
    - Advantage: one surgical intervention and one source of foreign HLA
    - Among pancreas recipients, those with an SPK transplantation were found to have the best pancreas graft survival rates.
  - Pancreas after kidney transplantation (PAK):

- Pancreas transplantation performed after successful kidney transplantation from a living or deceased kidney donor
- Advantage: important option for patients with a living donor kidney
- Disadvantage: Intensification of immunosuppression (particularly in the early postoperative period) after pancreas transplantation can adversely impact kidney allograft function due to CNI toxicity.
- Must have adequate baseline renal function to undergo PAK

- Pancreas transplantation alone (PTA):
  - Least common surgical procedures performed
  - Therapeutic option for diabetic patients with good native kidney function who have brittle diabetes, particularly those with hypoglycemic unawareness
  - Some controversy on survival benefit of patients undergoing PTA compared to those not having been transplanted
  - Main risks: surgical procedure and long-term effects of immunosuppression
- Selected ESKD patients with insulin-dependent type 2 diabetics (i.e., BMI < 30 kg/m^2, minimal insulin resistance, and worsening glycemic control) may be appropriate candidates for spk.

- Simultaneous liver-kidney transplantation (SLKT):
  - Liver transplant candidate with ESKD
    - SLKT is a well-established therapeutic option for liver transplant candidates with simultaneous end-stage kidney failure.
  - Liver transplant candidate with CKD or AKI
    - The UNOS/OPTN eligibility criteria for SLKT in liver transplant candidate with CKD or AKI is summarized in Table 9.33.

Table 9.33 The 2018 UNOS/OPTN eligibility criteria for simultaneous liver-kidney transplantation

Orthotopic Liver Transplant (OLT) Candidates With CKD	OLT Candidates With Sustained Acute Kidney Injury (Sustained AKI)	OLT Candidates With Confirmed Diagnosis of Metabolic Disease
Preexisting CKD defined as measured or calculated CrCl or GFR of ≤ 60 mL/min for greater than 90 consecutive days prior to	Sustained AKI defined as AKI present for at least 6 consecutive weeks (must be documented in patient's medical records every 7	

listing	d)	
SLKT eligibilityCKD defined above and at least one of the following criteria must be present: 1. Patient has begun regular dialysis as an end-stage kidney disease patient. 2. Most recent measured or calculated CrCl or GFR ≤ 30 mL/min 3. On a date after registration on the kidney waiting list, measured or calculated CrCl or GFR ≤ 30 mL/min	SLKT eligibilitySustained AKI defined above and at least one of the following criteria must be present: 1. AKI requiring acute dialysis or 2. Measured or calculated CrCl or GFR ≤ 25 mL/min or 3. Any combination of number 1 and 2	SLKT eligibilityAt least one of the following diagnoses must be present: 1. Hyperoxaluria 2. Atypical hemolytic uremic syndrome (aHUS) from mutations in factor H and possibly factor I 3. Familial non-neuropathic systemic amyloid 4. Methylmalonic aciduria

Abbreviations: GFR, glomerular filtration rate; UNOS/OPTN, United Network for Organ Sharing/Organ Procurement Transplantation Network.

- Safety net
  - Recipients of liver-alone transplant whose renal function does not recover (GFR remains ≤ 20 mL/min or dialysis dependent) between 60 and 365 days after a successful liver transplant are given a degree of "*increased priority*" in being offered a deceased donor kidney. Detailed discussion is beyond the scope of this chapter.
  - The implementation of the safety net may relieve the clinician's pressure to perform SLKT when a liver-alone transplant may suffice.

CHAPTER 10

Pharmacology

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PHARMACOKINETICS

Key Concepts

Bioavailability, volume of distribution, plasma clearance, half-life

Bioavailability

- Bioavailability is the percentage or portion of administered drug that reaches systemic circulation.
  - Intravenous (IV) route: Bioavailability is 100%.
  - Non-IV route: Bioavailability depends on:
    - Ease of absorption (i.e., through gut, skin, or mucosal membrane)
    - First-pass metabolism (i.e., hepatic metabolism prior to release into systemic circulation)

Factors that can alter bioavailability in reduced GFR

- Increased salivary urea in uremia increases salivary pH, which reduces absorption of drugs that are better absorbed in acidic pH.
- Nausea/vomiting causes loss of oral drugs.
- Gastroparesis/reduced peristalsis slow drug absorption and delay attainment of plasma peak concentration.
- The use of antacids and proton-pump inhibitors (PPIs) can increase

stomach pH, which reduces absorption of drugs that are better absorbed in acidic pH (e.g., iron, mycophenolate mofetil [MMF; Cellcept], but not mycophenolate sodium [Myfortic]).

- Phosphate binders can form nonabsorbable complexes with some drugs (e.g., quinolones).
- Bowel wall edema (e.g., nephrosis) reduces gut absorption.

Volume of Distribution

- The total amount of drug in the body, expressed as an imaginary volume with a uniform drug plasma concentration:
  - Volume of distribution (V_d) = Total amount of drug in the body ÷ Plasma concentration of drug.
  - V_d is traditionally expressed as L/kg of ideal body weight.
  - V_d is large for drugs with a high degree of lipid solubility, compartmentalization, and low plasma protein binding.

Plasma protein binding

- Plasma protein binding is a key determinant of V_d (**Fig. 10.1**).

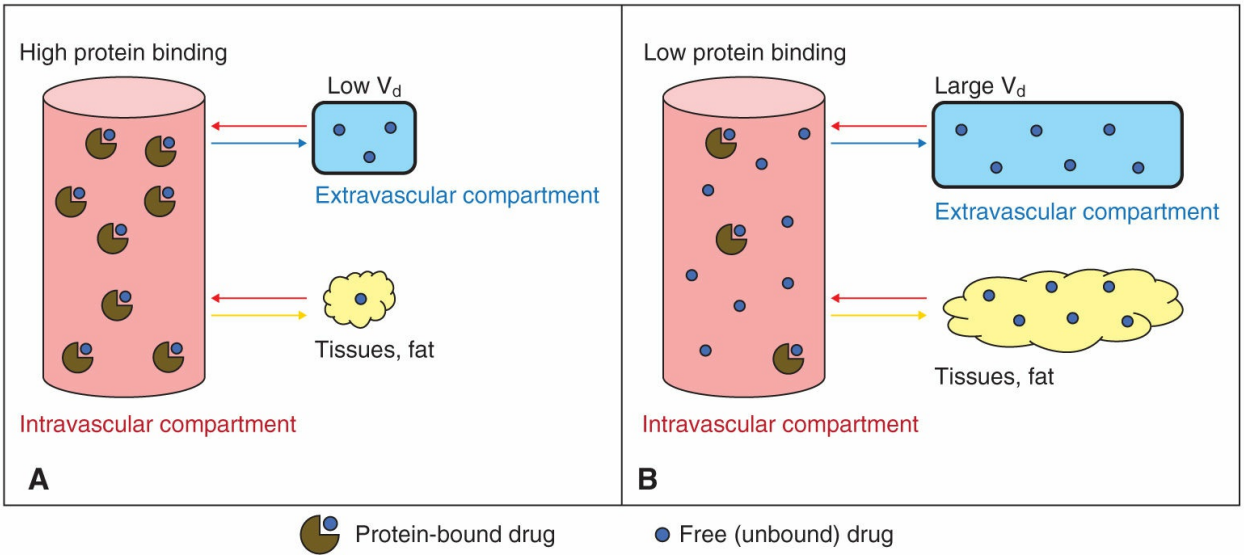

FIGURE 10.1 Volume of distribution (V_d). **A.** V_d is low for drugs with high plasma protein binding and high water solubility. **B.** V_d is large for drugs with low plasma protein binding, high lipid solubility, and compartmentalization.

- Drugs that are highly protein bound stay in the vascular compartment and

have a limited V_d.

- V_d is low for drugs with high water solubility and high plasma protein binding.
- Primary drug-binding proteins include albumin and α1-acid glycoproteins:
  - Organic acids generally bind to albumin.
  - Organic bases generally bind to glycoproteins. Increased synthesis of α1-acid glycoproteins may occur in inflammatory states and may alter free drug levels.

Factors that alter plasma protein binding in patients with reduced GFR

- Reduced serum proteins due to renal loss (e.g., nephrotic syndrome), malnutrition, and/or reduced synthesis

NOTE In patients with albuminuria, protein-bound drug may be lost in the urine, which may partly explain diuretic resistance in nephrotic syndrome.

- Competitive binding of uremic toxins to plasma proteins displaces protein-bound drugs into plasma, resulting in increased free (unbound) drug concentrations.
- Organic acids that accumulate in renal failure compete with acidic drugs for protein binding. Therefore, a larger fraction of acidic drugs will exist in the unbound active state (e.g., salicylates, warfarin, sulfonamides, phenytoin).
- Basic drugs bind more readily to nonalbumin proteins.
- Alteration in blood pH
- Predicting the effect of changes in protein binding on the kinetic parameters of drugs may be difficult. Although higher free drug concentrations are available at the site of action/toxicity, more is also available for metabolism or renal excretion.

Factors that can alter V_d in renal patients:

- Increased V_d: edema, ascites/effusions, adsorption onto apparatus (dialysis filters, extracorporeal membrane oxygenation [ECMO] circuits), volume expansion due to extracorporeal machinery (an extra 2,000 to 2,500 mL)
- Reduced V_d: older age, muscle wasting, amputations, loss of body fat,

volume depletion

- Effect of reduced plasma protein binding on V_d: Predicting the effect of reduced plasma protein binding on the V_d may be difficult. Although more free drug is available for redistribution into other extravascular compartments that can result in increased V_d, more is also available for metabolism or renal excretion. The latter can result in reduced V_d.

Loading dose is directly proportional to V_d:

$$\text{Loading dose} = \frac{(\text{Desired peak drug concentration} \times V_d \times \text{Ideal body weight})}{\text{Bioavailability}}$$

where bioavailability = 1 for IV drug infusion.

- In the absence of a loading dose, maintenance doses alone will not achieve steady-state level until five drug half-lives later. Thus, for some drugs, a loading dose is given to reduce the time to steady state when it is critical to rapidly achieve therapeutic concentrations (e.g., antibiotics in the setting of sepsis or septic shock).

NOTE A patient's actual V_d of drug A may be calculated as V_d = Loading dose of A ÷ (post[A] − pre[A]), where pre[A] and post[A] are plasma concentrations of drug A pre- and post-drug loading. When a patient's actual V_d of a drug is greater than that published in the drug insert, a higher dose may be needed. Similarly, if the patient's actual V_d is smaller than that published, dose reduction is necessary.

Plasma Clearance

- Most drugs are cleared/metabolized by the liver and/or kidneys. Plasma clearance is the sum of clearance of a drug by both renal and nonrenal routes.
- There is evidence that renal impairment may also reduce nonrenal (i.e., hepatic) metabolism of drugs, presumably via an increase in a circulating inhibitor of hepatic metabolic pathways (cytochrome P450). This factor is thought to be dialyzable.
- Drug clearance determines *maintenance dose.*
- Dose adjustment based on altered drug clearance in a patient with kidney failure:

  Example 1: A drug is 100% excreted by the kidneys. Normal maintenance

dose is 100 mg. If kidney function is now 30% of normal, what should be the new maintenance dose?

Maintenance dose should be reduced to 30% of normal dose, 30 mg.

Example 2: A drug is 40% cleared by liver and 60% by kidneys. Normal maintenance dose is 100 mg. If kidney function is now 40% of normal and assuming liver clearance is preserved, what should be the new maintenance dose?

Clearance of the drug is still 40% by liver, but now clearance by kidneys is only 40% of 60%, which is 24%. Total drug clearance would now be 40% by liver plus 24% by kidneys, or 64% total clearance. Maintenance dose should be reduced to 64% of normal dose, 64 mg.

Half-Life (t½)

- A drug t½ is the time needed for the plasma level of the drug to decrease by 50%.
- Generally, for an oral drug, 4 to 5 half-life duration are needed to reach steady state. Example: For a drug with t½ of 12 hours, it takes up to 5 × 12 hours = 60 hours (2½ days) to reach steady state. If an immediate therapeutic level is needed, a loading dose must be given.
- Half-life determines *dosing frequency*.

NOTE The pharmacokinetic t½ of a drug is not the same as its pharmacologic "*effect*" half-life. A drug may be cleared from the blood, but its *pharmacologic effect* (pharmacodynamics) may still persist (e.g., aminoglycosides [AGs], glucocorticoids, immunosuppressive agents).

Therapeutic Drug Monitoring

Therapeutic drug monitoring can be very valuable in guiding dosage adjustment for drugs with wide interpatient and intrapatient variation in pharmacokinetics or for drugs with a narrow therapeutic index or concentration dependent activity (e.g., AGs, digoxin, lithium, anticonvulsants, immunosuppressive medications). The pharmacokinetic and pharmacodynamic properties of the drug determine how therapeutic drug monitoring is performed (peak concentrations vs. trough concentrations).

Renal Handling of Drugs

- Renal drug clearance = UV/P of drug (and metabolites if applicable), where UV = total amount of drug in urine and P = plasma concentration of drug.
- Renal drug clearance is dependent on the drug characteristics (molecular size, charge, protein binding), glomerular filtration rate (GFR), tubular secretion and reabsorption, and renal epithelial cell metabolism.
- Drug t½ is directly proportional to V_d and inversely proportional to renal drug clearance (Cl). t½ = 0.693 × V_d/Cl, where 0.693 is the natural logarithm of 2 for half-life decay.

Drug adjustment in patients with reduced GFR

- Dose reduction in patients with chronic kidney disease (CKD) is generally indicated when ≥30% of a drug or its active metabolite is cleared by the kidneys. Similarly, when a drug is cleared by ≥30% with dialysis, the drug is considered "dialyzable."
- Estimation of kidney function for dose adjustment is traditionally done with the Cockcroft–Gault equation. GFR estimation using the Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formulas can lead to dosage recommendations different from those obtained by the Cockcroft–Gault equation, particularly if not corrected for body surface area. Read drug information provided by the pharmaceutical company regarding method of kidney function estimate used for dose adjustment.
  - Acute and severe kidney injury: Assume <10% kidney function and dose accordingly.
  - Rapidly improving kidney function: dose drug as if patient had normal kidney function

Maintenance dose adjustments in patients with reduced GFR

- Decrease dosage: This is the preferred method when maintaining constant drug level is more critical than achieving high peak levels for therapeutic effect (e.g., anticonvulsants, antiarrhythmics). Modified maintenance dose for renal insufficiency may be calculated as the (ratio of patient's to normal

creatinine clearance) × standard maintenance dose. Example: A patient with CrCl 69 mL/min (normal CrCl 120 mL/min) on a standard maintenance drug dose of 100 mg q8h. Modified dose = (69/120) × 100 = 58 or ~60 mg q8h.

- Reduce drug administration frequency: Preferred method if peak level is critical for therapeutic effect (e.g., antimicrobials such as AGs). Modified drug administration frequency for reduced kidney function may be calculated as the (ratio of normal to patient's CrCl) × current frequency. The modified frequency for the above example would be (120/69) × 8 hours = 14 hours. For simplicity, the drug can be given as 100 mg q12h.
- Combination of above: Preferred method for drugs with narrow therapeutic index (e.g., digoxin). For same patient above, the drug can be given as 80 mg q10h.
- Many medications have very specific CrCl cutoffs for dosing adjustments. Consult the manufacturers' drug information for details.

NOTE Dose adjustment in patients with CKD or end stage kidney disease (ESKD) may be needed, regardless of alterations in plasma clearance, because the *pharmacologic effects* of a drug may be exaggerated due to increased target organ sensitivity (e.g., exaggerated sedation with narcotics in patients with ESKD despite appropriate dose reduction).

Principles of Dialytic Drug Removal

- Dialysis drug clearance may occur via both diffusion and convection.
- Clearance is dependent on the characteristics of the drug and dialysis.
  - Drug characteristics: molecular size (<500 da for hemodialysis [hd], up to 5,000 da for continuous renal replacement therapy [crrt]), water solubility, protein binding, v_d, plasma clearance.
  - Dialysis characteristics: membrane pore size, blood and dialysate flow rates, dialysis frequency and duration, ultrafiltration rate, replacement solution location in CRRT (predialysis vs. postdialysis)
- Drug clearance by dialysis is considered clinically significant if drug clearance is increased by ≥30% with dialysis.
- Whenever feasible, close therapeutic drug monitoring is recommended.

Special considerations for different modes of dialysis

Hemodialysis (HD)

- Drug clearance is dependent on dialysis membrane characteristics, blood and dialysate flow rates, and dialysis frequency and duration.
  - Clearance = drug extraction ratio × blood flow, where extraction ratio = (predialysis concentration − postdialysis concentration) ÷ predialysis concentration
- "High-efficiency," "high-flux," and "high-permeability" dialysis membranes can lead to significantly higher drug clearance, particularly for highly water-soluble drug. Example: Vancomycin clearance is significantly increased with high-flux membranes. "High-permeability" membrane is defined as having an ultrafiltration coefficient K_{uf} > 12 mL/mm Hg/h.

Peritoneal dialysis (PD)

- Protein-bound drugs may be better cleared with PD compared with HD due to larger peritoneal membrane pore size.
- Drug clearance by PD is typically approximated at 10 mL/min.
- Drug clearance by PD may increase with the following:
  - Peritonitis due to increased blood flow
  - Increase number of daily exchanges

Continuous renal replacement therapy (CRRT)

See Chapter 12, Drug Dosing with CRRT

Plasmapheresis

- Literature on drug removal with plasmapheresis is lacking.
- Plasmapheresis may significantly remove drugs with high plasma protein binding and/or low V_d.
- Intravenous immunoglobulin (IVIG), rituximab, and antithymocyte globulin (used for the treatment of acute antibody-mediated and acute vascular rejection) are removed by plasmapheresis. Although the extent of drug removal by such procedure is unknown, as much as a 50% dose loss during plasmapheresis has been described. These agents should be administered immediately after plasmapheresis if possible.

DRUG SELECTION IN KIDNEY DISEASE

Antimicrobials Agents

Many agents are small (<500 da), water soluble, not highly protein bound, and appear unchanged in the urine. dosage reduction is thus usually necessary in patients with ckd and dialysis dependency.

Aminoglycosides (AGs)

- AGs are mostly excreted unaltered by glomerular filtration and, to a much lesser extent, by tubular secretion. Tubular reabsorption can lead to high renal cortical tissue concentrations even in advanced renal impairment.
- AGs can cause nephrotoxicity and ototoxicity due to intracellular accumulation and associated injury to lysosomes, Golgi apparatus, mitochondria, and endoplasmic reticulum in proximal tubular cells and inner ear hair cells, respectively. AG nephrotoxicity is typically evidenced by a rise in serum creatinine within 7 to 10 days of exposure.
- Electron microscopy reveals “myeloid bodies” in proximal tubular cells. Myeloid bodies are thought to arise from drug trapping, followed by a gradual accumulation of drug–phospholipid complexes within the internal lysosomal membranes. The increase in undigested materials interferes with normal membrane activity and results in the accumulation of concentric multilamellar lipid layers known as myeloid bodies, which may have similar appearance as those seen in Fabry disease (see **Chapter 7 Glomerular and Vascular Diseases**).
- Nephrotoxicity risks: older age, underlying CKD, diuretics, concurrent use of nephrotoxic agents or IV radiocontrast agents, hypokalemia, hypovolemia
- Bactericidal activity of AG is dependent on the initial rapid intracellular accumulation, followed by significant tissue release postantibiotic administration. The latter is termed “postantibiotic effect.” Drugs with “postantibiotic effect” depend on the loading dose but require less frequent dosing.
- In general, daily dosing or even q36h to q48h dosing of AG is thought to minimize nephrotoxicity in patients with GFR less than 60 mL/min.

- Dosing for all AGs is based on ideal body weight and adjusted body weight for obese patients. Serum levels should be measured to ensure therapeutic levels and avoidance of toxicity.
- In HD, predialysis dosing of AG allows for higher maximal concentration and theoretically better efficacy. Postdialysis dosing of half dose has also been suggested, but potential for higher toxicity must be noted.
- AG drug removal is thought to be greatest with CVVHDF (significant solute removal by both diffusion and convection), followed by continuous venovenous hemofiltration (CVVH) (significant solute removal by convection) and intermittent HD (predominantly diffusion).
- In peritonitis, AG should be given intraperitoneally.

NOTE AG and tetracycline can lead to proximal renal tubular acidosis (RTA) or Fanconi syndrome. Additionally, their ability to bind the calcium-sensing receptor (CaSR) can lead to Bartter-like syndrome where patients develop metabolic alkalosis and urinary K^+, Ca^{2+}, Mg^{2+}, and Na^+ wasting.

Glycopeptides (vancomycin and teicoplanin)

- Both are predominantly excreted by kidneys.
- When given IV, both agents are nephrotoxic and ototoxic, but teicoplanin is less nephrotoxic.
- Nephrotoxicity is thought to involve oxidative stress. Use of vitamin E and N-acetyl cysteine has been suggested to ameliorate vancomycin-induced nephrotoxicity.
- Nephrotoxic risks include underlying kidney injury, concurrent use of nephrotoxic drugs, prolonged therapy, and high plasma levels.
- Dialysis vancomycin dosing of 1 g can maintain plasma level above minimum inhibitory concentration (>15 µg/mL) for 3 to 5 days. Of note, trough levels >15 µg/mL are associated with greater nephrotoxicity. Random level monitoring may be used to determine the timing of subsequent doses among patients with renal replacement therapy or advanced kidney disease not on scheduled dosing.

β-Lactams

- Most (penicillins, cephalosporins, carbapenems, monobactams) require

dose reduction in CKD. β-Lactams are commonly combined with β-lactamase inhibitors (e.g., clavulanate, sulbactam, tazobactam, avibactam) to minimize antibiotic resistance and improve activity spectrum. Dose adjustment for combination drugs must take into account different metabolism rates of both agents. Whereas rates of metabolism of both agents in ampicillin/sulbactam and piperacillin/tazobactam are similar, clavulanate metabolism is much faster than that for ticarcillin in the ticarcillin/clavulanate combination.

- Unlike AG, most β-lactams have short half-life and no postantibiotic effect. Dose reduction is generally preferred over frequency reduction.
- Central nervous system (CNS) toxicity leading to lower seizure threshold is not uncommon with β-lactams (e.g., penicillins, imipenem) when used in high unadjusted dose in patients with advanced CKD.

NOTE Penicillin can lead to either hypokalemia or hyperkalemia depending on its formulation.

Hypokalemia: This is due to excess K^+ excretion that occurs with the high content of nonabsorbable anions in the penicillin formulation.

Hyperkalemia: This is due to the high content of K^+ in some formulations in association with inadequate kidney K^+ excretion.

Sulfonamides and trimethoprim

- Sulfonamides are typically combined with trimethoprim.
  - Both are renally excreted. However, alkaline urine enhances the excretion of sulfamethoxazole, whereas acidic urine promotes trimethoprim excretion.
  - Both accumulate in patients with reduced GFR and dosage adjustment is recommended.
- Sulfonamides are excreted following acetylation. Acetylated sulfonamides may crystallize in tubular lumen and cause kidney injury, particularly with cumulative dose >84 g. Good hydration and alkalinization may be both preventive and therapeutic.
- Sulfonamides may also cause tubulointerstitial nephritis.
- Trimethoprim may inhibit tubular secretion of creatinine and may cause a rise in serum creatinine without actually causing kidney injury.
- Trimethoprim may block the epithelial sodium channel (ENaC) and cause

both hyperkalemia and metabolic acidosis.

Rifamycins

- Rifamycins are predominantly hepatically metabolized and do not require renal dose adjustments..
- Rifamycins may cause orange-reddish discoloration of body fluids, such as urine, effusions, and PD fluids.
- Rifampin may cause various renal lesions, including acute tubular necrosis (ATN), acute tubulointerstitial nephritis (ATIN), light-chain proteinuria, and even rapidly progressive glomerulonephritis (RPGN). Intermittent use (e.g., noncompliant patient) is associated with ATN, with or without interstitial infiltrations, hemolysis, and thrombocytopenia. Continuous use is associated with light-chain proteinuria and RPGN.
- Rifampin is a potent CYP3A4 inducer and can cause subtherapeutic concentrations and treatment failure of various drugs, including calcineurin inhibitors (CNIs) (cyclosporine [CsA], tacrolimus [Tac]), mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus), corticosteroids, and statins. Significant dose increase of affected drugs is generally required.

Fluoroquinolones

- Ciprofloxacin, norfloxacin, and gatifloxacin are significantly cleared by the kidneys and must be dose reduced for GFR below 30 mL/min.
- Moxifloxacin is only 20% renally excreted and does not require dose adjustment.
- Quinolones may cause nonspecific CNS symptoms, including headaches, dizziness, restlessness, tremors, and kidney injury from interstitial nephritis, crystalluria.
- Quinolones absorption is reduced with metal-containing compounds and phosphate binders.

Nitrofurantoins

- There are concerns for toxic accumulation in patients with advanced CKD and potential for pulmonary and hepatic toxicity and peripheral neuropathy. The Food and Administration (FDA)-approved labeling states

that the use of nitrofurantoin is contraindicated in patients with a CrCl less than 60 mL/min. Nonetheless, data are lacking to support this recommendation. Retrospective studies have shown that short-term nitrofurantoin use is effective and generally well tolerated in patients with a CrCl of 30 mL/min or more, although higher adverse events have been noted in patients with renal impairment. However, the use of nitrofurantoin in the treatment of urinary tract infection in patients with low GFR is not recommended because the drug cannot accumulate to reach bactericidal concentrations in the urine, thus increasing the chance of treatment failure.

Other antibiotics

- Doxycycline, tigecycline, and standard-dose minocycline: No dose adjustment needed. For CrCl <80 ml/min, minocycline maximum dose is 200 mg/d.
- Linezolid: No dose adjustment needed.
- Linezolid and tetracyclines can lead to type B lactic acidosis. See **Chapter 2**.
- Metronidazole: Only 15% of the parent drug is renally cleared. Reduce to twice-daily dosing in dialysis patients.
- Macrolides:
  - Azithromycin, clarithromycin, roxithromycin (hepatically cleared): No dose adjustment needed.
  - Erythromycin (renally cleared): Dose reduction is required.

Antifungals

Amphotericin

- Kidney failure may occur after 2 weeks of therapy and is associated with the cumulative dose received. Lipid formulations can allow additional doses to be given by delaying the onset of nephrotoxicity.
- Risks: older age, underlying CKD, hypovolemia, hypokalemia
- Amphotericin may induce distal tubular injury, distal RTA, magnesium and potassium loss, nephrogenic diabetes insipidus, and arteriolar vasoconstriction (afferent greater than efferent arterioles).
- Other noted adverse effects: anemia with or without thrombocytopenia

presumably due to high inorganic content in liposomal formulations and, possibly, measurement interference/error

- Liposomal or lipid-based formulations confer lower electrolyte disturbances and are preferred in patients with any degree of residual kidney function. Acute allergic reaction may be seen with lipid-based formulations. Pseudohyperphosphatemia may be seen with liposomal amphotericin (see Chapter 3).
- Amphotericin is highly protein bound (~90% to 95%) with a large V_d and is thus not well dialyzable. The large V_d is thought to be due to uptake by tissues.
- Management of IV amphotericin B–induced nephrotoxicity:
  - Routine preventive measures: normal saline, use of lipid formulations of amphotericin B, reduce administration frequency if possible

NOTE Lipid formulations of amphotericin are not recommended for the treatment of fungal urinary tract infections (UTIs). The addition of the lipid component may reduce its therapeutic effectiveness by interfering with the drug's ability to achieve adequate levels in the urinary tract.

  - Continuous infusion may be less nephrotoxic compared with infusions given over 4 hours.
  - Theoretical benefits of low-dose calcium channel blockers (e.g., diltiazem) to reduce renal vasoconstriction may be considered if safely tolerated.

Azoles

- With the exception of fluconazole, most agents (keto-, itra-, vori-, posa-, and isavuconazole) are metabolized by the liver and do not require dose reduction.
- Fluconazole is significantly excreted in the urine and is preferred for the treatment of UTIs. After an adequate loading dose, maintenance dose should be reduced in in patients with reduced GFR.
- Most azoles are potent inhibitors of CYP3A4 and P-glycoproteins that are involved in the metabolism and absorption of various drugs, including CNIs (CsA, Tac), mTOR inhibitors (sirolimus, everolimus), and statins.

Significant dose reduction of the affected drug is generally required.

NOTE P-glycoproteins normally serve to secrete various drugs into the gastrointestinal (GI) tract and renal tubular lumen or increase exposure of drugs to CYP enzymes for metabolism, thereby reducing blood levels of the affected drugs. Diarrhea/enterocolitis may lead to reduced intestinal P-glycoprotein activity and significantly increase drug levels of drugs that are substrates of P-glycoproteins. It is well observed that patients receiving Tac, a P-glycoprotein substrate, can present with toxic levels during episodes of diarrhea or enterocolitis.

- Itraconazoles, voriconazole, and posaconazole are mixed with cyclodextrin in IV formulations. Accumulation of cyclodextrin in renal patients can lead to increased serum creatinine and CNS toxicity (e.g., agitation, myoclonus, visual and auditory hallucinations, colored or flashing light). IV formulations should be avoided for GFR <50 ml/min).
- Flucytosine is predominantly excreted in the urine and requires dose adjustment for patients with CKD. Flucytosine has a high rate of fungal resistance and is typically not used as a sole agent, but in combination with amphotericin for severe fungal infections.

Echinocandins (caspofungin, micafungin, anidulafungin)

- Echinocandins are inhibitors of the synthesis of β-D-glucan, a fungal cell wall component. These agents are effective against *Candida* species and azole-resistant *Aspergillus*.
- No dose adjustment is necessary in patients with kidney failure.
- Unlike azoles, echinocandins typically do not affect CNI levels. However, caspofungin has been shown to reduce Tac levels.

Other antifungals

- Terbinafine, an agent used to treat onychomycosis, is metabolized by CYP3A4, and 70% is renally excreted. Plasma clearance is reduced by 50% in patients with CrCl <50 ml/min. there are no safety data for terbinafine in ckd: 50% dose reduction is suggested in moderate-to-severe renal impairment.
- Topical azoles, including clotrimazole, econazole, ketoconazole, miconazole, bifonazole, and tinidazole, are minimally absorbed and have no drug interaction.

- Topical and oral nystatin is minimally absorbed. Their use in patients with renal impairment is safe.
- Griseofulvin: No dose adjustment needed.

Antiviral Agents

Hepatitis B–specific treatments

- Telbivudine, adefovir, tenofovir, and entecavir are extensively renally excreted. Dose adjustment for CrCl < 50 ml/min is recommended.
- Entecavir and telbivudine are dialyzable and should be administered postdialysis.
- Entecavir does not induce drug resistance unless patient has had prior therapy with lamivudine (3TC) or related drugs.
- Tenofovir does not induce drug resistance, irrespective of prior treatment. It can cause Fanconi syndrome and proximal tubular cell dysfunction and AKI.
- Tenofovir alafenamide (Vemlidy©) is a novel prodrug of tenofovir with significantly reduced renal and bone effects (i.e., decline in bone mineral density) compared with tenofovir disoproxil fumarate (Viread©). FDA approved for use in patients with mild-to-moderate renal impairment (CrCl ≥ 30 mL/min); dialyzable, should be administered postdialysis.

Hepatitis C–specific treatments

- Ribavarin and its metabolites are excreted by the kidneys. Its use should be avoided in patients with CrCl <50 ml/min. ribavarin is associated with hemolytic anemia, thrombotic thrombocytopenic purpura, and red cell aplasia.
- Pegylated interferons (INFs) α-2a and α-2b require dose adjustment for CrCl <50 ml/min. infs can upregulate cell surface expression of human leukocyte antigen (hla) class ii, leading to acute allograft rejection. however, with the advent of direct-acting antiviral (daa) agents, inf-based therapy has become obsolete.
- DAA agents:
  - The use of elbasvir/grazoprevir, sofosbuvir/velpatasvir, or glecaprevir/pibrentasvir combination therapy has been suggested to be

safe in patients with severe reduction in GFR. Safety data for other DAA agents in patients with advanced CKD are currently limited. Sofosbuvir can accumulate in severe reduction in GFR, but no dose reductions are provided for by the manufacturer.

- Anti-influenza agents (neuraminidase inhibitors):
  - Oseltamivir (Tamiflu) and peramivir (Rapivab) are excreted by the kidneys and require dose reduction for reduced GFR. Oseltamivir should be given at half dose (30 mg) with CrCl <60 ml/min, and at half dose once daily with crcl <30 ml/min.
  - Zanamivir (Relenza) is extensively renally excreted after IV doses. However, its bioavailability from inhaled doses is only ~2%, which does not require dose reduction.

Herpes simplex virus: famciclovir, acyclovir and its prodrug valacyclovir

- Renally excreted and may crystallize in tubules, leading to obstructive uropathy and acute kidney injury (AKI), especially when given in high dose via rapid infusion. Slow IV administration (1 to 2 hours) and hydration is critical if given in high doses IV.
- Associated with leukopenia, neurotoxicity
- Dose reduction based on kidney function is necessary.
- Approximately 60% dialyzable.

Cytomegalovirus: Ganciclovir and its prodrug valganciclovir

- Renally excreted, accumulation may lead to severe bone marrow toxicity.
- Dose reduction based on GFR is necessary.
- Highly dialyzable

Antiretroviral Agents (Table 10.1)

Table 10.1 HIV drugs and the kidney

	Mechanism of Action	Common Drugs	Dose Adjustments	Renal Effects
Nucleoside reverse transcriptase inhibitors (NRTIs)	NRTI incorporates itself into the DNA during reverse transcription of the viral genome and effectively terminates DNA polymerization.	Abacavir (ABC) Didanosine (ddI) Emtricitabine (FTC) Lamivudine (3TC) Tenofovir (TDF) Zidovudine (AZT, ZDV)	Yes	Fanconi syndrome has been reported with the use of ABC, ddI, 3TC, and both formulations of tenofovir (tenofovir disoproxil fumarate [TDF] and tenofovir alafenamide). Nephrogenic DI may occur with ABC, ddI, TDF. Type B lactic acidosis may occur with all NRTIs.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	NNRTIs are small hydrophobic chemical compounds that bind to a pocket near the active site of HIV reverse transcriptase, thereby reducing its ability to optimally catalyze DNA polymerization.	Efavirenz (EFV) Etravirine (ETR) Nevirapine (NVP) Rilpivirine (RPV)	Yes	
Protease inhibitors (PIs)	PIs bind to and inhibit the HIV aspartyl protease, an enzyme involved in the processing of viral proteins. This inhibits viral maturation, thus formation of a functional virion.	Atazanavir (ATV) Darunavir (DRV) Lopinavir (LPV) Ritonavir (RTV) Indinavir (IDV) Saquinavir (SQV)	No SQV use is not recommended in severe CKD.	PIs may crystallize in renal tubules and cause urolithiasis. IDV has been largely replaced by ATV and DRV. SQV is also associated with hypocalcemia and lactic acidosis.
Integrase inhibitors	Integrase inhibitors block the integration of HIV DNA into human DNA by the HIV integrase enzyme.	Raltegravir (RAL) Elvitegravir (EVG) Dolutegravir (DTG)	No	Elvitegravir is metabolized by CYP3A4 and may have potential CNI and drug–drug interaction. Dolutegravir may increase SCr via inhibition of renal tubular secretion of creatinine.
Fusion inhibitor	Fusion inhibitors inhibit the fusion of the HIV envelope with human cell membranes.	Enfuvirtide (ENF, T-20)	No	Enfuvirtide may be associated with MPGN.

CCR5 inhibitor	CCR5 inhibitor binds to the external portion of the transmembrane receptor CCR5 that serves as the co-receptor for virus entry.	Maraviroc (MVC)	No Avoid use in patients requiring dialysis or with CrCl <30 mL/min	
Pharmacokinetic (PK) enhancer	PK enhancers are inhibitors of cytochrome P450 (CYP) 3A enzymes that act as a drug level booster for the protease inhibitors atazanavir and darunavir.	Cobicistat (COBI)	No	Cobicistat is a strong CYP3A4 inhibitor. Dose reduction is generally required for CNI, mTOR inhibitors, and statins when used with COBI. Cobicistat may increase SCr via inhibition of renal tubular secretion of creatinine.

Abbreviations: CKD, chronic kidney disease; CNI, calcineurin inhibitor; CrCl, creatinine clearance; MPGN, membranoproliferative glomerulonephropathy; SCr, serum creatinine.

Drug classes that do not generally require dose reduction

- Integrase inhibitors (raltegravir, elvitegravir, dolutegravir)

NOTE Dolutegravir may cause an increase in serum creatinine, which is thought to be due to inhibition of tubular secretion of creatinine via the organic cation transporter OCT2 (similar to the interaction seen with cimetidine or trimethoprim).

- Fusion inhibitors (enfuvirtide)—Enfuvirtide may be associated with membranoproliferative glomerulonephropathy (MPGN).
- CCR5 antagonists (maraviroc)
  - Dose adjustment not required for mild-to-moderate CKD.
  - For CrCl < 30 ml/min or dialysis dependent: avoid
- Protease inhibitors (atazanavir, darunavir, indinavir, nelfinavir, ritonavir, saquinavir, and tipranavir)
- Non–nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs) (delavirdine, efavirenz, etravirine, nevirapine)

Drug class that requires dose reduction with CKD

- NRTIs (zidovudine, 3TC, emtricitabine, stavudine, didanosine [ddI], and

tenofovir)

- NRTIs reported to cause Fanconi syndrome: 3TC, abacavir (ABC), ddI, and tenofovir
- NRTIs reported to cause nephrogenic diabetes insipidus: ABC, ddI, tenofovir
- NRTIS may cause type B lactic acidosis.

Drugs that crystallize and cause urolithiasis

- Protease inhibitors (saquinavir, lopinavir/ritonavir, indinavir, atazanavir, darunavir). Currently, indinavir has largely been replaced by atazanavir and darunavir.
- Indinavir crystals have been described as “plate-like rectangles and fan-shaped or starburst forms.” (see Chapter 3)
- Saquinavir is also associated with hypocalcemia and lactic acidosis. Its use is not recommended in severe CKD.

Selected fixed-dose drug combination

- Cobicistat, a component of a fixed-dose four-drug combination of elvitegravir/cobicistat/emtricitabine/tenofovir (Stribild) and dolutegravir (HIV integrase inhibitor), can increase SCr via inhibition of tubular secretion of creatinine without affecting GFR. No dosage adjustment is required in CKD and dialysis patients. However, it should be noted that it is a strong CYP3A4 inhibitor and, hence, significant dose reduction is generally required with concomitant administration of the CNIs (CsA, Tac), mTOR inhibitors (sirolimus, everolimus), and statins. Enhanced nephrotoxicity may be observed with coadministration with tenofovir disoproxil fumarate.
- Truvada (emtricitabine/tenofovir disoproxil)
  - CrCl ≥ 50 mL/min: No dose adjustment required.
  - CrCl 30 to 49 mL/min: Dose adjustment required.
  - CrCl < 30 ml/min: do not use fixed-dose combination tablet. dosage adjustment is based on individual components.
- Descovy (emtricitabine/tenofovir alafenamide)
  - CrCl > 30 mL/min: No dose adjustment required.

- CrCl < 30 ml/min: do not use fixed-dose combination tablet. dosage adjustment is based on individual components.

Antihypertensive Selection in Patient Receiving HD

- Angiotensin-converting enzyme inhibitors (ACEIs): dialyzable: captopril, lisinopril; nondialyzable: benazepril, fosinopril, quinapril
- Angiotensin-receptor blockers (ARBs) are generally not dialyzable.
- β-Blockers:
  - Carvedilol, labetalol, metoprolol, propranolol, and pindolol are hepatically metabolized: No dose adjustment needed.
  - Atenolol and sotalol are renally excreted and require dose reduction.
  - Dialyzable: atenolol, metoprolol, acebutolol, sotalol, and nadolol;
  - Nondialyzable: carvedilol, labetalol, propranolol, timolol
- CCBs: Diltiazem, verapamil, amlodipine, and nifedipine are not dialyzable.

NEPHROTOXICITY OF MEDICATIONS

Principles/Mechanisms of Nephrotoxicity

Reduced renal perfusion

- Hypovolemia: excessive diuretics
- Predominant afferent vasoconstriction: nonsteroidal anti-inflammatory drugs (NSAIDs), amphotericin, CNI, interleukin-2 (IL-2), radiocontrast media
- Predominant efferent vasodilatation: ACEI, ARB

Direct tubular toxicity

- Commonly used drugs: cisplatin, AG, particularly combination of cisplatin and AG, cephalosporins, amphotericin B, rifampin, pentamidine, NSAIDs, radiocontrast media, CNI
- Proximal tubular epithelial cell injury resulting in Fanconi syndrome: lead, l-lysine supplement (used for antiviral, wound healing properties), AG, tenofovir, 3TC, ABC, ddI, valproic acid, cisplatin, ifosfamide
- Rhabdomyolysis-induced ATN: statins, drugs that cause neuroleptic malignant syndrome (e.g., phenothiazines, antipsychotics, narcotics,

antidepressants), cocaine, methamphetamine

- Histopathologic patterns associated with drug-induced nephrotic syndrome include membranous glomerulonephropathy (GN), minimal change disease (MCD), and focal segmental glomerulosclerosis (FSGS).

Acute tubulointerstitial nephritis (ATIN)

- Most antibiotics, NSAIDs, PPIs, cimetidine, thiazides, allopurinol, checkpoint inhibitors, and many others. See **Chapter 6**.
- PPI-associated ATIN and AKI may go unrecognized and present as CKD. PPI use is also associated with hyponatremia and hypomagnesemia. At-risk individuals for PPI-induced hypomagnesemia have been reported to have a single-nucleotide polymorphism in the apical epithelial magnesium channel TRPM6 in magnesium-absorbing small intestines. The cause-effect relationship between PPI and hyponatremia is currently not known. One study reported PPI-associated hyponatremia to only occur with newly initiated use and hospitalization, not with chronic use.

Chronic tubulointerstitial disease

- NSAIDs, thiazides, lithium, aristolochic acid (AA), germanium, cisplatin, ifosfamide

Obstructive uropathy

- Microtubular obstruction due to drug crystallization, referred to as crystal nephropathy:
  - Well-described causative agents: sulfadiazine, methotrexate, methoxyflurane, acyclovir, indinavir, nelfinavir, acetazolamide, triamterene, topiramate, zonisamide
  - Others: oral sodium phosphate preparation, and ciprofloxacin
  - Heroin-induced crystal nephropathy developing after massive amount of heroin injection has been described. Urine microscopy reveals broomstick-like crystals without renal tubular epithelial cells or casts. Characteristic kidney biopsy finding: Electron microscopy demonstrates intratubular crystals with peripheral radiating spicules within tubular epithelial cells.
- Methenamine/sulfonamide combination may lead to the precipitation of

sulfonamides with formaldehyde (methenamine is hydrolyzed to formaldehyde in acidic urine). The combination of methenamine/sulfonamide is contraindicated and should not be given to the same patient.

- Retroperitoneal fibrosis: methysergide, hydralazine, methyldopa

Small-vessel vasculitis (hypersensitivity angiitis)

- Common antibiotics: penicillin G, ampicillin, sulfonamides
- Diuretics: thiazides, metolazone
- Antineutrophil cytoplasmic antibody (ANCA)–associated glomerulonephritis: propylthiouracil, methimazole, allopurinol, hydralazine, levamisole, D-penicillamine, antitumor necrosis factor α agents (e.g., etanercept, infliximab, adalimumab), phenytoin, sulfasalazine, clozapine, levamisole (cocaine laced with levamisole)

Thrombotic microangiopathy (TMA)

- Transplant settings: CsA, Tac, sirolimus
- Others: mitomycin-C, 5-fluorouracil, quinine, cocaine, ticlopidine, clopidogrel

Proteinuria, nephrotic syndrome

- Common agents: gold, captopril (this is thought to be specific to captopril, not other ACEI, due to the thiol group in captopril), NSAIDs, D-penicillamine, IFN-α
- Histopathologic patterns associated with drug-induced nephrotic syndrome include membranous glomerulonephropathy (GN), minimal change disease (MCD), and focal segmental glomerulosclerosis (FSGS).

NOTE The risk of statin-induced rhabdomyolysis is increased with concurrent use of CsA or gemfibrozil. Rhabdomyolysis associated with Tac and statin use is generally only seen in patients on concomitant *diltiazem* therapy.

Antineoplastic Agents

Cisplatin

- Nephrotoxicity is thought to involve cisplatin-induced apoptosis and necrosis of renal epithelial cells and increased oxidative stress and

inflammatory response. Vascular and glomerular injuries may also be seen (TMA).

- Toxicity risks: dose related, typically > 25 to 33 mg/m^2/wk, concurrent use of AG
- Kidney injuries include ATN, ATIN, tubular damage with salt wasting (Na^+, K^+, Mg^{2+}, Ca^{2+}, PO_4^{2-}), Fanconi syndrome, nephrogenic diabetes insipidus. Hypomagnesemia can be severe.
- Preventive: Normal saline support during cisplatin therapy is key. Other suggested measures include the use of IV sodium-thiosulfate (if >200 mg/m^2 of cisplatin will be administered), methylprednisolone, N-acetyl cysteine, and antioxidants.
- Management: electrolyte replacement as needed

Cyclophosphamide

- Associated with hyponatremia, premature ovarian failure, hemorrhagic cystitis, bladder cancer
- Toxic metabolite: acrolein
- Management:
  - Hydration with normal saline
  - Administration of mesna to detoxify acrolein and reduce hemorrhagic cystitis risk
  - Use of agonist of pituitary gonadotropin-releasing hormone receptors leuprorelin for gonadal protection in women of childbearing age
  - Limit cumulative lifetime dose to <36 g to minimize malignancy risk. maximum cumulative dose for those who wish to conceive should not exceed 10 g.
- Significant interactions with other commonly used drugs:
  - Allopurinol reduces cyclophosphamide metabolism.
  - Cyclophosphamide increases bleeding risks with most anticoagulants due to reduced platelet count and/or other unknown mechanisms.

Ifosfamide

- Toxic metabolite: chloroacetaldehyde
- Associated with proximal tubular injury, proximal RTA, Fanconi

syndrome, nephrogenic diabetes insipidus, ATN

- Risks for nephrotoxicity: cumulative dose > 90 g/m^2, underlying CKD, concurrent use of other nephrotoxic drugs
- Management: supportive, consider mesna

Methotrexate

- Kidney injury due to intratubular crystallization and obstruction
- High dose of folinic acid has been shown to revert nephrotoxicity.

Bevacizumab: anti–vascular endothelial growth factor (anti-VEGF)

- Anti-VEGF agent induces endothelial injury (endotheliosis, swollen vacuolated endothelial cells occluding capillary lumen) and disrupts glomerular filtration barrier.
- Clinical manifestations are similar to those seen with preeclampsia: proteinuria, hypertension (HTN), AKI, TMA.
- Cetuximab, panitumumab: anti–epithelial growth factor receptor monoclonal antibody
  - Used to treat epithelial malignancies
  - Associated with hypomagnesemia

Bortezomib and carfilzomib: proteasome inhibitors

- Used to treat multiple myeloma and plasma cell dyscrasias
- AKI due to ATN, TMA, and tumor lysis have been reported.
- TMA is typically associated with normal levels of ADAMTS 13 (A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), but low levels have been reported.

Immune checkpoint inhibitors

- Immune checkpoints are regulators of the immune system that serve to prevent the immune system from self-attacking cells indiscriminately. Cancer cells can develop mechanisms to counteract these checkpoints, thereby evading immune attack and cell death. Checkpoint inhibitors have been developed to “activate” the immune system to attack tumor cells. Unfortunately, this activated immune system can simultaneously lead to the loss of recognition of self-antigens in kidneys and/or unmask subtle

immune responses against medications known to precipitate ATIN, such as PPI or NSAIDs.

- Checkpoint inhibitors in clinical use include anti-programmed cell death antibody (anti–PD-1 antibody) and anti–CTLA-4 antibody.
  - Nivolumab and pembrolizumab are anti–PD-1 antibodies: ATIN has been reported to occur between 3 and 12 months following drug exposure.
  - Ipilimumab is anti–CTLA-4 antibody: ATIN may occur within 12 weeks of drug exposure.
  - Mild ATIN in association with glomerular lesions has also been reported and include membranous nephropathy (MN), MCD, TMA, pauci-immune glomerulonephritis, C3 glomerulonephritis, immunoglobulin A nephropathy (IgAN), or amyloid A.
  - Immune checkpoint inhibitors are contraindicated posttransplant.

Lenalidomide and pomalidomide: immune-modulatory drugs

- Used to treat multiple myeloma and primary amyloidosis
- Associated with AKI, MCD, and DRESS (*D*rug *R*eaction with *E*osinophilia, *R*ash and *S*ystemic *S*ymptoms) syndrome (see Chapter 6)

Vemurafenib and dabrafenib: B-rapidly Accelerated Fibrosarcoma (BRAF) oncogene inhibitors

- Used to treat BRAF V600E mutation-positive melanoma, colorectal carcinoma
- Associated with interstitial nephritis and acute tubular injury

Iodinated Contrast and Other Imaging Agents

See contrast-induced AKI in **Chapter 11**.

Calcineurin inhibitors

- Acute vasoconstriction leading to HTN and significant afferent vasoconstriction:
  - Thought to be due to increased production of vasoconstrictive thromboxane A2 relative to vasodilatory prostaglandin E2
  - CCBs have been shown to reduce CNI toxicity, both short and long

term.

- Chronic CNI toxicity:
  - Obliterative arteriolopathy, tubular atrophy, and classic "striped" interstitial fibrosis

Diuretics

- Volume depletion (all diuretics, worst with loop diuretics)
- Hypokalemic nephropathy (seen with all agents, except potassium-sparing diuretics)
- Tubulointerstitial nephritis (thiazides, furosemide)
- Vasculitis (thiazides)
- Nephrolithiasis (triamterene, acetazolamide at low urine pH)
- Electrolyte abnormalities, hyponatremia (particularly thiazides), hypokalemia, hyperuricemia (particularly thiazides)

Supplements/Herbs (Toxic Agents): Renal/Urologic Manifestations

- *Aristolochic acid* species (AA): progressive chronic interstitial nephritis (CIN), proximal tubular injury, uroepithelial malignancies. Others: Fanconi syndrome, AKI due to ATN
- Balkan endemic nephropathy (BEN) resembles aristolochic acid nephropathy (AAN) in terms of CIN and association with uroepithelial malignancies, but its rate of disease progression spans over 20 to 30 years compared to a much more rapid course of months to 2 years with AAN.
  - Prospective monitoring in endemic areas showed that tubular proteinuria is usually the first manifestation of BEN. Early tubular dysfunction can also lead to glucosuria, amino aciduria, increased uric acid excretion, and impaired urinary acidification.
  - Chronically, there is progressive urinary concentrating defect with renal salt wasting and associated polyuria. Such defect may precede GFR decline and progression to kidney failure.
  - The inciting agent is unknown but has been suggested to be AA or other regional toxins (e.g., mycotoxins, heavy metals, viruses). Endogenous genetic and/or epigenetic factors are thought to be contributory.

- Bladder wrack, a large brown algae used as food or flavoring agent in Japan and Europe (associated toxins are thought to be heavy metal contamination): CIN
- Cat claw: acute allergic tubulointerstitial nephritis
- Chaparral tea made of leaves from the Native American shrub creosote (nordihydroguaiaretic acid): renal cysts and renal cell carcinoma
- Cranberry: oxaluria, oxalate stones
- Djenkol (djenkolic acid): nephrolithiasis
- *Echinacea* species, that is, coneflower (arabinogalactan): RTA
- Germanium: tubular degeneration with minor glomerular abnormalities
- Licorice (glycyrrhizic acid): HTN, hypokalemia, hypokalemic nephropathy, metabolic alkalosis
- L-Lysine: Fanconi syndrome and tubulointerstitial nephritis
- Ma huang (ephedras): HTN, nephrolithiasis secondary to ephedra, norephedrine, and pseudoephedrine stone
- Pennyroyal: hemorrhagic kidneys, hepatorenal syndrome, and associated ATN
- Rhubarb (anthraquinone): CIN, kidney failure
- Star fruit, rhubarb leaves, cranberry juice, or cranberry concentrate tablets (oxalic acid): nephrolithiasis, interstitial nephritis
- Willow bark (salicin, the precursor of salicylate): renal papillary necrosis
- Wormwood oil: AKI secondary to rhabdomyolysis
- Yellow oleander: renal tubular necrosis with vacuolization in glomerular spaces in the setting of hepatorenal syndrome
- Yohimbe (yohimbine): lupus nephritis

NEPHROTOXICITY OF ILLICIT DRUGS

- Heroin and other IV drug use:
  - Nonspecific histopathologic findings: arteriosclerosis, calcifications, interstitial fibrosis, tubular atrophy
  - Heroin-specific causes for kidney injury: renal amyloid, FSGS, rhabdomyolysis

- Ecstasy (methylenedioxymethamphetamine [MDMA]), *N*-benzylpiperazine (BPZ), also known as, “party pills”:
  - Both produce stimulant, euphoric effects.
  - Users may develop hyperthermia, rhabdomyolysis, kidney failure, interstitial nephritis, hyponatremia, and cerebral edema.
  - Other renal/electrolyte effects: hyperkalemia, metabolic acidosis, urinary retention, mesangial proliferative glomerulonephritis
- Cocaine: may cause renal ischemia, infarction, ANCA-associated vasculitis, rhabdomyolysis, accelerated atherosclerotic disease
- Synthetic marijuana (cannabinoids):
  - Brand names: K2, Spice, herbal incense, Bonsai, Cloud 9, Mojo, Arizona, Black Mamba, Lava Red, Banana Cream Nuke
  - Associated with hypokalemia, AKI due to ATN or ATIN or both. Creatinine phosphokinase is usually normal or only slightly elevated, but cases of rhabdomyolysis have been reported.
  - Synthetic cannabinoid and concomitant overuse of quetiapine can cause rhabdomyolysis, thought to be due to their synergistic effect in mediating muscle injury.
  - Management: Largely supportive. A tapering course of steroid may be beneficial in ATIN cases.
- “Bath salts”:
  - White powder containing 3,4-methylenedioxypyrovalerone
  - May be inhaled, ingested, or injected
  - May cause fulminant liver failure, rhabdomyolysis and kidney failure, disseminated intravascular coagulopathy
  - Supportive therapy

NEPHROTOXICITY OR ENVIRONMENTAL AND OCCUPATIONAL AGENTS

Lead (Pb) nephropathy

Mechanism of disease

- Pb is absorbed in proximal tubular cells where it binds to specific Pb-

binding proteins that facilitate entry into mitochondria and nuclei.

- Pb–protein complexes lead to mitochondrial dysfunction and subsequent reduction in adenosine triphosphate (ATP) production. Reduced ATP adversely affects normal tubular transports thus resulting in Fanconi syndrome.
- Major metabolic effects of chronic Pb exposure include HTN and hyperuricemia. Hypertension is likely due to alterations in the balance of vasoactive arachidonic acid metabolites favoring vasoconstriction, and hyperuricemia is due to enhanced net tubular reabsorption of uric acid.

Acute lead exposure

- Multiorgan involvement including headaches, malaise, peripheral neuropathy, poor memory, encephalopathy, seizures, coma, colicky abdominal pain, nausea, vomiting, constipation, anemia, muscle weakness, Fanconi syndrome
- Pb–protein complexes may be seen as intranuclear inclusions in acute lead nephropathy.

Chronic lead exposure

- Chronic tubulointerstitial nephritis (CTIN), gout, HTN
- Kidneys are typically contracted with granular surface appearance.
- Note that although hyperuricemia is common in CKD, gout is not a common manifestation of CKD. All patients with CKD and gout should be tested for Pb. Bone Pb levels may be better correlated with HTN than blood Pb levels.
- Notable physical finding: gingival lead line
- Differential diagnosis: uric acid nephropathy, arsenic exposure, CTIN, radiation nephritis, chronic glomerulosclerosis
- Diagnosis:
  - Nonspecific laboratory findings: anemia of chronic disease, microcytic hypochromic anemia, basophilic stippling of red blood cells, normal anion gap metabolic acidosis, hypophosphatemia, Fanconi syndrome, elevated serum creatinine
  - Pb-specific testing:

- Increase blood and urinary ALA due to inhibition of erythrocyte aminolevulinic acid dehydratase (ALAD) by Pb. Iron deficiency must be ruled out first because it can increase ALAD activity and mask Pb-induced reduction in ALAD activity.
- Blood Pb levels:
  - Significantly elevated in acute exposure but may not be elevated in chronic exposure
  - Assessment for total body Pb accumulation is recommended for chronic exposure:
    - Calcium disodium edetate (EDTA) chelation test (given at 1 g intramuscularly × two doses 12 hours apart or 1 g IV × one dose to immobilize stored Pb), followed by 24-hour urine collection to measure for Pb-EDTA. In patients with CKD, urine collection should be done over 3 to 6 days.
    - Radiographic fluoroscopy, a procedure whereby X-ray excitation of skeletal Pb atoms leads to fluorescence that can be detected and calculated
- Management: chelation therapy with EDTA

Organic Solvents

- Exposure to organic solvents (i.e., products or processes that contain solvents or petroleum products, such as paint, printing ink, adhesives, degreasers, cleaning agents, aerosols, pesticides, and gasoline) have been linked to various GNs.
- Chronic organic solvent exposure has been linked to various glomerular diseases, including RPGN with or without antiglomerular basement membrane antibodies, MN, IgAN, and FSGS.
- Limited studies suggest that organic solvent exposure may worsen the progression of existing GN rather than contributing to the development of glomerulonephritis.

SPECIFIC DRUG ADVERSE EFFECTS OF INTEREST TO THE NEPHROLOGIST

Toxic drug metabolite accumulation in patients with reduced GFR

- Allopurinol ◊ oxypurinol (tubulointerstitial nephritis)
- Glyburide ◊ hydroxyglibenclamide (hypoglycemia)
- Meperidine ◊ normeperidine (seizures)
- Morphine ◊ morphine-t-glucuronide (altered mental status, seizures)
- Nitroprusside ◊ thiocyanate (cyanide toxicity)
- Tramadol ◊ O-desmethyltramadol (M1) (altered mental status, seizures)
- Venlafaxine ◊ O-desmethylvenlafaxine (altered mental status). Other adverse effects: HTN (may be accelerated), orthostatic hypotension, prolonged QT

Notes regarding pain control in patients with reduced GFR

- Mild-to-moderate chronic pain: Tramadol is acceptable at adjusted dose. However, although tramadol is primarily hepatically metabolized, the metabolites are eliminated by the kidneys. Approximately 30% of the dose is excreted in the urine as unchanged drug and 60% as metabolites. The use of tramadol in severe CKD is not recommended.
- Severe chronic pain: oxycodone, fentanyl (black box warning of respiratory arrest, particularly in opioid-naïve patients), methadone
- Fentanyl is primarily (>90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the administered dose is excreted unchanged in the urine. Although it is recommended that fentanyl be titrated to clinical effect for all patients, special care should be taken in patients with severe hepatic or renal disease.
- Hydromorphone:
  - Extensively metabolized via glucuronidation in the liver
  - Only a small amount of hydromorphone is excreted unchanged in the urine.
  - No clinically significant opioid toxicity when given in low doses
- Not recommended in CKD:
  - Morphine: rapid accumulation of active metabolites in CKD resulting in clinically significant opioid toxicity (sedation, confusion, myoclonus,

seizures, respiratory depression)
    - Codeine and dihydrocodeine: risk for severe hypotension, respiratory arrest, narcolepsy
- Reversal of opioid intoxication: Naloxone may be used at normal dose.
- Neuropathic pain: Gabapentin and pregabalin are extensively cleared by the kidneys. Dose adjustment in CKD is required. Accumulation and toxicity can lead to reduced consciousness, confusion, ataxia, myoclonus, tremulous, and asterixis. **FDA warning:** Gabapentin or pregabalin use, either alone or with opioids (or other drugs that depress the CNS), can lead to life-threatening respiratory failure and increased risk of opioid overdose death. Elderly patients and those with underlying respiratory impairment are also at increased risk for respiratory failure.

Immunosuppressive therapy (see also Chapter 9)

Induction therapy

- Antithymocyte globulin (polyclonal antibodies that induces T-cell depletion): Cytokine release syndrome with flu-like symptoms and myelosuppression with leukopenia and thrombocytopenia. Premedications are required.
- Basiliximab and daclizumab (monoclonal IL-2 antagonists): well tolerated; no known drug interaction; no dose adjustment necessary for reduced GFR (**Note**: Daclizumab is no longer commercially available in the United States.)

Maintenance therapy

- CNIs (inhibit dephosphorylation of the nuclear factor of activated T-cell [NFAT] molecules, which results in reduced IL-2 synthesis):
    - CsA, derived from the fungus *Tolypocladium inflatum*:
        - Plasma concentration at 2-hour postadministration better correlates with the area under the curve (AUC) compared with that of 12-hour trough levels.
        - GI absorption varies depending on food fat content, GI motility (diabetic gastroparesis), diarrhea. Microemulsion formulation (Neoral) improved pharmacokinetic properties, but not proven graft

survival. Oral to IV conversion is one-third of oral dose.

- CsA is a substrate as well as an inhibitor of both CYP3A4 and P-glycoprotein.
- CsA is predominantly metabolized by CYP3A4.

NOTE St. John wort induces CYP3A4 and can lead to subtherapeutic CsA level and rejection. In contrast, grapefruit juice and the nondihydropyridine CCBs diltiazem and verapamil are moderate CYP3A4 inhibitors and can increase CSA level and associated toxicity. Changing the dose of diltiazem or verapamil is equivalent to changing CsA dosage. CNIs and drug–drug and drug–food interaction are also discussed in **Chapter 9 Kidney Transplantation**.

- Not dialyzable. No dose adjustment necessary for reduced GFR or dialysis.
- Side effects: HTN, nephrotoxicity, fluid retention, hyperchloremic metabolic acidosis, hyperkalemia, hyperuricemia, hypomagnesemia (CsA, Tac, and sirolimus can cause hypomagnesemia by inducing urinary magnesium wasting—thought to be due to downregulation of the Mg^{2+} transient receptor potential 6 channel at the distal convoluted tubule)
- Hirsutism and gingival hyperplasia are common with CsA, but not with Tac. Gingival hyperplasia may be treated with azithromycin.
- Rare adverse effect: TMA
- Histopathologic findings: afferent arteriolopathy, "striped: tubulointerstitial atrophy," and fibrosis

- Tacrolimus (FK-506), derived from the fungus *Streptomyces tsukubaensis*:
  - Oral bioavailability is highly variable (5% to 67%). Drug levels require close monitoring with dose adjustments.
  - Tac is highly bound to albumin, α1-acid glycoprotein, and erythrocytes.
  - Levels should be measured from whole blood, not plasma.
  - Oral to IV conversion is one-third of total oral daily dose. Sublingual dose is one-half the oral dose.
  - Metabolism is via cytochrome P450 CYP3A4 and CYP3A5, mainly in the liver and the gut. Inconsistent presystemic gut metabolism

likely contributes to the intrapatient variation in drug levels that are seen clinically. Polymorphisms in CYP3A5 significantly increase Tac metabolism and clearance. CYP3A5 expressors require much larger doses of Tac compared to nonexpressors to achieve therapeutic blood concentrations.

- Most drug interactions are similar to those of CsA (see also **Chapter 9**).
- Common adverse effects: nephrotoxicity (similar to CsA: striped interstitial fibrosis, arteriolar hyalinosis), posttransplantation diabetes mellitus (PTDM), hair loss, neurotoxicity, hyperkalemia, hyperuricemia, hypomagnesemia
- HTN and hyperlipidemia (both are less severe compared with CsA)
- Not dialyzable. No dose adjustment necessary for renal impairment or dialysis.

NOTE Enterocolitis can significantly increase Tac levels due to reduced presystemic metabolism in gut wall via CYP3A4/5 and reduced drug extrusion into gut lumen.

- Antiproliferative agents:
  - Azathioprine (AZA):
    - AZA is an imidazole analog of 6-mercaptopurine that inhibits both de novo and salvage pathways for T- and B-lymphocyte proliferation.
    - Oral bioavailability is 50% to 60%.
    - Major side effects: bone marrow suppression, veno-occlusive disease, pancreatitis
      - Can be used in pregnancy

NOTE Avoid or reduce dose (i.e., 0.5 mg/kg/d) AZA in patients on allopurinol. Allopurinol interferes with the metabolism of AZA, which leads to a significant increase in 6-mercaptopurine levels and resultant severe bone marrow suppression (pancytopenia).

  - Mycophenolic acid (MPA):
    - MPA inhibits de novo purine biosynthesis in both B and T cells via noncompetitive inhibition of inosine monophosphate dehydrogenase type II.

        - Formulated as MMF (Cellcept or generic formulation) or enteric-coated mycophenolate sodium (Myfortic). MMF is rapidly converted via plasma and hepatic esterases to MPA, the active form. Mycophenolate sodium is thought to reduce GI intolerance due to its absorption in the lower GI tract rather than gastric absorption with MMF.
        - MPA/MMF is used as adjunctive immunosuppressive therapy to improve long-term allograft survival as well as reducing acute rejection in kidney transplantation.
        - Major side effects of MPA/MMF include: GI intolerance, anemia, leukopenia
        - The use of mycophenolate is contraindicated in pregnancy. Replacement with AZA may be considered.
        - Level monitoring of mycophenolate is not necessary because plasma concentration does not seem to correlate with incidence of acute rejection or side effects.
- mTOR inhibitors:
    - mTOR inhibition leads to cell-cycle arrest at G1 and inhibition of T-cell proliferation.
    - Sirolimus and everolimus are mTOR inhibitors.
    - Used in combination with low-dose CNI or CNI-avoidance protocols
    - Adverse effects: myelosuppression (thrombocytopenia), delayed wound healing, hyperlipidemia, lymphedema, proteinuria (FSGS)
- Pregnancy and immunosuppressive therapy:
    - Drugs with limited risk for congenital anomalies: prednisone, CsA, Tac, AZA
    - Contraindicated immunosuppressive therapy in pregnancy: mycophenolate, sirolimus, everolimus

Parenteral Anticoagulants

Unfractionated heparin (UFH)

- Half-life is slightly prolonged in patients with reduced GFR, particularly at higher doses. However, UFH may be started at normal dose, with dose

titration based on activated partial thromboplastin time.

- Antidote: protamine sulfate

Low-molecular-weight (LMW) heparin

- Enoxaparin, dalteparin, tinzaparin
  - Lower molecular weight agents are more dependent on renal clearance and may accumulate more with reduced GFR.
  - Enoxaparin has the lowest MW of all and requires dose reduction if estimated GFR (GFR) < 30 ml/min.
  - Dalteparin (no dose adjustment needed, anti-Xa level monitoring advised for eGFR < 30 ml/min)
  - Tinzaparin has the largest MW of all LMW. (No dose reduction needed if eGFR > 20 mL/min; dose adjust per anti-Xa level if eGFR < 20 ml/min.)
- Drug accumulation may cause excessive bleeding, not easily reversed.
- Bleeding risk does not appear to be associated with the type of heparin use, but on the degree of uremia, increased age, concurrent treatment, and comorbidities.
- Anti-Xa monitoring for LMW heparin: Predose (trough) and peak (2 to 4 hours postdose) before and after the third dose, then follow twice weekly. Anti-Xa activity level (prophylactic dosing 0.1 to 0.3; therapeutic 0.4 to 1.0 U/mL)

Other parenteral anticoagulants

- Fondaparinux, melagatran, ximelagatran, bivalirudin, danaparoid (withdrawn from U.S. market)
  - Accumulate in patients with reduced GFR
  - The use of these agents should be avoided or dose reduced in the setting of reduced GFR.
  - Fondaparinux: may be used in patients with CrCl > 30 mL/min, but may accumulate and increase bleeding risk
- Argatroban:
  - Inhibits coagulation factor IIa (direct thrombin inhibitor)
  - Hepatically cleared; no dose adjustment needed for CKD.

  - Avoid use in liver patients.
- Prostacyclins (epoprostenol, iloprost, selexipag, treprostinil)
  - Potent inhibitors of platelet aggregation
  - Used to prevent platelet aggregation in HD circuits; primary use is treatment of pulmonary HTN; vasodilators
  - These are unaffected by reduced GFR; selexipag use should be avoided in severe liver disease.

Oral Anticoagulants

Warfarin

- Vitamin K antagonist
- >90% protein bound (poor dialyzability)
- Long t½ (40 hours); >90% renal elimination
- Antidote: vitamin K (phytonadione)
- Warfarin-related nephropathy (WRN)
  - Serum creatinine increase ≥ 0.3 within 1 week of INR ≥ 3.0
  - Thought to be due to glomerular bleeding and resultant tubular obstruction by red blood cells (see Fig. 7.24)

Direct oral anticoagulants (DOACs). Summarized in Table 10.2

Table 10.2 Direct oral anticoagulants

	Rivaroxaban [Xarelto]	Apixaban [Eliquis]	Edoxaban [Savaysa]	Dabigatran [Pradaxa]
Coagulation target	Xa	Xa	Xa	Thrombin
Bioavailability (%)	66–100	50	62	3–7
Protein binding (%)	>90	80–90	55	35
Drug–drug interactions	Pgp **Contraindicated:** rifampin, ritonavir **Precaution:** clarithromycin, erythromycin, fluconazole, ketoconazole	Pgp *and* CYP3A4 inhibitors **Contraindicated:** rifampin **Precaution:** clarithromycin, diltiazem, ketoconazole, naproxen	Pgp **Contraindicated:** dronedarone **Precaution:** amiodarone, cyclosporine, erythromycin, ketoconazole, quinidine, rifampin, verapamil	Pgp *and* 3A4 inhibitors **Contraindicated:** cobicistat, dronedarone, ketoconazole, rifampin **Precaution:** clarithromycin, ticagrelor, verapamil
Half-life (h)	5–13	9–14	6–11	12–14
Surgery hold time	24 h	24–48 h	24 h	CrCl > 50 mL/min: 1–2 d CrCl <50 mL/min: 3–5 d
Renal clearance (%)	60–70	25–30	50	85
Dialyzability	No	No	No	Yes
Use in advanced CKD	• Reduce dose for CrCl 15–30 mL/min • CrCl <15 mL/min and dialysis: "Avoid" use • Discontinue use during AKI episode	• No dose adjustment if CKD is the only factor • Half dose if ≥2 of the following: Cr ≥1.5 mg/dL, age ≥80 y, or body weight ≤60 kg • Safety data for dialysis patients are lacking	• Half dose for CrCl 15–50 mL/min • Use not recommended for CrCl <15 mL/min • Hemodialysis does not significantly contribute to edoxaban clearance	• 75 mg bid for CrCl 15–30 mL/min • Dosing recommendation not established for CrCl < 15 mL/min or dialysis
Antidote/ reversal agent	Andexanet alfa	Andexanet alfa	Specific reversal agent not available	Idarucizumab
Comments	• In general, DOACs are noninferior compared to VKAs in reducing stroke/ thromboembolic event, and all-cause and vascular mortality. However, EDOXABAN should *not* be used in patients with CrCl > 95 mL/min. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCl > 95 mL/min had an increased rate of ischemic stroke with EDOXABAN 60-mg once daily compared to patients treated with warfarin. • DOAC is associated with an approximately 50% reduction in intracranial hemorrhage risk and lower risk of vascular calcification and anticoagulant-associated nephropathy (i.e., warfarin-related nephropathy). • Compared to VKAs: DOACs are associated with increased risk for gastrointestinal bleeds except for APIXABAN. • CVVHDF may be beneficial in severe cases of dabigatran overdose.			

Abbreviations: bid, twice daily; Cr, creatinine; CrCl, creatinine clearance; CVVHDF, continuous venovenous hemodiafiltration; CYP3A4, cytochrome P450; Pgp, P-glycoprotein; VKA, vitamin K antagonist.

- Previously known as novel oral anticoagulants (NOACs) due to their novel mechanism of action compared with warfarin or heparin (or heparin derivatives)
- Currently approved DOACs include anti–factor Xa and antithrombin.
  - Anti-Xa: rivaroxaban, apixaban, edoxaban
    - Antidote for anti-Xa: Andexanet alfa reverses the anticoagulation effects of rivaroxaban and apixaban (has not been shown to reverse the anticoagulation effect of other factor Xa inhibitors). Only for use in patients with life-threatening bleeding or those who require emergent surgery. Increased risk of thrombotic events after its use. Very expensive.
    - Specific reversal agent is currently not available for edoxaban.
    - Of note, EDOXABAN should *not* be used in patients with CrCl > 95 mL/min. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCl > 95 mL/min had an increased rate of ischemic stroke with EDOXABAN 60-mg once daily compared to patients treated with warfarin.
  - Antithrombin: dabigatran
- For advanced CKD (CrCl < 15 ml/min) or eskd, warfarin remains the anticoagulation of choice due to the lack of safety data for doacs in this subpopulation.
- DOACs are still not approved for patients on dialysis due to lack of safety data.
- DOAC use is contraindicated in renal transplant waitlisted patients.

Antiplatelet Agents

- Aspirin, clopidogrel, dipyridamole
  - No dosage adjustment required, although CKD patients are often more susceptible to bleeding.
- Eptifibatide and tirofiban

Renally excreted and have been associated with bleeding in patients with reduced GFR
- Abciximab
  - Cleared by platelet binding
  - No dosage adjustment required.

Thrombolytic Agents

- Streptokinase, anistreplase, and alteplase: may be used as normal, but the increased bleeding risk should not be overlooked
- Urokinase: used for clot dissolution and restore dialysis catheter patency

Hemostatic Agents

- Protamine, vitamin K: do not require dose adjustment
- Tranexamic acid: Dose reduction required in moderate-to-severe renal impairment.

Miscellaneous Agents

Colchicine

- Colchicine accumulation with reduced GFR may be associated with increased risk of myopathy and polyneuropathy.
- Patients with reduced GFR or hepatic impairment should not be given colchicine in conjunction with Pgp or strong CYP3A4 inhibitors. Life-threatening and fatal colchicine toxicity has been reported.
- In patients with severely reduced GFR:
  - For gout prophylaxis: starting dose is 0.3 mg/day
  - For treatment of gout flares: no dose adjustment is required but the treatment course should not be repeated more than once within 2 weeks.
  - In FMF patients: Start with 0.3 mg/day. Any increase in dose should be done with close monitoring.
- For patients undergoing dialysis:
  - The total recommended dose for gout prophylaxis should be 0.3 mg twice weekly with close monitoring.
  - For treatment of gout flares, the total recommended dose should be

reduced to 0.6 mg and the treatment course should not be repeated more than once within two weeks.
    - For FMF patients, the starting dose is 0.3 mg daily and dosing can be increased with close monitoring.
- Selective serotonin reuptake inhibitors (SSRIs): Most do *not* require dose adjustment, except paroxetine (Paxil). SSRIs have increased risk of hyponatremia and GI bleed when taken with NSAIDs.
- Lithium: Acute lithium toxicity may be exaggerated by concurrent use of thiazide diuretics, NSAIDs, ACEI/ARB.
- Anticonvulsants:
    - Phenytoin: No dose reduction is generally required. However, monitoring free versus total phenytoin level is recommended due to reduce protein binding with uremia but higher plasma clearance by hepatic P450.
    - Most newer anticonvulsants require dose reduction: gabapentin, felbamate, levetiracetam (Keppra), pregabalin (Lyrica), topiramate, zonisamide
    - Lamotrigine does not require dose reduction.
- Calcium channel blockers (CCBs):
    - Mechanism of CCB-induced edema: CCB causes relaxation of the precapillary sphincter that transmits systemic HTN into the venous bed. The increased IV pressure (hydraulic pressure) favors net fluid filtration into the interstitium. CCB-induced edema is not thought to be due to sodium and water retention.
    - CCB are inhibitors of CYP34A and P-glycoproteins. Moderate inhibitors: diltiazem, verapamil (also discussed in the previous text). Weak inhibitors: amlodipine, felodipine
- Methyldopa, α-blockers, clonidine, and minoxidil are renally cleared.

NOTE Clonidine accumulates in advanced CKD and can lead to severe bradycardia or even asystole if used in high dose and in combination with β-blockers.

- Minoxidil:
    - Potent direct-acting peripheral vasodilator, which leads to increased

renin–angiotensin–aldosterone system (RAAS) activity, cardiac output, and salt and water retention. Associated side effects include tachycardia and peripheral edema.

- Warnings: Minoxidil can cause pericardial effusion, occasionally progressing to tamponade and exacerbation of angina pectoris. Minoxidil use should be reserved for hypertensive patients who do not respond adequately to maximum therapeutic doses of a diuretic and two other antihypertensive agents.
- Minoxidil typically requires the concurrent use a β-blocker and diuretic for optimal antihypertensive effect.

DRUG INTERACTION/ADVERSE EFFECTS (OTHER THAN NEPHROTOXICITY)

- PPIs can reduce GI absorption of MMF due to reduced acid-dependent dissolution of MMF (Cellcept) prior to absorption, but not enteric-coated mycophenolate sodium (Myfortic), which is absorbed at neutral pH in the small intestines.
- CsA inhibits hepatic recirculation of MMF and reduce MPA plasma levels. Tac does not. CsA to Tac switch may result in increased MPA levels.
- CsA can increase plasma hydroxymethyl glutaryl-CoA (HMG-CoA) reductase inhibitor (statin) level and increase the risk of rhabdomyolysis. Unlike CsA, Tac has limited effect on HMG-CoA reductase inhibitors. Rhabdomyolysis associated with Tac and HMG-CoA reductase inhibitors is only generally seen with concurrent use of diltiazem or other CYP3A4 inhibitor.
- Use of amphotericin B, AG, foscarnet, cidofovir, and NSAIDs can potentiate CNI toxicity.
- Use of ganciclovir, valganciclovir, and/or co-trimoxazole in combination with MMF and AZA can increase myelosuppressive risk.
- St. John wort reduces CNI levels, whereas grapefruit juice increases CNI levels.
- Amlodipine increases simvastatin blood levels, hence risk of rhabdomyolysis. Both amlodipine and simvastatin are metabolized by

P450 3A4.

- Barbiturate coma therapy (BCT) with thiopentone. Hypokalemia, a potentially life-threatening complication, has been reported to occur in up to 25%. Hypokalemia is thought to be due to increased cellular uptake. The severe rebound hyperkalemia following discontinuation of thiopentone is due to reshifting of intracellular space and high doses of potassium supplement during the hypokalemic phase. Gradual tapering of thiopentone has been suggested to reduce the risk of rebound hyperkalemia.

DIALYSIS AND OTHER TREATMENT OF POISONINGS

Pharmacokinetics of toxin removal by various dialytic methods are similar to those outlined for drug dialyzability. In addition, there are a few other extra considerations:

- Electrolytes: Electrolyte and acid–base disturbances in patients requiring HD for poisons are not necessarily similar to those seen with ESKD (i.e., serum concentrations of K^+, HCO_3^-, Ca^{2+}, Mg^{2+}, and PO_4^{2-} may be relatively normal). Dialysate should, therefore, reflect patient's needs. IV Mg^{2+} and PO_4^{2-} supplements may be necessary.
- Specialized dialysis systems to improve albumin-bound toxin removal:
  - Hemoperfusion: This is a form of dialysis where a cartridge containing an adsorbent material such as activated charcoal or resin is added to the circuit to compete for binding and removal of albumin-bound toxins from circulation. Not widely available.
    - Hemoperfusion may be needed for amanita mushroom, barbiturate, carbamazepine, valproic acid, phenytoin, meprobamate, theophylline, dapsone, and methotrexate.

NOTE Urinary alkalinization also facilitates renal elimination of barbiturate.

    - Hemoperfusion-related complications: hypocalcemia, charcoal embolization, leukopenia, thrombocytopenia, coagulopathy due to adsorption of coagulation factors
    - High-flux dialysis may improve solute removal, thus less need for hemoperfusion.

  - Molecular adsorbent recirculating system (MARS): This form of dialysis has an added albumin circuit to improve removal of albumin-bound toxins. Not widely available.
  - Hemofiltration alone may be considered for AG, desferrioxamine, sodium edetate, and theophylline.
- HD is the treatment of choice for water-soluble drugs, particularly those that have LMW and low protein binding. Such agents diffuse rapidly across the dialyzer membrane. High MW drugs are less well removed because they diffuse more slowly across dialyzer membranes. High-flux membranes and hemodiafiltration may improve their removal rates.
  - Drugs removable by HD: salicylates, lithium, methanol, ethylene glycol, isopropyl alcohol, theophylline, valproic acid, methotrexate, phenobarbital, metformin
  - Although acetaminophen (paracetamol) is removed by dialysis or hemoperfusion, *N*-acetylcysteine is the treatment of choice for acetaminophen toxicity/poisoning. *N*-acetylcysteine has been suggested to prevent or alleviate drug-induced hepatotoxicity by restoring hepatic glutathione stores.
- Plasma exchange:
  - One to two plasma volume exchanges may be considered for rapid removal of toxins that exist predominantly in the plasma (V_d < 1 l/kg).
  - Agents removable by plasma exchange: amanita mushroom, digoxin, snake envenomation, cisplatin, natalizumab (used for the treatment of multiple sclerosis)

Common Poisonings That May Require Extracorporeal Removal

Alcohols

Ethylene glycol, methanol (see Fig. 2.1)

- Significant ingestion of either alcohol can give rise to high serum anion gap metabolic acidosis and high osmolal gap > 12 mOsm/kg.
- Alkalinize blood to keep pH above 7.35 (correction of systemic acidosis limits the penetration of formic acid into end-organ tissues such as the retina by converting them into formate that cannot diffuse across cell membrane)

- Fomepizole should be given to inhibit hepatic alcohol dehydrogenase in patients with blood levels of either alcohol above 20 mg/dL or serum osmolal gap > 20 mOsm/kg. Fomepizole should be continued until alcohol level is below 20 mg/dL or below 1 mg/dL in the presence of end-organ damage.
- If fomepizole is not available, infuse 10% ethanol until blood ethylene glycol or methanol level is undetectable.
- Perform HD if the alcohol level is above 50 mg/dL in the setting of severe metabolic acidosis or end-organ damage (e.g., AKI or visual disturbances). Note that large surface area dialyzers (>1.5 m^2) should be used along with blood flow rate greater than 300 mL/min. Ethylene glycol and methanol levels should be monitored 2 hours postdialysis to assess for rebound. HD may be discontinued once the alcohol level is below 25 mg/dL.
- In malnourished patients with ethylene glycol poisoning, add thiamine 100 mg and pyridoxine 5 mg IV to increase the metabolism of glyoxylate.
- In methanol poisoning, add folinic acid 50 mg IV q6h to increase metabolism of formic acid to CO_2 and H_2O.

Isopropyl alcohol (i.e., isopropanol, rubbing alcohol)

- Both isopropranol and its metabolite acetone can cause CNS suppression, nausea/vomiting.
- Because isopropanol is metabolized to acetone (not an acid) by alcohol dehydrogenase, isopropanol ingestion does not cause a high anion gap metabolic acidosis. However, the acetone can be measured as positive “ketones” in either serum or urine. Low or absent serum ketones by the nitroprusside test after 2 hours from time of ingestion in the absence of alcohol dehydrogenase inhibition (e.g., concurrent ethanol ingestion or use of fomepizole) essentially rules out isopropanol ingestion.
- Increased serum osmolal gap reflects the presence of exogenous isopropanol molecules.
- isopropranol intoxication is not as toxic as ethylene glycol or methanol and rarely fatal. Fomepizole or ethanol infusion is thus not necessary.
- Management typically only requires routine supportive care, including IV fluid support and airway protection. For refractory and severe

hemodynamic instability in association with very high levels > 500 mg/dL and osmolal gap > 100 mOsm/kg, HD may be considered.

β-Blockers

- Activated charcoal should be administered to all patients presenting within 2 hours of β-blocker overdose.
- Supportive care with IV fluids for hypotension, atropine for severe bradycardia, β-agonist for bronchospasm, glucose for hypoglycemia
- Dialyzable β-blockers (hydrophilic, low protein binding): atenolol, metoprolol, acebutolol, nadolol
- Nondialyzable β-blockers: carvedilol, labetalol, propranolol, timolol
- There is evidence to suggest increased cardiovascular death in dialysis patients using dialyzable β-blockers compared to nondialyzable β-blockers.

Lithium

- Patients may present with hemodynamic instability, altered mental status, prolonged QT interval, arrhythmias, and/or renal insufficiency.
- Signs and symptoms of lithium toxicity do not correlate well with lithium levels.
- Lithium is highly dialyzable due to its LMW and low protein binding.
  - Indications for dialysis:
    - Lithium level > 3.5 to 4 mmol/L, or
    - Lithium level > 2.5 mmol/L with CNS manifestation (altered mental status, seizures, coma), reduced GFR, or hemodynamic instability
    - Between 2.5 and 3.5 mmol/L in asymptomatic patients with increasing lithium levels or kidney failure

NOTE Rebound is a common problem following dialytic cessation. Prolonged or continuous dialysis is recommended. Close postdialysis level monitoring (e.g., q6h) is necessary.

Metformin-induced lactic acidosis

- Supportive care and alkalinization with sodium bicarbonate to maintain pH above 7.15 until the acute toxicity resolves
- Metformin is dialyzable. However, the beneficial effect of HD in metformin-induced lactic acidosis is thought to be from the correction of

metabolic acidosis rather than metformin removal.

- HD is recommended if any of the following is present:
  - Lactate level >20 mmol/L
  - Severe metabolic acidosis (pH ≤ 7.0) or
  - Medical treatment failure (as determined by pH, lactate levels, or clinical status within 2 to 4 hours), despite appropriate supportive care and bicarbonate therapy
- HD may be considered if any of the following is present (limited evidence):
  - Lactate levels between 15 and 20 mmol/L
  - Metabolic acidosis (pH 7.0 to 7.1)
  - Presence of comorbidities (e.g., shock, kidney injury, liver failure, or decreased level of consciousness): Kidney injury is defined as creatinine > 2 mg/dL (adults) or > 1.5 mg/dL (elderly), eGFR < 45 ml/min/1.73 m^2, oliguria, or anuria. liver failure is defined as liver injury with coagulopathy (inr > 1.5) and any degree of encephalopathy.

NOTE Metformin dosing in patients with CKD: Kidney Disease: Improving Global Outcomes Organization (KDIGO) suggests that metformin should be continued in patients with eGFR > 45 mL/min/1.73 m^2, "reviewed" in patients with eGFR 30 to 44 mL/min/1.73 m^2, and discontinued/contraindicated with eGFR < 30 ml/min/1.73 m^2.

Digitalis toxicity

- Clinical manifestations: CNS symptoms ranging from drowsiness, lethargy to hallucinations, seizures, visual disturbances with classic yellow halos around lights, nonspecific GI symptoms, cardiac arrhythmias. Electrolytes: hyperkalemia in acute toxicity
- Toxicity risks: advanced age, hypothyroidism, reduced GFR, hypothyroidism or hyperthyroidism, alkalosis or acidosis, myocardial disease, ischemia or infarction, hypoxemia, electrolyte abnormalities (hypokalemia, hypercalcemia, hypomagnesemia, hypernatremia)
- Management:
  - Routine supportive care, fluids, airway protection, drug discontinuation
  - Activated charcoal in acute overdose or accidental ingestion

Cholestyramine may bind enterohepatically recycled digoxin in acute overdose.

- Hyperkalemia: insulin plus glucose, sodium bicarbonate if metabolic acidosis
- Concurrent hypokalemia and hypomagnesemia: supplement as needed
- Indication for digoxin immune Fab (digibind):
  - Life-threatening dysrhythmias
  - Acute ingestion dose > 10 ng/mL in acute ingestions or > 6 ng/mL in chronic ingestion
  - Hyperkalemia > 5 mmol/L
  - Altered mental status
  - Rapid clinical deterioration
- Digoxin is not dialyzable. However, dialysis is indicated for hyperkalemia and kidney failure. Digibind is also minimally dialyzable.
- If digibind is not available or contraindicated, hemoperfusion should be considered.

Salicylates (aspirin)

- Initial presentation may be respiratory alkalosis alone due to activation of respiratory center, followed by high anion gap metabolic acidosis due to accumulation of lactic acids and ketoacids. Other characteristic manifestations: fevers, tinnitus, vertigo, blurry vision
- Gastric lavage should be considered within 12 hours of ingestion if airway is protected.
- Urinary alkalinization to keep urine pH > 7.5 in nonoliguric patients to increase the levels of ionized salicylates ($NaHCO_3$ 1 to 2 mEq/kg bolus followed by infusion [100 to 150 mL/h] of 100 to 150 mEq mixed in 1 L of 5% dextrose). Ionized salicylates are more easily excreted by the kidneys and less likely to penetrate and accumulate in tissue than the nonionized form.

NOTE Acidemia increases salicylate CNS toxicity.

- Glucose supplementation to avoid CNS hypoglycemia, which may occur

despite serum normoglycemia

- Indications for HD: serum levels > 90 to 100 mg/dL or lower if presence of AKI, marked acidemia, noncardiogenic pulmonary edema, or neurologic involvement (altered mental status, hyperthermia, seizure)

Theophylline

- Theophylline is highly dialyzable due to its low V_d and protein binding.
- High-efficiency HD is more effective than hemoperfusion in theophylline removal.
- HD indications for acute intoxication:
  - Severe symptoms such as shock, seizure, or life-threatening arrhythmias
  - Serum level ≥ 100 mg/L, regardless of symptoms
  - Clinical deterioration despite optimal supportive care and multiple-dose activated charcoal
  - Rising theophylline levels despite optimal supportive care and multiple-dose activated charcoal
    - If the initial level is ≥ 80 mg/L, then one additional rising level measured 2 hours later.
    - If the initial level is < 80 mg/l, then a subsequent level that rises above 80 mg/l.
- In patients in whom administration of activated charcoal is not possible (e.g., protracted vomiting, altered mental status)
- HD may be beneficial in patients at increased risk for seizure (e.g., history of seizure, concomitant use of medications that lower seizure threshold) or in those with history of any arrhythmias.
- HD indications for chronic intoxication:
  - Severe symptoms such as shock, seizure, or life-threatening arrhythmias
  - Serum level ≥ 60 mg/L, regardless of symptoms
  - Serum levels > 40 to 50 mg/L in patients older than 60 to 65 years
- Combining HD with hemoperfusion may enhance clearance and prevent saturation of hemoperfusion cartridge.

Bisphosphonates

- Kidney injury associated with bisphosphonates:

- AKI has been reported with IV bisphosphonates, particularly when administered as rapid infusion and frequent doses to patients with malignancy. Biopsy reveals tubular injury with low Na^+-K^+-ATPase expression. Oral bisphosphonates have not been associated with increased risk of AKI.
- Collapsing FSGS has been reported with pamidronate, alendronate, zoledronate, and ibandronate.
- Toxic ATN has been reported, predominantly with zoledronate.
- Other possible lesions associated with bisphosphonates: CTIN with Fanconi syndrome
- Cardiovascular effects:

- Bisphosphonates can bind to soft-tissue calcifications, but clinical significance is yet to be determined.
  - Kim et al. meta-analysis in 2015: Bisphosphonates do not have beneficial or harmful effects on atherosclerotic cardiovascular events, but zoledronate may modestly increase the risk of atrial fibrillation.
- Use of bisphosphonates in CKD:
  - FDA warns against the use of bisphosphonates in patients with GFR <30 ml/min/1.73 m^2.
  - KDIGO suggests *not* to prescribe bisphosphonate to patients with eGFR <30 ml/min/1.73 m^2 without a strong clinical rationale.

ANTIPARASITIC AGENTS

See Table 10.3. For interested readers, review Campbell S, Soman-Faulkner K. Antiparasitic drugs. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020.

Table 10.3 Antiparasitic agents

Class of Infection	Specific Organisms	First-Line/Common Therapies	Comments on Selected Drugs
Protozoa	Sarcodina (*Entamoeba, Dientamoeba*)	Metronidazole, tinidazole	*Albendazole:* May cause bone marrow suppression, aplastic anemia, and agranulocytosis; not studied in patients with reduced GFR.

	Mastigophora (*Giardia*, *Trypanosoma* [*Trypanosoma brucei gambiense*, *Trypanosoma rhodesiense*: sleeping sickness; *Trypanosoma cruzi:* Chagas disease], *Leishmania*, *Trichomonas*)	Metronidazole, tinidazole, albendazole (*Giardia*); benznidazole (*Chagas*); pentamidine (*T. brucei*); sodium stibogluconate (leishmaniasis)	*Benznidazole:* Alcohol or propylene glycol consumption contraindicated for at least 3 days from last benznidazole dose (disulfiram-like reaction); use of either agent in patients with reduced GFR has not studied; absolute contraindication: liver failure; relative contraindication: severely reduced GFR; benznidazole is a Pgp substrate. *Chloroquine:* No dose adjustment for reduced GFR, HD, or PD; dose adjustment may be necessary with chronic use in patients with GFR 10 ml/min; hemolysis with g6pd deficiency. *Diethylcarbamazine:* Reduce dose in moderate-to-severe impairment. *Ivermectin:* No dose adjustment for reduced GFR per manufacturer's labeling. *Lindane:* No dose adjustment for reduced GFR per manufacturer's labeling. *Metronidazole/tinidazole:* No dose adjustment for pre-ESKD; HD: dialyzable, dose supplement is needed; PD: minimal dialyzability, no dose adjustment. *Pentamidine:* May block ENaC and give rise to hyperkalemia and metabolic acidosis; reduced dose may be necessary with CrCl 10 ml/min; hypotension may occur with rapid infusion. *Permethrin:* Likely no dose adjustment for reduced GFR; drug is metabolized by liver. *Praziquantel:* Excretion may be delayed, but no dosage adjustment is necessary for reduced estimated GFR. *Pyrimethamine:* No dose adjustment for reduced GFR per manufacturer's labeling; use "with caution" in patients with reduced GFR. Concurrent administration of folinic acid is strongly recommended in all patients.
	Apicomplexa (*Babesia*, *Plasmodium*, *Toxoplasma*, *Isospora*, *Sarcocystis*, *Cryptosporidium*)	Chloroquine (malaria); atovaquone, azithromycin (babes); sulfonamides with pyrimethamine (toxoplasma)	
	Pneumocystis	Trimethoprim–sulfamethoxazole	
Helminths	Trematodes (schistosomiasis, fascioliasis)	Praziquantel	
	Cestodes (cysticercosis, echinococcosis)	Praziquantel	
	Nematodes (onchocerciasis, loiasis, ascariasis, trichinosis, lymphatic filariasis, toxocariasis)	Albendazole (ascariasis, trichinosis); diethylcarbamazine (filariasis, loiasis); ivermectin (onchocerciasis)	
Ectoparasites	Mites, fleas, lice, scabies	Lindane, permethrin, benzyl benzoate, ivermectin	

Abbreviations: bid, twice daily; Cr, creatinine; CrCl, creatinine clearance; CVVHDF, continuous venovenous hemodiafiltration; CYP3A4, cytochrome P450; Pgp, P-glycoprotein; VKA, vitamin K antagonist.

CHAPTER 11

Acute Kidney Injury/ Intensive Care Unit Nephrology

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ACUTE KIDNEY INJURY

Clinical Impact of Acute Kidney Injury

- Acute kidney injury (AKI) increases the risk for chronic kidney disease (CKD) progression and de novo CKD in patients with and without underlying CKD, respectively.
- In patients with diabetes mellitus (DM) type 2, any AKI episode independently increases the risk for the development of stage 4 CKD. The adverse impact of AKI on the development of CKD is similar to that seen with proteinuria.
- AKI is associated with higher rates of cardiovascular events (heart failure, acute myocardial infarction) and cardiovascular mortality.
- Worse stages of AKI are associated with increased mortality.
- AKI episode prior to incident end-stage kidney disease (ESKD) is associated with higher adjusted odds of 1-year mortality compared with pre-ESKD without AKI episodes.

Classification of AKI

- Purpose for classification system for AKI:

- Early identification and management of AKI
- Standardized AKI definitions for AKI-related research

- KDIGO definition of AKI (**Table 11.1**):

Table 11.1 KDIGO staging of acute kidney injury

Stage	Serum Creatinine Criteria	Urine Output Criteria
1	↑SCr 1.5–1.9 × baseline within 7 d or ↑SCr by ≥0.3 mg/dL within 48 h	0.5 mL/kg/h for 6–12 h
2	↑SCr >2.0–2.9 × baseline	0.5 mL/kg/h for ≥12 h
3	↑SCr >3.0 × baseline or ↑ in SCr to ≥4.0 mg/dL or initiation of KRT	0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

Abbreviations for simplified table would be as follows:

Abbreviation: KDIGO, Kidney Disease Improving Global Outcomes; SCr, serum creatinine; KRT, kidney replacement therapy.

- Increase in serum creatinine (SCr) by ≥ 0.3 mg/dL within 48 hours or
- Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days or
- Urine volume <0.5 ml/kg/h for 6 hours or longer

Early Identification of AKI

- Biomarkers: As the rise in SCr occurs late after the onset of AKI, the search for an ideal biomarker for the early identification of AKI has been an active area of research. Early detection of AKI is thought to improve outcome. Selected biomarkers for the early detection of AKI are listed in Table 11.2:

Table 11.2 Selected biomarkers that have been studied in the setting of AKI: The ideal biomarker is expected to have an early increase in level with AKI, correlate with AKI course and severity, and clear with AKI recovery

Biomarkers	Comments
Liver-type fatty acid–binding protein	• Involves in fatty acid transport; protects against oxidative stress injury • Detected within 1 h, peaks within 6 h
Neutrophil gelatinase-associated lipocalin (NGAL)	• Functions as chelator of labile iron released from damaged tubules; upregulates the renoprotective enzyme heme-oxygenase-1 • Detected at 3 h, peaks at 6 h with sustained elevation up

	to 5 d • NGAL level may be affected by systemic infections, inflammatory conditions, anemia, hypoxia, and malignancies
Interleukin-18	• Upregulated in acute kidney injury; proinflammatory • Detected within 6 h, peaks at 12–18 h
Kidney injury molecule-1	• Activates immune cells and promotes apoptotic and necrotic cell clearance and remodeling of injured epithelia • Detected within 6 h, peaks at 48–72 h
Tissue inhibitor of metalloproteinases-2 and insulin-like growth factor binding protein	• Induces transient cell cycle arrest in face of injury • Detected within 12 h
Cystatin-C (Cys-C)	• Cysteine protease inhibitor • Detected at 12–24 h, peaks at 24–48 h • **Note:** Albuminuria ↑urinary Cys-C due to competitive proximal tubular endocytosis of albumin

Neutrophil gelatinase-associated lipocalin (NGAL)

- NGAL is predominantly detected in proliferating nuclear antigen–positive proximal tubular cells. In healthy individuals, urine and plasma levels of NGAL are low but increase significantly with ischemic or nephrotoxic kidney injury.

Kidney injury molecule 1 (KIM-1)

- A transmembrane glycoprotein that is undetectable in normal kidney tissue or urine but is expressed at high levels in dedifferentiated proximal tubular cells after ischemic or toxic injury and in renal cell carcinoma

Tissue inhibitor of metalloproteinase-2 (TIMP-2) and tissue insulin-like growth factor binding protein 7 (IGFBP7)

- TIMP-2 and IGFBP7 function as both autocrine and paracrine signals to arrest cell cycle and shut down cell function with early kidney injury.
- Urinary levels of both TIMP-2 and IGFBP7 are increased in early kidney injury.
- Current data suggest that early optimized kidney care or prompt nephrology consultation based on elevated IGFBP7*TIMP-2 values reduces the severity of AKI.

AKI Risk Stratification and Prognostication

- Multiple AKI risk stratification and prognostication scoring systems based on patients' baseline characteristics and kidney function, clinical context, and early signs of kidney injury have been developed in recent years. For interested readers, see **Selected Reading** list.

Renal functional reserve testing (RFR)

- RFR is defined as the increase in glomerular filtration rate (GFR) following protein loading.
- An increase in GFR <15 ml/min/1.73 m^2 following a protein load of 1.2 g/kg body weight has been suggested to predict an 11.8-fold increase in postoperative risk for aki among patients undergoing elective cardiac surgery.

Furosemide stress test (FST)

- FST may be used in euvolemic to hypervolemic patients with AKI to predict the risk for severe AKI and need for renal replacement therapy (RRT).
- Protocol:
  - Infuse 1.0 to 1.5 mg/kg of furosemide (the former dose is for furosemide-naïve individuals, and the latter is for individuals with prior exposure).
  - Urine output <200 ml within 2 hours in patients with stage 1 aki predicts risk of progression to stage 3 aki and need for rrt. in the kidney transplant recipient, poor fst response predicts delayed graft function.
- Combining FST with urinary IGFBP7*TIMP-2 level has been shown to be superior to using either test alone in predicting AKI.

Proteinuria

- Preexisting proteinuria (albuminuria) predicts AKI risk, AKI requiring RRT, unfavorable prognosis for renal recovery in those who develop AKI requiring RRT, and prolonged hospital stay.

Mechanisms of AKI

Ischemia-related acute tubular necrosis (ATN)

- Proximal and distal tubules may be affected in a patchy distribution.

Functional changes

- Loss of tubular cell polarization, that is, loss of differentiation between apical and basolateral sides, leading to reabsorption of urine instead of urine excretion. This is also known as “urine back-leak.”
- Microvascular injury, vascular congestion, intraglomerular vasoconstriction

Histopathology (Fig. 11.1)

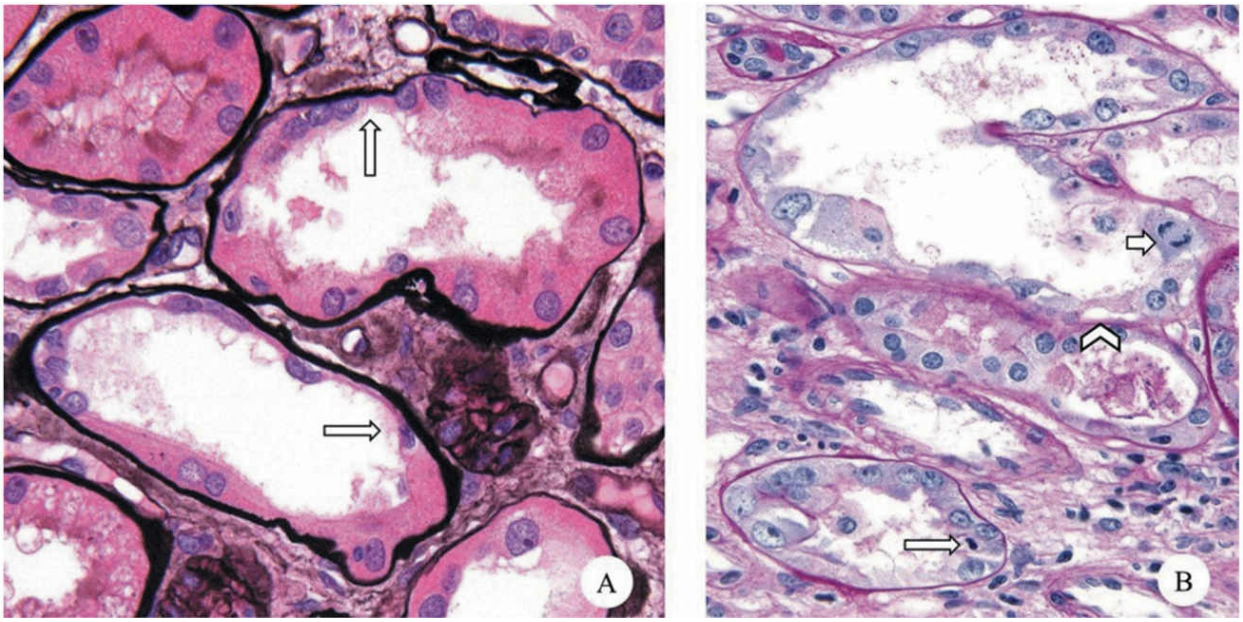


FIGURE 11.1 Acute tubular necrosis. Acute tubular cell injury and necrosis in proximal tubules. **A.** There is acute tubular injury with loss of the microvillus brush border and cell cytoplasm with epithelial cell flattening (*arrows*) and relative dilatation of the tubular lumens (Jones silver ×40). **B.** In addition to tubular cell loss of brush borders and cytoplasm, there are tubular cell necrosis (*long arrow*), a mitotic figure (*short arrow*) reflecting regeneration and repair, and epithelial cell detachment with a focus of denuded tubular basement membrane (*arrowhead*) (periodic acid methenamine silver ×40).

- Irregular vacuolization within proximal tubular cells, loss of proximal cell brush border, disruption and sloughing of epithelial cells lining the tubule, intratubular epithelial cell casts
- Necrosis of tubular cells is typically only seen in a small portion of cells.
- Apoptosis of proximal tubular cells

Nephrotoxin-related AKI

- Typically involves proximal tubular injury
- Mechanisms of action are drug specific and may include alterations in intraglomerular hemodynamics, direct tubular cytotoxic effects with generation of local inflammatory response and reactive oxygen species, local or systemic drug-allergic response, systemic endothelial injury with associated immunologic and nonimmunologic responses, or drug-crystallization and microtubular obstruction.

Recreational drugs associated with AKI

- Cocaine (rhabdomyolysis, severe renal vasoconstriction with possible renal infarction, levamisole-laced cocaine with associated antineutrophil cytoplasmic antibody [ANCA] vasculitis)
- Oxymorphone (Opana): thrombotic microangiopathy, rhabdomyolysis
- Methamphetamines, ecstasy (rhabdomyolysis, acute tubulointerstitial nephritis [ATIN], ATN, hyponatremia, malignant hypertension [HTN])
- Synthetic cannabinoids (ATN, ATIN, mild elevation of creatine phosphokinase [CPK], rare reports of rhabdomyolysis)
- Heroin (amyloidosis, nephrotic syndrome, heroin crystal nephropathy, rhabdomyolysis)
- Bath salts—synthetic cathinones (rhabdomyolysis, hyperuricemia)
- NMDA—potent hallucinogens (rhabdomyolysis)
- Ketamine (lower urinary tract dysfunction, obstructive uropathy, rhabdomyolysis)
- See **Chapter 10,** for specific drug-related AKI.

Sepsis-related AKI

- Activation of the innate immune system in response to an inciting pathogen leads to increased oxidative stress, procoagulant state, endothelial injury, and recruitment of inflammatory cells, all acting in concert to induce a milieu favorable to promote and exacerbate underlying AKI.
- The septic/shock state is also associated with increased glomerular blood flow due to dilatation of both afferent and efferent arterioles. However, net glomerular filtration pressure (hence GFR) is reduced because there is

greater efferent vasodilation than afferent vasodilation. The reduced GFR may partially contribute to sepsis-related AKI. It is plausible that the use of angiotensin II (AII) in the setting of septic shock may improve sepsis-related renal and survival outcomes. More data are needed.

Routine Diagnostic Tools for the Diagnosis of AKI

Microscopic examination of urinary sediment

- The use of a scoring system based on the number of granular casts (muddy- brown casts) and renal tubular epithelial cells may improve the differential diagnostic and prognostic evaluation of AKI.
- Evaluation of cells, cellular casts:
  - Hyaline casts:
    - Predominantly made up of Tamm–Horsfall/uromodulin proteins
    - Indicate reduced renal perfusion (e.g., volume depletion, reduced cardiac output)
  - Red blood cell (RBC) casts: acute glomerulonephritis until proven otherwise
  - White blood cell (WBC) casts: pyelonephritis or tubulointerstitial nephritis
  - Granular casts: nonspecific, indicates the presence of cells that have degenerated
  - Broad casts: chronic low urine flow
  - Muddy-brown casts: ATN
  - Waxy casts: degraded cellular casts seen in CKD with poor urine flow
- Crystalluria:
  - Consider drug-induced crystals
  - High amount of uric acid crystals may be observed with tumor lysis syndrome (TLS).

Urine eosinophils

- Poor sensitivity and specificity in the diagnosis of ATIN
- No longer recommended in the evaluation of ATIN

Urine volume

- Anuria is more likely seen with complete urinary obstruction, vascular catastrophe, bilateral renal cortical necrosis, severe ATN, or severe rapidly progressive glomerulonephritis.
- Oliguric AKI, defined as urine output <500 ml/d, is associated with worse outcome than nonoliguric aki.

Fractional excretion of sodium (FeNa) and fractional excretion of urea (FeUrea)

- FeUrea versus FeNa: FeUrea is typically used in patients receiving diuretics because urea reabsorption occurs primarily in the proximal tubules and is less affected by loop and thiazide diuretics. In contrast, Na^+ excretion, hence FeNa, can be elevated with diuretic use even in the prerenal state.
- In nonoliguric AKI, FeNa <1% or feurea <35% generally indicates prerenal aki as opposed to atn.

NOTE

- FeNa may be <1%, *despite the presence of ATN* in patients with sepsis, hemoglobinuria, myoglobinuria, radiocontrast exposure, heart failure, and advanced cirrhosis presumably due to severe vasoconstriction.
- In patients with cirrhosis, FeNa of <0.1 may be consistent with hepatorenal syndrome (hrs), fena >0.3 ATN, and FeNa 0.1 to 0.3 may be indicative of prerenal AKI.

Kidney/bladder ultrasound

- Kidney size is generally normal to enlarged with AKI. However, enlarged kidneys may be seen in advanced subacute/chronic diabetic kidney disease, infiltrative disease, amyloidosis, HIV-infected–related nephropathy, or the presence of large cysts.
- Bladder ultrasound with postvoid retention volume may be indicated in at-risk individuals (e.g., enlarged prostate, neurogenic bladder [associated with DM, neurologic complications, or drug induced], AKI posttraumatic Foley insertion).
- Other imaging studies are listed in Table 11.3.

Table 11.3 American College of Radiology appropriateness criteria for the diagnosis of acute kidney injury 2013

Imaging Study	Comments	ACR Rating
Ultrasound	Assess kidney size Exclude obstruction Doppler may be added to assess	9

	renal perfusion or vascular stenosis/thrombosis	
Tc-99m MAG3 kidney scan	May be useful if SCr is elevated May be performed as a follow-up after ultrasound as needed	4
MRI of the abdomen without IV contrast	Evaluate unclear causes of ureteral obstruction	3
MRI of the abdomen with and without IV contrast	Gadolinium-enhanced studies are very effective for renal artery evaluation; gadolinium use should be avoided in patients with eGFR 30 mL/min/1.73 m^2 due to increased risk of nephrogenic systemic fibrosis.	3
MRA without IV contrast	Assess renal arterial or venous patency when vascular stenosis or thrombosis may account for AKI	3
Arteriography of the kidney	Potentially helpful in trauma evaluation for renal artery occlusion. Consider using CO_2 to avoid nephrotoxicity.	3
CT of the abdomen without IV contrast	Trauma evaluation Noncontrast helical CT is more sensitive than KUB for the evaluation of calculi. Evaluation of ureteral obstruction due to retroperitoneal fibrosis or masses	3

ACR rating scale: 7-9: Usually appropriate; 4-6: May be appropriate; 1-3: Usually not appropriate
Abbreviations: ACR, American College of Radiology; CT, computed tomography; eGFR, estimated glomerular filtration rate; IV, intravenous; KUB, kidney urinary tract bladder; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; SCr, serum creatinine; Tc-99m MAG3, technetium-labeled mercaptoacetyltriglycine.

HEMODYNAMIC (PRERENAL) AKI

Etiologies of Prerenal AKI (Fig. 11.2)

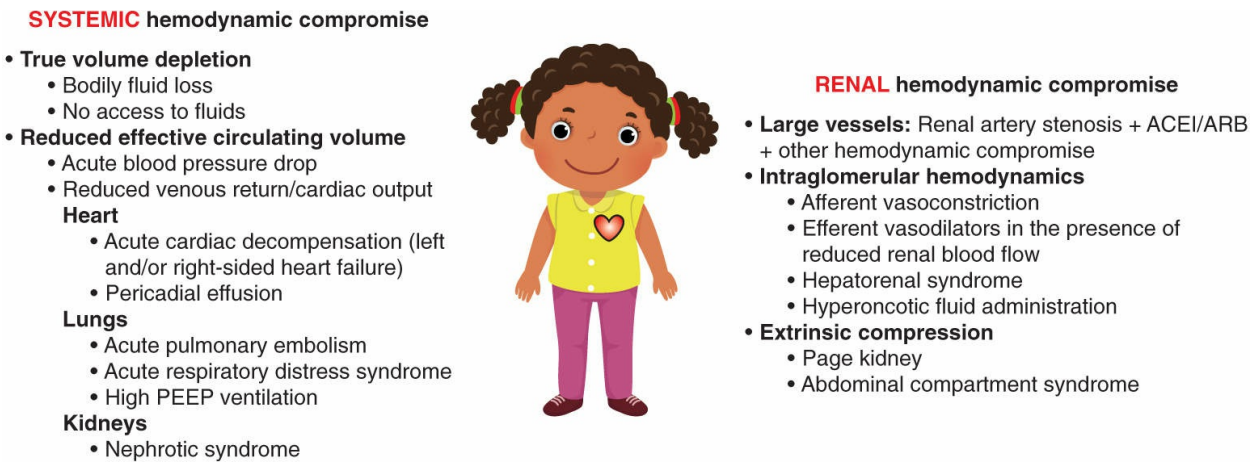


FIGURE 11.2 Differential diagnoses for prerenal acute kidney injury. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; PEEP, positive end-expiratory pressure.

Rapid fall in baseline blood pressure (BP)

- May be seen with overly rapid treatment of HTN or acute volume loss

Volume depletion

- True volume depletion: bodily fluid loss, no access to adequate fluid intake
- Reduced effective circulating volume: heart failure, cirrhosis, nephrosis

Third-spacing

- May be seen in sepsis, severe acute pancreatitis or muscle trauma

Cardiorenal syndrome (CRS)

- Pathologic disorder of the heart and kidneys whereby acute or chronic dysfunction of one organ induces acute or chronic dysfunction of the other

Cardiorenal syndrome types

- CRS type 1 (acute CRS):
  - Abrupt worsening of cardiac function (e.g., acute pulmonary embolism, myocardial infarction, valvular rupture, rapid [re]-accumulation of pericardial effusion) → AKI
- CRS type 2 (chronic CRS):
  - Chronic abnormalities in cardiac function → progressive CKD
- CRS type 3 (acute renocardiac syndrome):
  - AKI → acute cardiac dysfunction
- CRS type 4 (chronic renocardiac syndrome):
  - CKD → decreased cardiac function, cardiac hypertrophy, and/or increased risk of adverse cardiovascular events
- CRS type 5 (secondary CRS):
  - Systemic condition → both cardiac and renal dysfunction

Risk factors

- Older age, female gender, baseline CKD, Caucasian American race, diastolic heart failure, history of congestive heart failure (CHF), DM, systolic BP (SBP) >160 mm Hg

Pathophysiology of CRS

- Reduced cardiac output leads to renal hypoperfusion.

- Reduced cardiac output with associated venous congestion or severe right ventricular dysfunction also leads to increased renal venous pressure, increased renal resistance, and, ultimately, impaired intrarenal blood flow.
- Endothelial stretch from peripheral venous congestion leads to a vascular endothelial proinflammatory state.
- Neurohormonal activation involving the sympathetic nervous system, renin–angiotensin–aldosterone system (RAAS), and nonosmotic vasopressin release leads to systemic vasoconstriction and enhanced renal Na^+ and H_2O excretion.

Management

- Optimization of cardiac function per underlying etiology. Management of heart failure is discussed in **Chapter 1**

Renovascular compromise

- Examples include acute obstruction of renal artery, such as aortic dissection extending into renal artery, use of angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker [ACEI/ARB] in severe bilateral renal artery stenosis

Intraglomerular hemodynamic compromise

- Predominant afferent vasoconstrictors: nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, calcineurin inhibitors, amphotericin, contrast agents
- Predominant efferent vasodilators in patients with suboptimal baseline glomerular filtration: ACEI/ARB

Hepatorenal syndrome (HRS)

Definition of HRS by the Ascites International Club: *HRS is a clinical condition that occurs in patients with chronic liver disease, advanced hepatic failure, and portal hypertension characterized by impaired renal function and marked abnormalities in the arterial circulation and activity of the endogenous vasoactive systems. In the kidney, there is marked renal vasoconstriction that results in a low GFR. In the extrarenal circulation, there is predominance of arterial vasodilation that results in reduction of*

total systemic vascular resistance and arterial hypotension.

- Ascites International Club criteria for the diagnosis of HRS (**Table 1.5**) and underlying mechanisms of ascites formation and HRS are discussed in Chapter 1.
- **Note:** Routine evaluation for causes of AKI other than HRS must be performed in patients with end-stage liver disease. Etiologies relevant to this setting include intra-abdominal hypertension (IAH) (tense ascites with or without peritonitis), concurrent infections or nephrotoxins leading to both kidney and liver failure, and pigmented cast nephropathy (particularly in cases with total bilirubin level >20 mg/dL).
- Urinary biomarkers in AKI and HRS:
  - Urinary NGAL levels have been shown to be much higher in ATN (417 µg/L) compared with prerenal azotemia and HRS (30 and 76 µg/L, respectively). Urinary NGAL measurements may be useful when clinically available.

Subtypes of HRS

1. Type 1: ≥Doubling of initial SCr to >2.5 mg/dL or a 50% reduction of the initial creatinine clearance (CrCl) to <20 ml/min within 2 weeks; type i may occur spontaneously, but frequently occurs in close relationship with a precipitating factor: severe bacterial infection (spontaneous bacterial peritonitis [sbp]), gastrointestinal (gi) hemorrhage, major surgical procedure, or acute hepatitis superimposed on cirrhosis.
2. Type 2: Moderate and stable reduction in GFR. Renal failure does not have a rapidly progressive course; type 2 is thought to represent the extreme expression of renovasoconstriction; dominant clinical feature of type 2: severe ascites with poor or no response to diuretics.

- Incidence: 18% at 1 year; 39% at 5 years
- Prognosis: Renal function rarely spontaneously improves (<5%). median survival without dialysis support for type 1 hrs: 2 weeks; type 2 hrs: 6 months

Management of HRS (Table 11.4)

Table 11.4 Management of hepatorenal syndrome

Category	Specifics	Therapeutic Options[a]
Prophylactic therapies	Spontaneous peritonitis	Prophylactic antibiotic in at-risk individuals
		Albumin infusion in patients who present with SBP
	Acute alcoholic hepatitis	Glucocorticoids Pentoxifylline may reduce HRS, but not survival
Improve hemodynamics	Diversion of portal blood to hepatic vein and central venous circulation to reduce splanchnic blood pooling thereby improving central venous volume	Transjugular intrahepatic portosystemic shunt Limited to patients with less advanced liver disease due to high risk of complications with advanced liver disease
Treatment of HRS	Systemic/splanchnic vasopressors	Terlipressin plus albumin (not available in the United States) Norepinephrine plus albumin Vasopressin plus albumin Midodrine plus octreotide plus albumin Angiotensin II (ongoing study) If positive response, effect is generally seen within 3 days. Consider therapy switch if no response to any selected combination above after 3 days.
	Renal vasodilators	Serelaxin (ongoing studies)
Removal of protein-bound toxins	Albumin dialysis	Molecular Adsorbent Recirculating System Fractionated plasma separation and adsorption Single-pass albumin dialysis
Liver replacement		Liver transplant

[a]See text for specific indications and drug dosing.
Abbreviations: HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis.

Preventive measures to reduce HRS risk

- Prophylactic antibiotic therapy for SBP in at-risk individuals:
  - Short-term prophylactic therapy:
    - Patients hospitalized for GI bleed (ceftriaxone 1 g/d); transition to oral quinolone or trimethoprim–sulfamethoxazole twice daily ×7 days after stabilization
    - Patients hospitalized for other reasons with ascitic total protein <1 g/dl
- Prolonged prophylactic therapy (quinolone or trimethoprim–

sulfamethoxazole double strength daily):
  - Patients with ≥1 episode of SBP
- Patients with cirrhosis and ascitic fluid total protein <10 g/l with child-pugh score >9, serum bilirubin >3 mg/dL, SCr >1.2 mg/dL or blood urea nitrogen (BUN) >20 mg/dL or S[Na^+] <130 mmol/l
- The use of pentoxifylline, a tumor necrosis factor inhibitor, in severe alcoholic hepatitis (AH) may reduce risk of HRS, but not short-term survival. Corticosteroid remains the key therapeutic option. The American College of Gastroenterology does not support the use of pentoxifylline for patients with severe AH based on existing evidence. Severe AH is defined as a Maddrey discriminant function score >32 or model for end-stage liver disease (MELD) score >20.
- Avoidance of nephrotoxins, NSAIDs, and overly aggressive diuresis
  - Albumin infusion for the following conditions:
    - Initial presentation of kidney injury as volume expanding challenge:
      - 1 g/kg/d up to 100 g/d for ≥48 hours
    - At diagnosis of SBP:
      - 1.5 g/kg at diagnosis and 1 g/kg intravenous (IV) 48 hours later
- Large volume paracentesis >4 to 5 L:
  - 6 to 8 g/L of ascitic fluid removed. **Note:** Patients without peripheral edema are at increased risk for circulatory collapse and development of AKI following large volume paracentesis.

Transjugular intrahepatic portosystemic shunt (TIPS)

- Divert portal blood flow to hepatic vein, thereby redistribute portal/splanchnic blood to central volume
- Improve variceal bleed and renal perfusion
- Complications: bleeding, infections, hepatic encephalopathy, kidney failure
- Typically, TIPS is not well tolerated in patients with end-stage liver failure due to high risk for complications above (Child-Pugh class C).

Vasoconstrictors

- Improve short-term mortality (i.e., 15 days), but not beyond

- The International Club of Ascites recommends the use of vasoconstrictors in patients with HRS stage 2 or 3 AKI.
- Therapy with vasoconstrictors may be considered once HRS criteria are fulfilled and no response observed over 48 hours following volume expansion with albumin.
- Clinically available vasoconstrictors:
  - Terlipressin plus albumin:
    - Terlipressin is a synthetic analog of vasopressin-1a receptor agonist. It raises peripheral vascular resistance, hence BP, and decreases portal venous blood flow and hepatic venous pressure gradient. Its use is contraindicated in patients with ischemic cardiovascular disease. *Terlipressin is available in Europe, but not in the United States (not Food and Drug Administration [FDA] approved).*
    - *Dosing:*
      - *Terlipressin 1 mg over 4 to 6 hours infusion, increase to maximum of 2 mg over 4 to 6 hours if SCr decreases by <25% at day 3. Alternatively, terlipressin may be given at 2 mg/d mixed with 250 mL of 5% dextrose water as a continuous infusion. Treatment is maintained until SCr has decreased <1.5 mg/dL.*
      - *Albumin 1 g/kg/d up to 100 g/d on day 1, followed by 20 to 40 g/d; may increase to 40 g daily if central venous pressure (CVP) <12 mm Hg (or plasma renin activity [PRA] not reduced by >50% of basal value after 3 days of treatment)*
- Norepinephrine (NE) plus albumin:
  - *2014 meta-analysis revealed equivalent reversal of HRS with terlipressin as it is a combination of NE and albumin.*
  - *Dosing:*
    - *NE 0.5 mg/h, to increase mean arterial blood pressure (MAP) by ≥10 mm Hg or increase in 4-hour urine output >200 mL. If goals are not met, increase dose every 4 hours in steps of 0.5 mg/h, up to maximum dose of 3 mg/h.*
    - *Albumin dosing as above*
- Vasopressin plus albumin:

- *Dosing:*
  - *Vasopressin 0.01 U/min, increase dose to a maximum of 0.8 U/min to achieve increase in MAP ≥10 mm Hg*
  - *Albumin dosing as above*
  - *Monitor for hyponatremia*
- Combination midodrine (systemic vasoconstriction) plus octreotide (splanchnic vasoconstrictor) plus albumin has been widely used in the United States due to the unavailability of terlipressin. Octreotide is a synthetic analog of the pancreatic hormone somatostatin, a hormone that normally serves as a splanchnic vasoconstrictor by inhibiting glucagon, a splanchnic vasodilator.
  - It should be noted, however, that a randomized trial revealed a lower response rate in patients receiving midodrine/octreotide combination compared to those receiving terlipressin (4.8% vs. 55.6%, $p < 0.01$).
  - Data for comparative efficacy between midodrine/octreotide combination versus NE are not available. Nonetheless, midodrine/octreotide combination is likely inferior to NE because NE has been shown to be comparable in efficacy compared with terlipressin whereas midodrine/octreotide combination has been shown to be inferior to terlipressin.
  - *Dosing:*
    - *Midodrine (systemic vasoconstrictor): start at 7.5 mg orally three times daily (tid), titrate up to 12.5 to 15 mg tid to increase MAP by at least 15 mm Hg plus*
    - *Octreotide (splanchnic vasoconstrictor): start at 100 µg tid subcutaneously, then, if necessary, increase to 200 µg tid plus*
    - *Albumin dosing as above*
- Predictors of response to vasopressors:
  - Baseline serum bilirubin level <10 mg/dl and increase in map ≥5 mm hg
- If positive response, effect is generally seen within 3 days. Therapy switch should be considered if there is no response to any selected combination therapy above after 3 days (e.g., failure to midodrine plus octreotide plus albumin after 3 days should prompt a switch to NE plus albumin or

vasopressin plus albumin).

Renal vasodilators

- Serelaxin: a recombinant form of the human peptide hormone relaxin-2, shown to increase renal blood flow by 65% in a pilot study involving cirrhotic patients. More data are needed.

Albumin dialysis

- An albumin circuit is used to compete for protein-bound toxins not metabolized by the diseased liver.
  - Systems designed with albumin dialysis include Molecular Adsorbent Recirculating System (MARS), fractionated plasma separation and adsorption (Prometheus), and single-pass albumin dialysis.
  - Currently, data suggest improvement with the use of albumin dialysis in hepatic encephalopathy and reduction of bilirubin level, but not survival.
  - Definitive data to support routine use are still lacking.

Liver transplantation

- Currently only cure to end-stage liver disease. The incidence of ESKD following liver transplantation is 7% in patients with HRS versus 2% in those without HRS.
- Prioritization for liver allocation is based on United Network of Organ Sharing (UNOS) MELD Score in Liver Disease (See Appendix A).

IAH leading to abdominal compartment syndrome (ACS)

- Updated consensus definitions and practice guidelines from the World Society of the ACS
  - IAH is defined as sustained intra-abdominal pressure (IAP) ≥12 mm Hg. IAP is measured at end expiration in supine position after ensuring absence of abdominal muscle contractions, with transducer zeroed at level of midaxillary line.
  - ACS is defined as a sustained IAP ≥20 mm Hg and/or abdominal perfusion pressure (APP) <60 mm hg that is associated with new organ dysfunction/failure, where app is defined as

$$APP = MAP - IAP$$

Risks for IAH/ACS

- Diminished abdominal wall compliance: abdominal surgery, major trauma/burns, prone positioning
- Increased intraluminal contents: gastroparesis/gastric distention/ileus, ileus, colonic pseudo-obstruction, volvulus
- Increased intra-abdominal contents: acute pancreatitis, distended abdomen, hemo-/pneumoperitoneum or intraperitoneal fluid collections, intra-abdominal or retroperitoneal tumors, laparoscopy with excessive insufflation pressures, liver dysfunction/cirrhosis with ascites, peritoneal dialysis (PD)
- Capillary leak/fluid resuscitation: acidosis, damage control laparotomy, hypothermia, massive fluid resuscitation or positive fluid balance, polytransfusion
- Others: age, bacteremia, coagulopathy, increased head of bed angle, massive incisional hernia repair, mechanical ventilation, obesity or increased body mass index, positive end-expiratory pressure (PEEP) >10 mm Hg, peritonitis, pneumonia, sepsis, shock or hypotension

Clinical manifestations of IAH/ACS

- Increased IAP with typically tense abdomen
- Increased peak inspiratory pressure, decreased tidal volume (due to abdominal compartment encroaching into thoracic cavity)
- Increased CVP, pulmonary arterial wedge pressure
- Reduced cardiac index (blood pumped against high-pressure abdominal cavity)
- Oliguria (reduced blood flow in renal vein and direct cortical pressure)

Management of IAH/ACS

- If IAP ≥12 mm Hg, begin medical therapy to reduce IAP:
- Measure IAP ≥ every 4 to 6 hours. Titrate therapy to maintain IAP ≤15 mm Hg
- Therapeutic measures to reduce IAP:
  - Evacuate intraluminal contents: nasogastric and/or rectal tube, initiate gastro-/colo-prokinetic agents, minimize or discontinue enteral nutrition,

lower bowel decompression with enemas or even colonoscopy as needed.

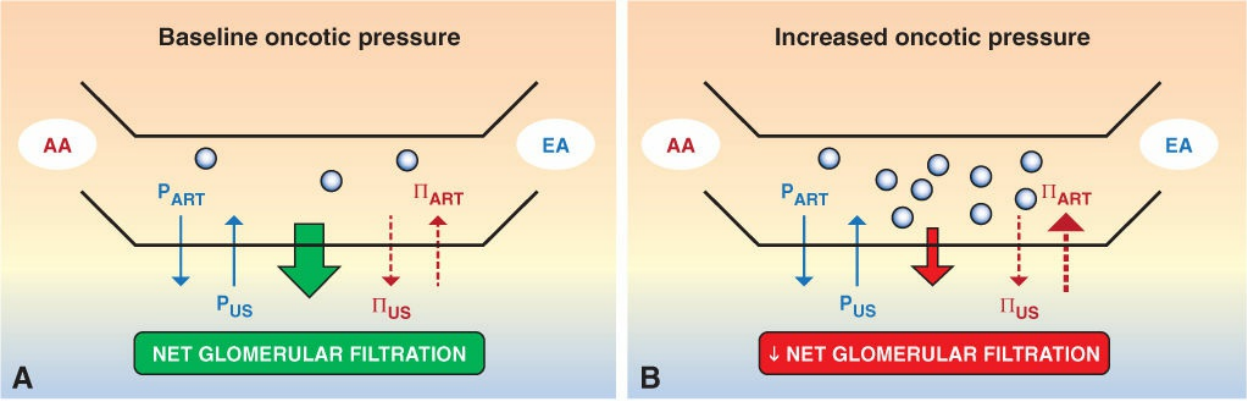
- Evacuate intra-abdominal space occupying lesions or fluids as applicable (e.g., large volume paracentesis if safely tolerated).
- Improve abdominal wall compliance, ensure adequate sedation and analgesia, remove constrictive dressings, consider reverse Trendelenburg position and/or neuromuscular blockade.
- Minimize fluid administration, remove excess fluids with use of diuretics or even ultrafiltration (UF) if necessary, consider hypertonic fluids, colloids.
- Optimize systemic/regional perfusion.
- If IAP >20 mm Hg and new organ dysfunction/failure occurs despite maximal medical intervention, consider surgical abdominal decompression.

Page kidney

- Results from external compression of kidney (e.g., perinephric subcapsular hematoma, lymphocele around transplanted kidney, large simple cyst, retroperitoneal compression)
- Compression of intrarenal vessels leads to renal hypoperfusion, ischemia, activation of the RAAS and associated HTN.
- Treatment: decompression of underlying cause

Hyperoncotic AKI

- This is seen with the rapid infusion of large quantities of osmotically active substances such as mannitol, dextran, and hyperoncotic albumin.
- Glomerular oncotic pressure far exceeds glomerular hydrostatic pressure, resulting in *net* reduction in glomerular filtration, hence oliguric/anuric AKI (**Fig. 11.3**).



Net glomerular filtration (Starling Law) = LpS x (Δ hydraulic pressure – Δ oncotic pressure)
$= LpS \times ([P_{ART} - P_{US}] - s[\pi_{ART} - \pi_{US}])$
Lp is the arteriolar permeability and S is the surface area

FIGURE 11.3 Reduction in net glomerular filtration with rapid increase in intra-arteriolar oncotic pressure. The lower intra-arteriolar oncotic pressure in **(A)** provides a greater net glomerular filtration compared with **(B)** where the higher oncotic pressure drives the force of filtration into the intra-arteriolar space. Abbreviations: AA, afferent arteriole; EA, efferent arteriole; P_{ART}, arteriolar hydraulic pressure; π_{ART}, arteriolar oncotic pressure; P_{US}, urinary space hydraulic pressure; π_{US}, urinary space oncotic pressure.

PARENCHYMAL (INTRINSIC) AKI

Vascular Causes of AKI

Acute intrinsic diseases

- Microangiopathy and hemolytic anemia (MAHA), thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP/HUS), scleroderma, malignant HTN
- Renal vasculitis (**see Chapter 7**)

Large vessel involvement

- Aortic dissection extending into renal artery, renal artery aneurysm
- Systemic thromboembolism

Atheroembolic disease

- May occur spontaneously or following invasive arterial procedure, arteriography, vascular surgery, or thrombolytic therapy
- May occur up to months following inciting event

Presentation

- unexplained fevers, weight loss, myalgias, anorexia, end-organ

infarction/injury occurring weeks to months following inciting event (e.g., stroke, myocardial/bowel/renal infarction, pancreatitis, adrenal failure, muscle infarction)

Diagnosis

- Clinical risk above *plus* classic triad of livedo reticularis, AKI, and eosinophilia
- Fundoscopic examination may be reveal cholesterol emboli, known as Hollenhorst plaque.
- Laboratory findings: leukocytosis, eosinophilia, anemia, thrombocytopenia, elevated BUN, SCr, hematuria, liver function tests, CPK, amylase, inflammatory markers: hypocomplementemia, elevated rheumatoid factor, antinuclear antibody, C-reactive protein, and sedimentation rate

Histopathology

- As cholesterol dissolves during tissue processing, cholesterol crystal embolization is seen as clear needle-shaped structures within vascular lumens or walls, sometimes with surrounding multinucleated giant cells. They may be seen in large or small arteries, arterioles, or capillaries (**Fig. 11.4**).

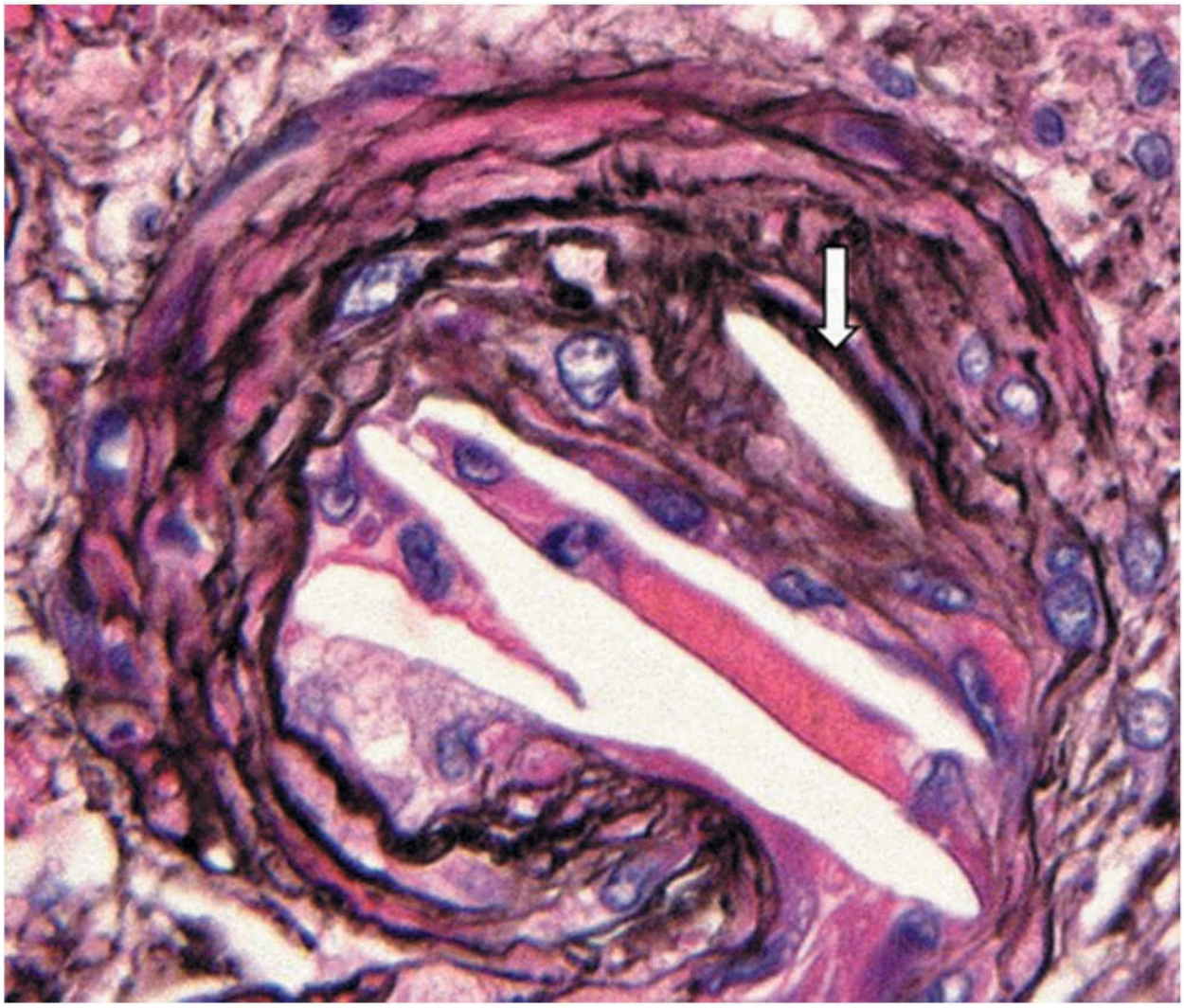


FIGURE 11.4 Atheroembolus. A small artery lumen is occluded by clear needle-shaped crystals (cholesterol) with admixed fibrin indicating recent embolization. There is a smaller cholesterol crystal in the fibrotic interstitium (*arrow*) representing an older lesion (Jones silver ×60).

Management

- Supportive, nutritional support given high catabolic state in these patients
- Avoid further invasive procedures if possible.
- Do not use anticoagulants or thrombolytics due to the possibility of more atheroembolic rupture

Increased renal venous pressure

- Severe right-sided heart failure
- Intra-abdominal compartment syndrome

Renal vein thrombosis (RVT)

Risks

- Severe nephrotic syndrome, most commonly membranous nephropathy, followed by minimal change disease and membranoproliferative glomerulonephritis
- External compression: retroperitoneal fibrosis, lymphadenopathy, tumors, adjacent aneurysm
- Hypercoagulable states
- Others: malignant renal tumors extending into renal vasculature, trauma, hyperacute renal rejection, infections, renal collagen vascular diseases, sickle cell nephropathy, pregnancy, estrogen therapy, amyloidosis, diabetic nephropathy, antiphospholipid syndrome, Behçet syndrome

Clinical manifestations

- Gross or microscopic hematuria, flank pain, AKI, left-sided RVT may lead to gonadal vein thrombosis and cause pelvic congestion in females and left testicular swelling or varicocele in males. Patients with chronic RVT may be asymptomatic.

Diagnosis

- Computed tomography (CT) angiography or contrast-enhanced magnetic resonance venography has reported sensitivity and specificity of nearly 100%. Ultrasound with Doppler may be done but may not be sensitive enough to detect RVT.

Management

- Anticoagulation (unfractionated or low-molecular-weight heparin [LMWH] bridging with warfarin to achieve an international normalized ratio [INR] of 2 to 3) for 6 to 12 months or until underlying inciting etiology has been treated.
- Surgical thrombectomy may be considered in rare cases with acute bilateral RVT and AKI when percutaneous thrombectomy/thrombolysis is not possible.

Glomerular Diseases

Many glomerular and vascular diseases may present with a rapidly

progressive course and AKI. See **Chapter 7**.

Tubulointerstitial Diseases

In addition to the following conditions, also see **Chapter 6** for other tubulointerstitial conditions that may present as AKI.

Heme-pigment–induced AKI (hemoglobin, myoglobin)

- Pathogenesis of AKI associated with heme-pigment–induced AKI:
  - Tubular obstruction, with or without association with uric acid crystals
  - Direct proximal tubular cell injury
  - Vasoconstriction (explains why FeNa may be <1% in patients with hemolysis and rhabdomyolysis)
- AKI risks: volume depletion, low urine pH

Hemolysis

- Causes: ABO-incompatible blood transfusions, G6PD deficiency, poisoning, snake/insect envenomation, drugs (methyldopa, cephalosporins, dapsone, paroxysmal nocturnal hemoglobinuria, malaria)
- Laboratory findings: reduced haptoglobin, increased lactate dehydrogenase (LDH) and bilirubin, increased reticulocytes and spherocytes, hyperkalemia

Rhabdomyolysis

- Causes: trauma (crush injury, electric shock), immobilization (particularly morbidly obese patients), prolonged vascular/orthopedic surgery, extreme exertion (exacerbated by heat, underlying metabolic/inflammatory myopathies), seizures, neuroleptic malignant syndrome, alcoholism (particularly if concurrent electrolyte abnormalities, e.g., hypophosphatemia, hypokalemia, hypomagnesemia), drugs/toxins, infections (HIV, influenza, Legionella), myositis associated with rheumatologic disorders, ischemic muscle injury, familial disorders
- Diagnosis:
  - Myalgias
  - Elevated CPK

        - Levels <5,000 u/l: aki uncommon
        - Levels >40,000 U/L may be associated with severe AKI.
    - Reddish-brown urine due to myoglobinuria (Reddish-brown urine can be due to myoglobinuria, hemoglobinuria, hyperbilirubinemia, or agents with reddish brown–coloring effect such as beets, phenazopyridine, porphyria.)
    - Centrifuged urine:
        - Red sediment → hematuria
        - Red supernatant → myoglobinuria *or* hemoglobinuria *or* agents with coloring effect (see examples above)
    - Heme dipstick (presence of "blood" on urine dipstick):
        - Positive myoglobinuria or hemoglobinuria
        - Negative (agents with coloring effect)
- Plasma color:
    - Clear: myoglobinuria (due to its low molecular weight, myoglobinuria is easily filtered and does not remain/accumulate in plasma)
    - Red/pink: hemoglobinuria (high molecular weight, binds to haptoglobin, not easily filtered, remains in plasma as red/pink color). Hemoglobinuria suggests high plasma hemoglobin concentration.
- Complications of rhabdomyolysis:
    - Electrolyte abnormalities: hyperkalemia (potassium levels may increase by >1.0 vs. 0.3 mmol/L/d from baseline compared with other nonhypercatabolic AKI), hyperphosphatemia (release from injured muscle cells), hypocalcemia (due to calcium phosphate deposition into injured muscles, reduced bone sensitivity to parathyroid hormone), hyperuricemia, and metabolic acidosis
    - Transaminitis (elevated intramyocyte aspartate aminotransferase [AST], alanine aminotransferase [ALT], LDH, and aldolase) in rhabdomyolysis, but not in hemolysis
    - AKI
- Management:
    - Early and aggressive volume administration:
        - Start normal saline at 100 to 200 mL/h. If good diuresis, aim for goal

urine output 200 to 300 mL/h. Monitor volume status.

- Theoretical benefits of normal $NaHCO_3$ over NaCl solutions:
  - If urine pH raised to >6.5, renal toxicity from heme may be reduced.
  - Reduced pigment cast formation of heme-protein with Tamm–Horsfall proteins
  - Reduced release of free iron from myoglobin
  - Despite theoretical benefits above, there is no clear clinical evidence of benefits of $NaHCO_3$ over NaCl, except possibly in severe rhabdomyolysis.
  - In general, sodium $NaHCO_3$ infusion should be avoided in patients with hypocalcemia, hypokalemia, existing CO_2 retention (chronic obstructive pulmonary disease [COPD] patients), or markedly elevated calcium × phosphorus product.

- Benefits of mannitol remain undefined and not routinely recommended.
- Loop diuretics do not change outcome in AKI. Use in volume overload only.
- Benefit of dialysis to remove myoglobin, hemoglobin, or uric acid has not been shown.

Hyperbilirubinemia

- Severe hyperbilirubinemia (serum bilirubin levels >20 mg/dL) has been reported to be associated with ATN, with bile granules in tubular epithelial cells and bile thrombi in tubules. Kidneys appear green on autopsies.

Hypercalcemia

- May be associated with AKI
- Mechanisms attributable to AKI include volume depletion (nephrogenic diabetes insipidus), calcium phosphate/oxalate precipitation and microtubular obstruction, tubulointerstitial nephritis, and intrarenal vasoconstriction and reduced renal perfusion.

Radiocontrast-induced AKI (CI-AKI)

Pathogenesis

- Medullary hypoxia (radiocontrast induces vasoconstriction of both afferent

and efferent arterioles, but greater effect in afferent arterioles)
- Direct cytotoxicity
- Generation of reactive oxygen species

Histopathology

- Poximal tubular cell isometric vacuoles

Risks

- Mehran risk score may be calculated based on the following factors: hypotension, intra-aortic balloon pump, CHF, age >75 years, anemia, DM, contrast media volume >100 mL, reduced GFR
- Well-controlled DM with normal kidney function likely does not increase risk of CI-AKI.

Prevention is *key*

- Use of nonionic low or iso-osmolal agents:
  - Low-osmolal nonionic agent: iohexol, ioxaglate
  - Iso-osmolal (~290 mOsm/kg) nonionic agent: iodixanol
  - Controversy: Iso-osmolal iodixanol may be better than low-osmolal iohexol among patients with DM and CKD, but not better than other low-osmolal agents.
  - It is possible that iohexol has specific adverse effect on kidneys and not necessarily the “low-osmolal” effect.
  - KDIGO recommends the use of low-osmolal or iso-osmolal rather than high-osmolal contrast agents. Current evidence is not reliable to preferentially recommend one agent over the other.
- Use of carbon dioxide as alternative contrast agent:
  - Satisfactory imaging
  - Risk of neurotoxicity if injected close to cerebral circulation or presence of right-to-left intracardiac shunt
  - Use of carbon dioxide as contrast agent is limited to below diaphragm imaging.
- Use of magnetic resonance imaging with gadolinium:
  - Concerns for the development of nephrogenic systemic fibrosis

- Possible nephrotoxicity has been reported.

- Hydration:
  - Normal saline or isotonic sodium bicarbonate: 3 mL/kg over 1 to 2 hours prior to contrast study, followed by 1 mL/kg/h × 6 to 12 hours postcontrast— assuming patient can tolerate volume expansion
  - POSEIDON trial: Left ventricular end diastolic pressure-guided fluid administration among patients undergoing cardiac catheterization lowered the risk of CI-AKI.
  - Rationale for bicarbonate over normal saline hydration: added protection against free radical injury
    - Meta-analysis only revealed trend for better outcome.
    - Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial 2018:
      - N = 5,177 patients at high risk for CI-AKI, 2 × 2 factorial design where patients were randomized to receive either IV 1.26% sodium bicarbonate or 0.9% saline IV and either oral acetylcysteine or oral placebo
      - No benefit for either sodium bicarbonate or acetylcysteine
  - Fluid tonicity: Isotonic is preferred over one-half isotonic saline.
  - Outpatient oral hydration: Salt-containing fluids likely better than water.
  - No or undefined benefit and potentially harmful agents/therapy and *not* recommended: diuretics, mannitol, dopamine, atrial natriuretic peptide (ANP)
- Hemofiltration, hemodialysis for the sole indication of CI-AKI prevention:
  - In patients on established dialysis: Any benefit for immediate dialysis (i.e., within 24 hours of contrast exposure) versus waiting for next regularly scheduled dialysis treatment is unclear.
  - In pre-ESKD patients, dialysis initiation for the sole indication of CI-AKI is not recommended.
- In patients with CHF: Optimize cardiac function. If volume overload, continue diuretics to improve cardiac contractility, hence cardiac output.
- Ongoing use of ACEI/ARB in *stable* patient: Discontinuation may be beneficial.

- Acetylcysteine (Mucomyst):
  - Has antioxidant and vasodilatory properties
  - Benefits unproven—see PRESERVE trial above
- Inhibition of renal vasoconstriction (inadequate data or unproven benefit):
    - Theophylline, iloprost, fenoldopam, nonselective endothelin receptor antagonist
- Remote ischemic preconditioning (RIPC):
  - Deliberate induction of transient nonlethal ischemia to an organ (e.g., inflating BP cuff to 50 mm Hg above patient's SBP × 4 cycles of 30-second on/off duration) to activate systemic vasodilatory response/release of vasodilators such as nitric oxide to protect other ischemic organs (e.g., kidneys exposed to radiocontrast)
  - Initial small studies in patients undergoing elective coronary angiography and percutaneous coronary intervention (PCI) suggested benefits in reducing risk of CI-AKI as well as short-term rehospitalization and death. Two studies in 2018 revealed conflicting data. More data are needed prior to recommendation for routine use.
- Atrial natriuretic peptide (ANP):
  - Available data suggest *no* benefit compared to placebo. It is possible that negative result was due to short duration of treatment (30 minutes pre and 30 minutes post).
  - A larger prospective, controlled, randomized trial of 254 patients with SCr ≥1.3 mg/dL receiving either ANP (0.042 mg/kg/min vs. Ringer solution alone) for 4 to 6 hours prior to angiography and continued for 48 hours, the incidence of CI-AKI (defined as ≥25% or ≥0.05 mg/dL increase in SCr within 48 hours) was reduced in treatment group (3.2% vs. 11.7%). Confirmatory studies are still needed.
- Statins:
  - Rationale: Statins have anti-inflammatory and antioxidant properties. Statins also improve endothelial function and reduce endothelin-induced arterial vasoconstriction.
  - 2015 meta-analysis of short-term, high-dose statin revealed benefit in prevention of CI-AKI in patients undergoing cardiac angiography.

- Recommendation: reasonable to start statins in patients who will need statins, but not everyone
- Ascorbic acid: insufficient data to support use
- Forced diuresis: likely increases risk of CI-AKI and is not recommended
- Avoid NSAIDs, nephrotoxins

Tumor lysis syndrome (TLS)

- Associated with high cellular turnover following chemotherapy for large tumor burdens
- May be spontaneous due to high cellular proliferation and rapid cellular turnover

Risks

- High-risk malignancies:
  - Advanced Burkitt lymphoma/leukemia or early disease with elevated baseline LDH
  - Acute lymphocytic leukemia (ALL) (WBC >10,000/mL or LDH ≥two times upper limit of normal [ULN])
  - Acute myeloid leukemia (AML) (WBC > 10,000/mL)
  - Diffuse large B-cell lymphoma with baseline LDH ≥two times ULN
- Elevated LDH level (i.e., ≥two times ULN) prior to treatment
- Reduced kidney function prior to treatment

Diagnosis of TLS (Table 11.5)

Table 11.5 Diagnosis of tumor lysis syndrome

Criteria for Laboratory TLS Having ≥2 of the Following	Clinical Criteria for TLS
Hyperuricemia: uric acid ≥8 mg/dL or ≥25% increase from baseline	Meeting laboratory criteria *plus*
Hyperkalemia: potassium ≥6 mmol/L or ≥25% increase from baseline	One or more of associated complications involving AKI, cardiac arrhythmias (due to severe hyperkalemia and/or hypocalcemia), seizures, or death
Hypocalcemia: calcium 7 mg/dL or ≥25% decrease from baseline	
Hyperphosphatemia: phosphorus	

>6.5 mg/dL or >25% increase from baseline	

Abbreviations: AKI, acute kidney injury; TLS, tumor lysis syndrome.

- Criteria for laboratory TLS: ≥2 of the following:
  - Hyperuricemia: uric acid ≥8 mg/dL, or ≥25% increase from baseline
  - Hyperkalemia: potassium ≥6 mmol/L, or ≥25% increase from baseline
  - Hyperphosphatemia: phosphorus >6.5 mg/dL, or ≥25% increase from baseline
  - Hypocalcemia: calcium <7 mg/dl, or ≥25% decrease from baseline
- Criteria for clinical TLS:
  - Meeting laboratory criteria above *plus*
  - One or more of associated complications involving AKI, cardiac arrhythmias (due to severe hyperkalemia and/or hypocalcemia), seizures, or death

Etiologies of AKI associated with TLS

- Hyperuricemia:
  - Tubular obstruction from uric acid crystallization
  - Uric acid–induced inflammatory response, ATIN
  - Uric acid–induced renal vasoconstriction
- Hyperphosphatemia: tubular obstruction from calcium oxalate crystals

Management of TLS

- Prevention is *key*:
  - Volume expansion with crystalloid solutions
  - **Note**: Urinary alkalinization to increase uric acid solubility is *no longer* routinely recommended due to:
    - Inability to increase xanthine solubility (purine metabolite that may also precipitate and cause tubular obstruction) and
    - Increased risk for metabolic alkalosis and calcium phosphate precipitation
  - Dietary potassium and phosphorus restriction
  - Renal replacement therapy as needed
  - Management of hyperuricemia:

- Purine metabolites of nucleic acids are converted to uric acid via a multistep process requiring the enzyme xanthine oxidase (*XO*) (**Fig. 11.5**).

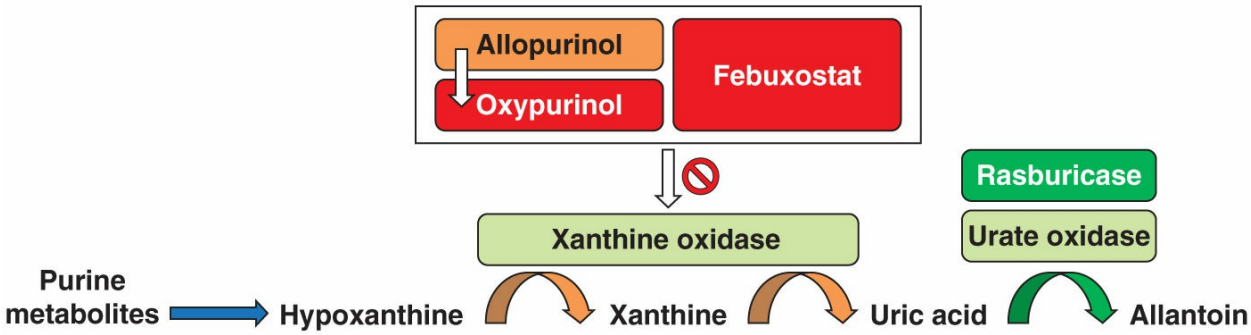


FIGURE 11.5 Metabolism of purine metabolites. Purine metabolites of nucleic acids are metabolized to uric acid via a multistep reaction requiring the enzyme xanthine oxidase. Allopurinol is converted to oxypurinol, a competitive inhibitor of *xanthine oxidase* to decrease downstream uric acid formation. Febuxostat is a nonpurine *xanthine oxidase* inhibitor that also acts to reduce downstream uric acid formation. Both allopurinol and febuxostat are *not* effective in reducing preexisting uric acid. Rasburicase is a recombinant form of urate oxidase that can convert uric acid into the more soluble metabolite allantoin, which can be renally excreted.

- Allopurinol is converted to oxypurinol, a competitive inhibitor of *XO* to decrease uric acid formation. Allopurinol can reduce uric acid production, but cannot reduce *preexisting* hyperuricemia.
- Febuxostat is a nonpurine *XO* inhibitor that is commonly used for the treatment of hyperuricemia associated with gout. A 2019 meta-analysis involving 658 patients revealed similar efficacy to allopurinol in terms of lowering uric acid level and tumor lysis incidence. Of note, febuxostat has the warning label: “Gout patients with established cardiovascular (CV) disease treated with febuxostat tablets had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study.”
- Rasburicase: recombinant form of urate oxidase, converts uric acid to the more soluble metabolite, allantoin, which can be renally excreted
  - **Note:** Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase and catalase deficiencies due to the development of hemolytic anemia and methemoglobinemia.
  - Rasburicase is associated with hypersensitivity (including

anaphylaxis) in 1% of patients.

- Rasburicase effectively reduces hyperuricemia but has not been shown to reduce the incidence of clinical TLS.

Hematopoietic stem cell transplant (HCST)–associated AKI

- Associated complications: veno-occlusive disease involving liver, hepatic failure, and HRS
- Higher risk in association with myeloablative compared with nonmyeloablative therapy
- Management: supportive care

Viral-associated AKI

- Hantavirus infection (most commonly subtype Puumala) is associated with flu-like symptoms and acute kidney failure: Reported biopsy findings include tubulointerstitial nephritis, hemorrhage into medullary tissues, interstitial edema, and tubular cell necrosis. Podocyte effacement in association with glomerular proteinuria has been described.
- H1N1 influenza A: AKI is common and predominantly associated with ATN and/or rhabdomyolysis. The latter is typically mild and does not cause AKI. AKI requiring RRT has been reported to be ~20%.
- COVID-19: AKI is most commonly due to severe ATN with or without rhabdomyolysis-associated kidney injury. Collapsing FSGS has also been reported. Other etiologies including acute tubulointerstitial disease, vasculitis, and thromboembolic complications may be possible.

AKI related to pregnancy (Table 11.6)

Table 11.6 Pregnancy-related acute kidney injury

Time of Onset	First Trimester	Second to Third Trimesters			Third Trimester	Postpartum
History of Present Illness						
Signs and symptoms	**Intractable N/V in the first trimester with inadequate fluid intake**	Onset >20 wk **Epigastric or RUQ pain, N/V, HA, blurred vision, sudden-onset edema**	Chest pain, RUQ pain, N/V, HA	± Fevers, HA ± Altered mental status, ± neurologic symptoms	Malaise, N/V, abdominal pain	May occur up to 6 mo **postpartum**;
Physical Examination						
Vital signs	± ↓BP, ± ↑heart rate	**↑BP >> 140/90 mm Hg**	± ↑BP	± ↑BP, ± fever	± ↑BP	↑BP
Examination findings	Dry oral mucosa	**++ Peripheral, pulmonary edema** ± Neurologic deficits, ± Seizures	± Ecchymosis, ± Jaundice	± Neurologic deficits, ± Seizures	Hepatic encephalopathy, **Jaundice, ascites**	± Edema (associated with kidney failure)
Laboratory Findings						
Complete blood count and peripheral smear	± ↑Hb, no schistocytes	± ↓Hb, ± schistocytes, ± ↓platelets	↓Hb, ±schistocytes, ↓↓**Platelets 100 × 10^3 cells/mm^3**	↓Hb, ± schistocytes, ↓↓**Platelets**	↑WBC, ± ↓Hb, typically no schistocytes ± ↓Platelets	↓Hb, ± schistocytes, ↓↓**Platelets**
Chemistry	↑BUN/SCr ratio	± ↑SCr, ↑Uric acid	± ↑SCr	± ↑SCr	Hypoglycemia, ± ↑SCr	↑↑SCr
Lactate dehydrogenase	Normal LDH	± ↑LDH	**LDH > 600 U/L**	**↑LDH**	± ↑LDH	**↑LDH**
Coagulation studies	Normal	± ↑PTT, ± ↓fibrinogen, and ± ↑FDP (±DIC)	± ↑PTT, ± ↓fibrinogen, and ± ↑FDP (±DIC)	**Normal PTT, fibrinogen, and FDP**	**↑PT, ↓fibrinogen, ↓Antithrombin III**	**Normal PTT, fibrinogen, and FDP**
Liver function tests	Normal	± Transaminitis	**++Transaminitis, ALT > 70 U/L**	± Transaminitis	**++Transaminitis, ↑Bilirubin**	± Transaminitis
Urinalysis	↑SG, hyaline or muddy-brown casts	± Proteinuria	± Proteinuria	± Blood, ++ proteinuria	± Proteinuria, ++ Bilirubin ± pigmented, casts	+ Blood, ++ proteinuria
[a]ADAMTS-13	Normal	Normal to low	Normal to low ADAMTS-13	**<10%**	Normal	Normal to low
Assessment and Plans						
Diagnosis	Volume Depletion: Hyperemesis Gravidarum	Preeclampsia/ Eclampsia	[b]**H**emolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets (HELLP)	Thrombotic Thrombocytopenic Purpura (TTP)	Acute Fatty Liver of Pregnancy (AFLP)	[c]Atypical Hemolytic Uremic Syndrome (aHUS)
Management	IVF, antiemetics	Delivery	Delivery	PLEX	Delivery	Eculizumab
Prognosis	Good	Good	Good	Good	Good	High risk for ESKD

[a]A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13

[b]Typically third trimester; second trimester; and postpartum possible; may complicate 20% of women with PE/E

[c]May be triggered by infections or bleeding; Nonspecific, N/V, ↓Urine output

Note: Each column lists classic signs and symptoms over the course of pregnancy and corresponding physical examination findings, laboratory findings, likely diagnosis, and treatment. Classic findings for each condition are bolded.

Abbreviations: ALT, alanine aminotransferase; BP, blood pressure; BUN/SCr ratio, blood urea nitrogen to serum creatinine ratio; DIC, disseminated intravascular coagulation; FDP, fibrinogen degradation products; HA, headache; Hb, hemoglobin; LDH, lactate dehydrogenase; N/V, nausea, vomiting; PLEX, plasma exchange; PT, prothrombin time; PTT, partial thromboplastin time; RUQ, right upper quadrant; SCr, serum creatinine; SG, specific gravity; WBC, white blood cells count.

Early before 20 weeks' gestational age

- Volume depletion due to hyperemesis gravidarum with poor oral intake, septic abortion

After 20 weeks to postpartum

- Bleeding (e.g., placenta abruption), preeclampsia/eclampsia (PE/E), HELLP (**H**emolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets), TTP, acute fatty liver of pregnancy (AFLP), pregnancy-associated atypical HUS (aHUS), renal cortical necrosis, obstructive uropathy, recurrence/relapse of underlying glomerular diseases

Preeclampsia/eclampsia

- Pathogenesis of preeclampsia:
  - What happens in normal pregnancy:
    - Circulating vascular endothelial growth factor (VEGF) and transforming growth factor β1 (TGF-β1) bind to their respective receptors VEGFR and TGFR on endothelial cell surface to maintain endothelial health in the kidneys and placenta.
  - What happens in preeclampsia/eclampsia:
    - There is excessive placental secretion of soluble fms-like tyrosine kinase 1 (sFLt1) and soluble truncated endoglin (sEng) that bind to circulating VEGF and TGF-β1, respectively. The lowering of free VEGF and TGF-β1 levels in circulation leads to suboptimal maintenance of endothelial health.
    - This results in endothelial cell dysfunction, decreased prostacyclin and nitric oxide production, and release of procoagulant protein.
    - In addition, proangiogenic factors such as placental growth factor (PlGF) and adiponectin are decreased, whereas antiangiogenic factors such as endostatin are increased.
    - Histopathology (**see Chapter 5; Fig. 5.4.**): Glomerular tufts are described as "bloodless"; capillary lumina are narrowed due to endothelial cell swelling, referred to as "endotheliosis." In contrast, capillary loops are wide open in normal glomeruli. Foam cells with lipid vacuoles may also be seen in this condition.
  - Preeclampsia and future risk of cardiovascular disease: Meta-analyses suggest an increased cardiac risk, albeit small absolute risk.
    - Association may be related to risk factors common to both preeclampsia and cardiovascular disease (e.g., obesity, glucose intolerance, high BP, kidney disease).

        - Diffuse endothelial injury occurring during preeclampsia may contribute to increased risk.
- Clinical manifestations:
    - Presents after 20 weeks of gestation
    - Presence of new HTN plus sudden-onset edema plus symptoms of epigastric/right upper quadrant pain, nausea/vomiting, blurry vision
- Diagnostic criteria for preeclampsia:
    - SBP ≥140 and diastolic BP ≥90 mm Hg *and*
    - Proteinuria ≥300 mg/d or UPCR ≥0.3 g/g *or*
    - If no proteinuria, new onset of any of the following:
        - Platelet count <100 × 10^3/μl, scr >1.1 mg/dL or doubling of SCr in the absence of other known kidney disease, transaminitis >2× ULN, pulmonary edema, cerebral or visual symptoms (new onset and persistent headaches, blurred vision, flashing lights)
- Preventive measures:
    - Initiate low-dose aspirin 81 mg after 12 weeks of pregnancy, preferably prior to 16 weeks, and continue until delivery for women with high risk for preeclampsia.
    - High preeclampsia risks: chronic HTN or kidney disease prior to pregnancy, obesity, women >40 years of age, multiple gestation, African American ethnicity, family history or preeclampsia, history of preeclampsia and preterm delivery at <34 weeks, history of preeclampsia in ≥2 pregnancies
- Management:
    - BP management (see **Chapter 5**)
    - IV magnesium (Note that calcium channel blockers [CCBs] and magnesium have synergistic hypotensive effect. In the case of hypotension associated with combined CCB and magnesium, administer IV calcium.)
    - Delivery; expectant management may be considered in milder forms of preeclampsia with goal of prolonging pregnancy to full term at 37 weeks.

Hemolysis, Elevated Liver enzymes, Low Platelets (HELLP)

- Pathogenesis: thought to be a variant of PE/E
- Clinical manifestations: headaches, chest pain, right upper quadrant abdominal pain, laboratory findings notable for hemolytic anemia, thrombocytopenia (platelet count < 100×10^3 cells/mm^3), transaminitis (alt > 70 U/L), and/or AKI. Twenty percent of patients with HELLP do not have either HTN or proteinuria, and 20% of women with severe PE/E are complicated with HELLP.
- Management: delivery

Thrombotic thrombocytopenic purpura (TTP)

- Pathogenesis: During normal pregnancy, ADAMTS-13 level (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) tends to be decreased during the last trimester, whereas von Willebrand factor level is increased. Individuals with low but clinically adequate ADAMTS-13 levels in the nonpregnant state may be at risk for TTP during the second and third trimesters of pregnancy.
- Clinical manifestations: fevers, headaches, altered mental status, neurologic symptoms, and/or seizures; laboratory findings: thrombotic microangiopathy, thrombocytopenia, elevated LDH, normal partial prothrombin time and fibrinogen, reduced ADMTS-13 activity <10%, and/or aki
- Management: plasma exchange

Acute fatty liver of pregnancy (AFLP)

- Pathogenesis: Fetal deficiency of long-chain 3-hydroxyl coenzyme A dehydrogenase leads to excess fetal free fatty acids that cross the placenta and induce maternal hepatotoxicity.
- Clinical manifestations: anorexia, nausea, vomiting, ascites; laboratory findings notable for marked transaminitis, coagulopathy, hypoglycemia, and/or AKI. There is no hemolytic anemia.
- Management: delivery; supportive care; correction of coagulopathy with infusions of fresh-frozen plasma (FFP), blood, or cryoprecipitate as needed; monitor and treat hypoglycemia

Atypical HUS (aHUS)

- Pathogenesis: thought to be due to the loss of placental regulatory proteins that normally protect against alternative complement activation (ACP). Susceptible individuals are those who have mutations of complement regulatory proteins factor H, factor I, C3, and/or membrane cofactor proteins. Inciting events for ACP and subsequent aHUS of pregnancy have been suggested to include bleeding and infectious complications with delivery.
- Clinical manifestations: postpartum hemolytic anemia, thrombocytopenia, normal partial prothrombin and fibrinogen, AKI
- Management: eculizumab (humanized monoclonal anti-C5 antibody)
- Prognosis: 70% to 80% of pregnancy-associated aHUS develop ESKD.

Other pregnancy-associated etiologies of AKI

- Obstruction:
  - Late pregnancy: The enlarged uterus may compress on the ureters to cause obstruction. This may be evident by ultrasound in the first trimester and typically involves the right kidney. This is an uncommon cause of AKI but if AKI occurs, renal recovery occurs within 2 to 3 weeks postpartum. Advise positional changes with sleeping.
  - Postpartum: consider injury of soft tissues surrounding the urethra or urethra itself with marked inflammation and resultant obstruction of urine flow
- Acute bilateral renal cortical necrosis:
  - Associated with severe hypotension
  - Clinical manifestations: oliguria or persistent anuria
  - Diagnostic imaging: Pericortical rim due to infarction may be seen on CT.
  - Histopathology: There is a complete loss of nuclei in affected glomeruli and tubules while the underlying connective tissue framework is still preserved.
- Other common etiologies not related to pregnancy should also be ruled out. Although rare, peripartum cardiomyopathy may be considered if clinically indicated.

Dialysis in pregnancy

- Early start is recommended (i.e., eGFR < 20 ml/min/1.73 m^2).
- High dialysis dose: Daily dialysis should be performed with duration of at least 20 h/wk.
- Maintain BUN <50 mg/dl.
- Maintain narrow physiologic range of electrolytes in dialysate: bicarbonate 25 mmol/L and sodium 135 mmol/L.

POSTRENAL AKI

Definitions

- Obstructive uropathy refers to structural or functional changes in the urinary tract that adversely affect urine flow. Obstruction may be complete or partial and may involve upper or lower collecting system and unilateral or bilateral systems.
- Obstructive nephropathy refers to kidney injury due to impaired urine flow.

Etiologies of Postrenal AKI

Intrinsic causes

- Stones/calculi (kidney or bladder), transitional cell carcinoma, blood clots, sloughed papillae from papillary necrosis (e.g., excessive NSAIDs, sickle cell disease, diabetics, renal tuberculosis), fungus balls, intratubular obstruction from drug crystallizations (e.g., acyclovir, sulfonamides, ciprofloxacin, sulfadiazine, ethylene glycol, methotrexate, indinavir, triamterene), calcium phosphate precipitation (e.g., from high phosphate-containing enemas), oxalate crystals, light-chain deposits, debris
- Warfarin-related kidney injury: Mechanisms thought to be related to RBC casts, causing renal tubular obstruction. Risks: older age, DM, HTN, cardiovascular disease, over-anticoagulation with, INR >3

Extrinsic causes

- Malignancy (particularly female pelvic malignancies, GI malignancies, retroperitoneal fibrosis), prostate hypertrophy or malignancy, pregnancy
- Retroperitoneal fibrosis:

- Thought to arise from exaggerated local inflammatory response to aortic atherosclerosis, tissue injury, or autoimmune disease (e.g., immunoglobulin G4 [IgG4]–related disease)
- Etiologies: idiopathic, drug induced (e.g., ergot derivatives, methysergide, bromocriptine, β-blockers, methyldopa, hydralazine, analgesics), infections, malignancies, prior surgeries or retroperitoneal hemorrhage, radiation therapy, smoking, asbestos exposure
- Clinical manifestations: nonspecific back pain, abdominal pain, or lower flank pain that may radiate to inguinal area (testicular pain/lymphocele), nonspecific constitutional symptoms of malaise, weight loss, fevers, nausea/vomiting, constipation, symptoms associated with mesenteric ischemia, upper leg claudication, lower extremity phlebitis or deep vein thrombosis (DVT), new-onset HTN, elevated erythrocyte sedimentation rate or C-reactive protein levels, AKI due to obstructive uropathy and/or ATIN associated with IgG4-related disease
- Diagnosis: CT scan (may be seen as mass encasing anterior and lateral sides of aorta, often also encasing and compressing inferior vena cava [IVC], thus tendency for DVT), tissue biopsy (particularly to rule out underlying infections/malignancy/IgG4-related disease)
- Management: relief of obstruction (e.g., ureteral stenting, nephrostomy, anti-inflammatory medical therapies such as corticosteroids)

- Collecting system malformations or strictures: phimosis, meatal stenosis, urethral or ureteral strictures from recurrent infections, manipulations

Functional obstruction

- Diabetic neurogenic bladder

- Large output urine volume that overwhelms the patient's ability to void may be seen in, severe diabetes insipidus
- Drugs that can lead to neurogenic bladder:
  - Anticholinergics (tricyclic antidepressants, diphenhydramine): reduce bladder detrusor muscle contraction
  - NSAIDs: inhibit prostaglandin-mediated detrusor muscle contraction
  - Sympathomimetics: α-Adrenergic agents increase tone in prostate and

bladder neck.

Transplant setting

- Ureteral strictures due to trauma, ischemia, or BK virus infection
- External compression by lymphoceles
- Bladder dysfunction (i.e., small shrunken bladder from prolonged anuria)

Pathogenesis of Obstructive Kidney Injury

- Urinary obstruction leads to increased intratubular pressure, which opposes and reduces glomerular filtration. The reduced filtration pressure leads to local renal vasoconstriction, a process mediated by AII and thromboxanes.
- Subsequently, there is an influx of inflammatory cells and synthesis and release of TGF-β, inflammatory cytokines, proteases, and oxygen-free radicals, all acting to induce local tissue injury and fibrosis.
- Histopathology may reveal tubulointerstitial fibrosis, tubular atrophy, and glomerulosclerosis.

Clinical Manifestations of Obstructive Uropathy

- Reduced urine output: partial reduction versus anuria:
  - Anuria: consider lower tract obstruction (bladder neck or urethral obstruction), clotted Foley catheter, bilateral ureteral (papillary necrosis, large tumors)
  - **Note:** Having a "good" urine output does not necessarily imply absence of obstruction. Patient may still have a partial obstruction.
- Pain, HTN, sensation of incomplete voiding, suprapubic tenderness or fullness, sometimes with mass-like effect from distended bladder, frequency, nocturia, overflow incontinence

Laboratory Findings of Obstructive Kidney Injury

- Elevated SCr unless unilateral obstruction in the setting of normal kidney function in contralateral kidney
- Hyperkalemia, metabolic acidosis out of proportion to the degree of kidney injury. This is essentially a form of distal renal tubular acidosis (see Renal Tubular Acidosis in **Chapter 2**).

- Elevated BUN-to-creatinine ratio may be seen due to tubular reabsorption of urea with urinary stasis.
- Urinary studies: microscopic hematuria, pyuria (may be sterile), stones/crystalluria, necrotic papillary tissues

Diagnostic Imaging Studies for Obstructive Uropathy

- Ultrasound: inexpensive, readily available
  - False positive in up to one-fourth of cases as hydronephrosis can be present in the absence of obstruction.
  - False negative for obstruction may be seen in severe volume depletion, oliguric state, as seen in severe ATN, retroperitoneal fibrosis.
- CT urogram:
  - Avoid in childbearing age women due to radiation exposure
  - Consider study if suspicious for obstructing kidney stones or stones in patients with polycystic kidney disease
- Magnetic resonance imaging with or without gadolinium:
  - No radiation exposure
  - Poor visibility for stones
  - No gadolinium if eGFR <30 ml/min/1.73 m^2
- Interpretation of common findings
  - Parenchymal (cortical thickness): Thinning implies long-standing obstruction, hence poor recovery potential.
  - Ureteral obstruction with an empty bladder indicates obstruction at the ureteral orifice or more proximal segments.
  - Hydronephrosis in patients with a ureteral stent in the presence of a full bladder does not necessarily imply obstruction because the pressure from the full bladder can be transmitted up to the kidneys via the ureteral stent.
  - Doppler imaging showing “ureteral jets” typically implies ureteral patency. Absence of ureteral jets, however, does not rule in obstruction.

Management of Obstructive Kidney Injury

Relief of obstruction

- Removal of source of obstruction if possible
- Foley insertion for bladder neck obstruction; ureteral stenting for ureteral obstruction; nephrostomy placement for obstruction proximal to proximal ureters
- Removal of extrinsic compression (e.g., treatment of malignancy, evacuation of compressing lymphocele)

Correction of functional obstruction

- Discontinue responsible medications
- Use of α-adrenergic blockers in diabetic neurogenic bladder
- Treat diabetes insipidus if etiologic

Postobstructive diuresis

- Causes of postobstructive diuresis:
  - Excessive fluid administration
  - Appropriate diuresis of accumulated sodium/water retention during kidney failure
  - Osmotic diuresis from accumulated urea, other toxins/solutes during kidney failure
  - Obstruction induced tubular dysfunction and nephrogenic diabetes insipidus (may be transient or chronic)
  - Increased ANP during obstructive period
  - Delayed tubular function recovery relative to glomerular filtration recovery. The filtered sodium and water cannot be adequately reabsorbed by the recovering tubules.
- Typical fluid replacement: ½ mL of fluid for every milliliter of urine output above 100 mL/h with ½ normal saline; Oral fluid replacement may be adequate in mild cases
- Monitor serum potassium and magnesium levels and replete as needed

Prognosis of Obstructive Kidney Injury

- Depends on duration, severity, preexisting CKD, and kidney mass affected (i.e., one or two kidneys involved)
- Functional recovery typically occurs by 7 to 10 days following relief of

obstruction. Recovery may take longer in more severe and prolonged cases.

MANAGEMENT OF AKI

In general, the management of AKI relies on prevention, prompt removal or correction of contributing factors, optimization of hemodynamics, and avoidance of potential nephrotoxins.

AKI Prevention in Surgical Setting

Cardiac surgery, coronary artery bypass grafting (CABG)

Causative factors for AKI

- Renal hypoperfusion, inflammatory response induced by cardiopulmonary bypass pump (CPB), intraoperative anemia/hemolysis and hemoglobinuric nephrotoxicity, use of IV contrast, thromboembolic events

Risk factors for AKI

- Age >70 years, females, large body surface area (>2.1 m^2), (insulin requiring) DM, CHF, ejection fraction <35%, atrial fibrillation, copd, urgent surgery, cpb duration, preoperative intra-aortic balloon pump, underlying ckd, use of aprotinin

Off-pump versus on-pump CABG

- Potential benefits of off-pump: reduced AKI, neurologic complications such as strokes, intensive care unit (ICU) and hospital stays, and mortality
- Potential risks: hemodynamic instability; risks may be minimized with surgeons/anesthesiologists' experience
- Definitive data for preferential use of on-CPB versus off-CPB pump CABG are lacking.

- KDIGO 2012 suggests that off-pump CABG surgery not be selected solely for the purpose of reducing perioperative AKI or need for RRT.

Sodium bicarbonate infusion during cardiac surgery requiring CPB

- Benefits thought to be due to reduced hemoglobinuria-induced nephrotoxicity via urinary alkalinization and/or reduced generation of

CPB-induced oxygen-free radicals produced by ischemia–reperfusion and inflammation.

- In a double-blind, randomized controlled pilot trial involving 100 cardiac surgical patients at risk for postoperative AKI, the incidence of AKI decreased with sodium bicarbonate compared to normal saline (32% vs. 52%, $p = 0.043$).
- Subsequent prospectively planned individual patient meta-analysis revealed that alkalinization with sodium bicarbonate infusion was not associated with a lower overall incidence of AKI but reduces severe AKI and need for RRT in elective CABG.

Perioperative use of RAAS inhibitors

- Systematic review and meta-analysis 2018 confirmed insufficient evidence to recommend routine discontinuation of RAAS inhibitors on the day of surgery.
- Discontinuation should be considered in patients with hypotension, hyperkalemia, and/or requirement for vasopressors.

Other considerations in cardiac perioperative management

- Avoid NSAIDS, nephrotoxins, hyperglycemia
- Monitor and optimize hemodynamic parameters to avoid hypotension
- Remote ischemic preconditioning prior to cardiac surgery has not been shown to reduce the rate of post-operative AKI or adverse patient outcomes.
- Protocolized use of inotropes to optimize oxygen delivery in late critical illness has not been shown to reduce incidence of AKI or improve outcomes.

Abdominal aortic aneurysm surgery

- Endovascular aortic aneurysm repair (EVAR) versus open laparotomy:
  - EVAR avoids aortic cross-clamp, but still requires general anesthesia and aortic manipulation with associated atheroembolic complications.
  - Potential problem with EVAR: radiocontrast use, contrast-induced AKI
- Current data are inadequate to suggest that EVAR is better than open repair

in terms of postoperative AKI.

Combat injury/surgery

- Associated rhabdomyolysis increases AKI risk. Aggressive management of rhabdomyolysis is warranted.

Unestablished Pharmacologic Options

- Erythropoietin (EPO):
  - Experimental models: effective if used within 6 hours of ischemia–reperfusion injury
  - Clinical studies: No definitive renoprotective effect shown thus far.
- Levosimendan:
  - Calcium-sensitizing agent with inotropic properties
  - Use of levosimendan in adults with sepsis or undergoing cardiac surgery has not been shown to be effective in terms of renoprotection or mortality.
  - There is no role for the use of levosimendan in critically ill patients based on current data.
- Low-dose ANP:
  - 2019 systematic review and meta-analysis involving 18 randomized controlled trials revealed a significant reduction in RRT requirement and lower ICU and in-hospital stay.
  - However, small size and qualities of involved trials render data as “insufficient to conclude efficacy of low-dose ANP” for the prevention or treatment of AKI.

Renal Replacement Therapy

Timing of RRT

- Ideal timing for RRT initiation remains unclear.
- Consider isovolumic FST: Nonresponders predict progression to more severe AKI and likely impending need for RRT.
- Fluid overload at the time of RRT initiation in critically ill patients with AKI may be associated with adverse outcomes.
- The Standard vs. Accelerated Initiation of RRT in AKI trial revealed that

early start did not reduce 90 d mortality compared with standard RRT initiation.

Dialysis modality selection

- RRT modalities used in the management of AKI include intermittent hemodialysis (IHD), sustained low-efficiency dialysis (SLED), sustained low-efficiency daily dialysis (SLEDD), prolonged intermittent renal replacement therapy (PIRRT), continuous renal replacement therapy (CRRT), and PD.

Dialysis modality comparative studies

- Good direct comparative data are lacking for various reasons: lack of CRRT in some centers, cost difference, IHD cannot be used in hemodynamically unstable patients
- 2017 meta-analysis comparing CRRT, IDH, and SLED in critically ill patients with AKI: There was no definitive advantage for any RRT modality on short-term kidney or patient survival.
- Current data suggest *no definitive mortality benefit* between IHD versus CRRT. Nonetheless, IHD or prolonged IHD provides faster solute removal than CRRT and is preferred for hyperkalemia, severe metabolic acidosis, and poisoning.
- In terms of CRRT, current data have not demonstrated survival benefit difference between diffusive versus convective mode of clearance (i.e., CVVHD vs. CVVH).
- KDIGO:
  - Use of CRRT is suggested over intermittent therapies in patients with hemodynamic instability, acute brain injury, or other causes of increased intracranial pressure (ICP) or generalized cerebral edema.
  - Use IHD, CRRT, or hybrid modalities (e.g., PIRRT or SLED) as complementary, not competing, techniques in patients with AKI.

Understanding different dialysis modalities

- SLED, SLEDD:
  - Sustained low-efficiency dialysis ≥6 hours per session every other day
  - Provides similar degree of hemodynamic stability as CRRT

- Typical regimen for a 70-kg patient:
  - Blood flow: 100 to 300 mL/min
  - Dialysate flow: 100 to 300 mL/min, to run over 6 to 8 hours
- PIRRT:
  - Suggested regimen:
    - Dialysate dosing/rate: 20 mL/kg/h × 24 hours divided by duration of PIRRT
    - Example: For a 70-kg patient with PIRRT being performed over 8 hours,
      - Perform PIRRT at 20 × 70 × 24 mL = 33,600 mL over 8 hours, which is
      - Dialysate rate of 33,600 mL/8 h = 4,200 mL/h
    - Blood flow: 100 to 300 mL/h
  - Advantages: less nursing time, off-dialysis time may allow time for diagnostic testing, patient ambulation, and so on. **Note:** Although PIRRT requires a higher number of filters, the cost may be offset by reduced nursing time.
  - PIRRT has been shown to provide similar hemodynamic control as CRRT.
- CRRT (see Chapter 12):
- Peritoneal dialysis (PD):
  - Single-center studies have suggested the safe use of high-volume PD and tidal PD in selected critically ill patients with AKI. Tidal PD refers to partial drainage of peritoneal fluid with each exchange.

Follow-Up

KDIGO AKI guidelines recommend that physicians "evaluate patients 3 months after AKI for resolution, new onset, or worsening of preexisting CKD" and manage per KDIGO CKD or CKD-at-risk guidelines as appropriate.

ICU NEPHROLOGY

Management of Acute Lung Injury/Acute Respiratory Distress Syndrome

Berlin definition of ARDS

- Arterial oxygen pressure to fraction of inspired oxygen ratio (PaO_2/FiO_2 ratio) ≤300 when using PEEP at 5 cm H_2O minimum (Example of calculation: A patient with PaO_2 of 100 mm Hg and FiO_2 of 40% has a PaO_2/FiO_2 ratio of 100/0.4 = 250)
  - Mild: PaO_2/FiO_2 ratio 200 to 300 (previously denoted acute lung injury [ALI])
  - Moderate: PaO_2/FiO_2 ratio 100 to 199
  - Severe: PaO_2/FiO_2 ratio <100
- Onset within 1 week of a known clinical insult or new or worsening respiratory symptoms
- Chest imaging revealing bilateral opacities not fully explained by effusions, lobar collapse, or nodules
- Origin of edema not fully explained by cardiac failure or fluid overload must be objectively evaluated (e.g., echocardiography) if no clear predisposing factor for ARDS is present.

Clinical impact of ARDS

- Patients with ARDS have mortality of 30% to 40%. The occurrence of AKI with ARDS may increase mortality up to 60%.
- ARDS survivors have been shown to suffer long-term physical, psychological, and cognitive dysfunction.

The link between ARDS and AKI

- AKI increases production and reduces clearance of inflammatory cytokines, which can lead to increased pulmonary neutrophil chemotaxis and capillary permeability.
- AKI downregulates ion and water transport channels involved in the removal of solute and water from injured alveoli in animal models.

Management of ALI and ARDS

- Use of low tidal volumes (6 mL/kg of predicted body weight) to decrease

plateau airway pressures

- Maintenance of airway pressures <30 cm h_2o to avoid alveolar over-distension
- Use of PEEP:
  - Rationale:
    - Improve oxygenation by recruiting collapsed alveoli
    - Reduce ventilator-induced lung injury by preventing repetitive alveolar collapse and re-expansion
  - Concerns:
    - Circulatory depression due to increased intrathoracic pressure
    - Lung over-distension
  - High PEEP strategy may be considered in patients with *severe* ARDS. *However*, PEEP >10 cm H_2O may adversely affect kidney hemodynamics and the renin–angiotensin–aldosterone axis, especially in patients not yet adequately volume resuscitated.

Fluid management in ARDS

- The Fluids and Catheters Treatment Trial (FACCT):
  - Patients with ARDS and without shock (i.e., no end-organ hypoperfusion), conservative fluid management (goal CVP <4 vs. cvp of 10 to 14 cm h_2o) with fluid restriction and/or diuresis improves lung function and shortens duration of mechanical ventilation. (conservative group: net zero balance vs. liberal fluid group: 7 l positive after 7 days)
  - Conservative fluid management did not predispose patients to AKI and was associated with a trend toward decreased RRT requirement, more successful extubations, and lower ICU length of stay.
  - There was no survival benefit with the conservative fluid strategy.
- FACCT-Lite fluid management:
  - Fluid management was based on CVP and/or pulmonary artery occlusion pressure (PAoP), and urine output. Furosemide was administered as a 20-mg bolus, followed by 3 mg/h infusion (with titration to reverse oliguria or meet intravascular pressure target) when CVP >8 and/or PAoP >12 mm Hg, whereas fluid may be given when

CVP ≤8 with frequent reassessment.
- AKI was less prevalent in FACCT-Lite protocol compared to liberal fluid administration.

Venovenous extracorporeal membrane oxygenation (ECMO)

- Use of ECMO in patients with severe ARDS was not shown to lower 60-day mortality compared with a strategy of conventional mechanical ventilation that included ECMO as rescue therapy (EOLIA trial).
- More complications were noted in the ECMO group (bleeding requiring transfusion and severe thrombocytopenia but fewer cases of ischemic stroke).

Fluid Management in ICU Patients With AKI

Fluid overload is associated with adverse outcomes

- In general, volume overload is thought to delay diagnosis of AKI and has been shown to be associated with worse outcomes.
- Program to Improve Care in Acute Renal Disease (PICARD) trial:
  - Fluid overload was associated with higher mortality at 60 days and hospital discharge.
  - Fluid overload at the time of AKI diagnosis or at peak SCr was *not* associated with favorable renal recovery.
- Finland AKI (FINNAKI) trial: Patients with fluid overload at RRT initiation had an increased risk of 90-day morality after adjusting for disease severity, time of RRT initiation, modality, and sepsis compared to those without.
- Intensive Care over Nations study: Higher cumulative fluid administered over the first 72 hours, but not the first 24 hours, in critically ill patients was associated with increased hazard of death.

Use of diuretics in AKI

KDIGO recommends not using furosemide to prevent or treat AKI, except
- for the management of volume overload.
- There is no clear benefit with the use of diuretics on kidney function recovery.

Colloids versus crystalloids

- Theoretical benefit: Colloids remain intravascularly better than crystalloids, hence lower requirement for high-volume resuscitation and less complications with pulmonary and peripheral edema. Total amount of fluid required for volume resuscitation has been shown to reduce by one-third with the addition of colloids to crystalloid fluids. Clinical data regarding benefits of colloids versus crystalloids are mixed and situation-dependent.
- 2011 Cochrane Collaboration group review: Colloids are *not* superior to isotonic crystalloids in terms of mortality when used for intravascular volume repletion in patients with trauma, burns, or after surgery.
- 2016 meta-analysis involving 59 randomized controlled trials involving critically ill, trauma, or surgical patients:
  - There was no difference in mortality in patients who received colloids versus crystalloids.
  - Use of colloids in patients with trauma was associated with a 50% reduction in incidence of AKI.
  - Use of colloids in critically ill patients or those with sepsis was associated with an increased risk of AKI.
- Albumin Italian Outcome Sepsis open-label randomized trial:
  - There was no difference in overall short-term survival.
  - In the subgroup with septic shock, albumin was associated with improved survival. **KDIGO suggests** that isotonic crystalloids be used ahead of synthetic and nonsynthetic colloids for intravascular volume expansion in patients at risk or presenting with AKI in the absence of hemorrhagic shock.
- Special considerations regarding colloids: albumin and synthetic colloids (hydroxyethyl starch [HES], gelatin, dextran):
  - Albumin remains the colloid of choice clinically.
  - Colloids are associated with increased adverse effects, increased AKI risk, particularly hyperoncotic colloids (including hyperoncotic albumin) if used without crystalloids.
  - Risks of albumin:

        - Virus transmission, Creutzfeldt–Jakob disease
        - 4% albumin infusion in patients with traumatic brain injury may be associated with higher mortality.
    - Albumin (4%) may be considered in other clinical scenarios, including severe sepsis.
    - Hyperoncotic albumin (20% to 25%) appears to be safe and renoprotective in cirrhotic patients but should probably be avoided in non-cirrthotic patients due to the lack of data.
    - HES: The use of HES is not currently recommended due to possible adverse renal outcome.
    - Gelatin: Multicenter study comparing gelatin with crystalloid is ongoing in Europe.
    - Dextran: almost entirely abandoned from clinical use

Balanced solutions versus normal saline

- The Isotonic Solutions and Major Adverse Renal Events Trial [SMART trials]:
    - Among critically ill adults, the use of balanced crystalloids (n = 7,942) versus normal saline (n = 7,860) resulted in a lower rate of *m*ajor *a*dverse *k*idney *e*vent at 30 days (MAKE30) (14.3% vs. 15.4%, $p = 0.04$) and trend in improved in-hospital mortality at 30 days (10.3% vs. 11.1%, $p = 0.06$). MAKE30 is defined as a composite of death, new requirement for RRT, or final SCr ≥200% from baseline at 30 days.
    - Among noncritically ill adults, balanced crystalloids (n = 6,708) administered in the emergency department resulted in a lower incidence of MAKE30 than saline (n = 6,639) infusion in the emergency department (4.7% vs. 5.6%, adjusted odds ratio 0.82, $p = 0.0.01$). There was no difference in hospital-free days between the two groups.
- Possible problems to consider with the use of balanced solutions:
    - Lactated Ringer:
        - Hypotonic solution may contribute to cerebral edema in neurosurgical patients.
        - Inability to convert lactate to bicarbonate in patients with shock liver

- Plasma-lyte: unclear effect of acetate on myocardial contractility
- Infusion of other unwanted premixed electrolytes such as potassium and calcium in patients with existing hyperkalemia or hypercalcemia

Fluid Management in Surgical Patients

Restrictive versus liberal fluid therapy for major abdominal surgery trial (RELIEF)

- Patients at increased risk for complications during major abdominal surgery were randomized to receive one of two treatments: 1,490 patients received a restrictive fluid regimen (fluid administered to solely achieve net zero fluid balance), and 1,493 patients received a liberal fluid regimen (10 mL/kg during anesthesia, 8 mL/kg intraoperatively, then 1.5 mL/kg/h over the first 24 postoperative hours).
- During and up to 24 hours after surgery, patients in the restrictive fluid group had a median IV fluid intake of 3.7 L compared with 6.1 L in the liberal fluid group ($p < 0.001$).
- The rate of disability-free survival at 1 year and death was not statistically different.
- However, the rates of AKI and RRT requirement were higher in the restrictive fluid group compared with the liberal fluid group.

Transfusion in Nonhemorrhagic Critically Ill Patients

Red blood cell transfusion

- Storage injuries: RBC membrane injuries: carbohydrate loss, oxidative injuries, potassium leakage; altered oxygen affinity and delivery; increased RBC adhesions to endothelial cells
- Safety of aged versus fresh blood transfusions: The storage age of RBCs does not affect patient mortality or AKI event rates based on current data.
- Recommended indications:
  - Hemoglobin ≤7 g/dL for patients without cardiac disease
  - Hemoglobin <7 to 8 g/dl in patients with coronary artery disease
  - Hemoglobin <8 g/dl or when symptomatic in patients with acute coronary syndrome
  - Transfusions for higher hemoglobin if symptomatic in isovolemic patients (e.g., cardiac chest pain, CHF, unexplained tachycardia, or

hypotension not responsive to fluid replacement)

- Transfusion for hemoglobin <7.5 g/dl in moderate- to high-risk patients undergoing cardiac surgery has been shown to be noninferior to a liberal strategy of transfusion for hemoglobin <8.5 g/dl in a non-icu ward or <9.5 g/dl in the operating room or icu in terms of all-cause mortality, cardiovascular complications, or an episode of aki requiring rrt (trics investigators and perioperative anesthesia clinical trials group).

Platelet transfusion

- Most bleeding occurred at a platelet count <7,000/µl.
- Transfuse for platelets <10,000/µl.
- Prophylactic transfusion for invasive procedures: poor data; current expert opinion suggests transfusion for platelets <50,000/µl.
- For central nervous system (CNS) injury, multisystem trauma, neurosurgery: transfuse for platelets <100,000/µl.
- In patients requiring massive blood transfusion, that is, >10 units of packed RBCs within 24 hours, transfuse 1:1:1 ratio for RBCs, plasma, and single-donor platelets.

Plasma transfusion, FFP

- Contains albumin, coagulation factors, fibrinolytic proteins, and immunoglobulins
- May be given for patients with coagulopathy and active or anticipated bleeding
- FFP may not correct INR of 1.85 or less.
- Plasma transfusion is associated with an increased risk for lung injury and trend toward increased mortality. FFP should not be used for the sole purpose of plasma expansion.

Complications associated with transfusions of blood products

- Febrile reaction (1:60 event per 1 unit of RBC transfusion), volume overload (1:100), allergic reaction (1:250), transfusion related acute lung injury (1:12,000), fatal hemolysis (1:2 million)
- Transfusion-related acute lung injury (TRALI):

TRALI: new-onset ALI within 6 hours of receiving a plasma-containing
- blood component in the absence of other causes of ALI
- Risks:
  - Recipient factors: high interleukin-8 (IL-8) levels, high peak airway pressures (e.g., >30 cm H_2O), shock, tobacco and alcohol abuse, positive fluid balance
  - Blood product factors: plasma-rich products, increased antihuman leukocyte antigen class II antibodies and antihuman neutrophil antibodies, blood from female donors
- Transfusion-related immunomodulation (TRIM):
  - Immunosuppressive effect on recipients from donor antigens
  - Increased risk of malignancy recurrence and hospital-acquired infection

Vasopressors

- Indication for vasopressors: end-organ dysfunction due to vasodilatory shock not responding to volume resuscitation (i.e., fall in baseline SBP by >30 mm Hg, or MAP is below 60 mm Hg)
- Different types of vasoactive agents are summarized in **Tables 11.7 and 11.8**.

Table 11.7 Clinical effects of receptor stimulation by agonists

Receptor	Clinical Effect With Receptor Stimulation by Agonists
α1	Vasoconstriction; smooth muscle contraction
α2	Norepinephrine (noradrenaline) inhibition; mixed effects on smooth muscle; platelet activation
β1	Positive chronotropic and inotropic effects
β2	Smooth muscle relaxation; Glycolysis (side effect of hyperlactatemia is possible with use of β2-agonists)
AVPR1a	Vasoconstriction; aldosterone synthesis and vasopressin release
AVPR1b	Adrenocorticotropic hormone (ACTH) release
AVPR2	Antidiuresis
ATR1	Vasoconstriction, increased aldosterone synthesis and vasopressin release; ATR1 may be downregulated in sepsis
ATR2	Vasodilation
DA1	Vasodilation in cerebral, coronary, renal, and mesenteric vascular beds
DA2	Cognitive function

Abbreviations: ATR, angiotensin receptor; AVPR, arginine vasopressin receptor; DA, dopamine receptor.

Table 11.8 Commonly used vasoactive and inotropic agents

Drugs	Site of Action	Comments
Norepinephrine	α1, α2 less potent on β1, β2	• First-line vasopressor for septic (distributive) shock • Vasoconstriction; some positive inotropic activity (increased ventricular contractility)
Vasopressin	AVPR1a, AVPRlb, AVPR2	• Second-line vasopressor for septic (distributive) shock • There are data to suggest that vasopressin may preserve renal perfusion but potentially depress cardiac function. • When both NE and vasopressin are used, NE should be weaned first due to potential hemodynamic instability if vasopressin is weaned first.
Epinephrine	Similar to NE except for more β1-agonist	• Second-line vasopressor for septic (distributive) shock • Comparable in efficacy as NE but with increased risk of splanchnic vasoconstriction, tachyarrhythmias, hyperlactatemia
Phenylephrine	Nearly pure α1-agonist	• Can cause reflex bradycardia • Not recommended for septic shock: should be last resort • Phenylephrine was associated with a small increase in mortality in patients with septic shock when there was a shortage of NE
Dopamine	α1, β1 DA1, DA2	• Receptor selectivity is dose dependent: low dose acts on DA, moderate dose acts on β1 and DA, and high dose acts on α1 receptors • May be used in highly selective bradycardic patients • Although low-dose dopamine in preclinical and small trials suggested splanchnic and renal vasodilation, subsequent RCT did not show any renal or survival benefits.
Angiotensin II	ATR1, ATR2	• May be used in early resuscitation for profoundly hypotensive patients • May increase glomerular filtration rate due to increased efferent arteriolar vasoconstriction • More data are needed; currently recommended as third-line agent
Dobutamine and milrinone	Inotropic agent	• May be added to NE and vasopressin to improve cardiac output from sepsis-induced depressed ventricular function (at the expense of tachyarrhythmias and increased myocardial consumption). Milrinone is also an inotropic agent that may be used. However,

		milrinone has greater vasodilating action (may drop blood pressure) compared with dobutamine and is less often used.

Abbreviations: ATR, angiotensin receptor; AVPR, arginine vasopressin receptor; DA, dopamine receptor; NE, norepinephrine; RCT, randomized controlled trial.

General recommendations

- NE is the first-line vasopressor, followed by vasopressin or epinephrine.
- Dopamine is only recommended for highly selected bradycardic patients.

General considerations regarding the use of vasoactive agents

- Optimize fluid status *prior* to use of vasopressors (e.g., pulmonary capillary wedge pressures of 18 to 24 mm Hg for cardiogenic shock and 12 to 14 mm Hg for septic or hypovolemic shock prior to consideration for use of vasopressors).
- Avoid excessive rise in systemic vascular resistance (SVR), hence cardiac workload, in patients with poor cardiac function (e.g., keep SVR 700 to 1,000 dynes × s/cm^5)
- Absorption of subcutaneous medications (e.g., heparin, insulin) may be reduced due to peripheral vasoconstriction.
- Dopamine: Clinical effects are dose dependent.
  - Low dose (1 to 2 µg/kg/min): predominantly vasodilates cerebral, coronary, renal, and mesenteric vascular beds via dopamine-1 receptors
  - Intermediate dose (2 to 5 µg/kg/min): mix of vasodilation plus increased stroke volume and some degree of α-adrenergic receptor activation; overall net effect may be seen as increased MAP.
  - High dose (5 to 10 µg/kg/min): increases stroke volume, cardiac output; variable chronotropic effect via β-1-adrenergic stimulation
  - Very high dose >10 µg/kg/min: predominantly vasoconstrictive via α-1 receptors
  - Caution: dysrhythmias with doses >2 µg/kg/min

Specific uses of vasoconstrictors

Hyperdynamic septic shock (distributive shock)

- First line: NE (Levophed, acts on both α-1 and α-2 receptors to cause vasoconstriction and increase in cardiac output, leading to reflexive

bradycardia that is offset by the mild α-2–positive chronotropic effect; thus no change or only minimal decrease in heart rate)

- Alternative/second agent:
  - Epinephrine (Neo-Synephrine, acts on α-1 receptor to cause vasoconstriction, thus increasing MAP via increasing SVR, without altering cardiac inotropy or chronotropy)
    - Useful in hypotensive patients (e.g., hyperdynamic sepsis, neurologic or anesthesia-related hemodynamic instability, with SVR <700 dynes × s/cm^5)
    - Contraindicated if SVR >1,200 dynes × s/cm^5
  - Vasopressin: VANISH study compared NE versus early vasopressin revealed less RRT utilized in the vasopressin arm, but no reduction in the incidence of kidney failure.
- Third-line agent:
  - Angiotensin II (AII)
    - FDA approved the use of AII in patients with distributive shock, predominantly septic shock in December 2017.
    - Of interest, a post hoc analysis of the 2017 Angiotensin II for the Treatment of High-Output Shock (ATHOS3) trial revealed that the rate of RRT liberation at day 7 (i.e., discontinuation of RRT) was better for those receiving AII versus placebo (38% vs. 15%). Confirmatory data are needed.
    - May have increased risk of DVT: FDA recommends DVT prophylaxis while on AII.
- Last resort:
  - Phenylephrine may reduce stroke volume and should be last resort option.
  - Phenylephrine may be considered in patients with β-adrenergic–associated tachyarrhythmias.

Hypodynamic shock (e.g., neurologic or anesthesia-related)

- First-line therapy: NE

Anaphylactic shock, hypotension following CABG

- Epinephrine (adrenalin: potent β-1-adrenergic receptor activity and moderate β-2- and α-1-adrenergic receptor effects; at high dose, predominant effects include increased cardiac output and SVR).
- Epinephrine may be considered as second-line agent for patients with septic shock (who failed NE).
- Considerations: dysrhythmias and splanchnic vasoconstriction

Cardiogenic shock

- First line: NE
- *Once adequate perfusion pressure has been achieved*, dobutamine may be added as safely tolerated. Dobutamine acts predominantly on β-1-adrenergic receptor, thus leading to increased inotropy and chronotropy to reduce left ventricular filling pressure and improved cardiac output. **Note:** There may be an overall slight reduction in BP as a reflex response to the increased cardiac output.

NOTE Dobutamine is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.

Others

- Vasopressin 0.3 IU/min:
  - Used as second-line or add-on vasopressor in refractory vasodilatory shock, such as septic shock or anaphylaxis
  - Potential adverse effects: coronary and mesenteric ischemia, skin necrosis, pulmonary vasoconstriction, hyponatremia
  - Rebound with drug discontinuation: Dose tapering is recommended.
- Isoproterenol (Isuprel):
  - Acts on β-1-adrenergic receptors, resulting in prominent chronotropic effect as well as β-2 receptor to cause vasodilation and decrease in MAP
  - Only indication: bradycardia-induced hypotension

Complications of vasopressor therapy

- Hypoperfusion (e.g., blue distal extremities, skin necrosis, bowel ischemia, reduced kidney perfusion, myocardial ischemia). For skin necrosis due to IV infiltration, consider local subcutaneous injection with phenolamine (5 to 10 mg in 10 mL normal saline).

- Dysrhythmias (e.g., tachycardia, atrial fibrillation, reentrant atrioventricular node tachycardia, or ventricular tachyarrhythmias may be seen with agents with potent chronotropic effects via β-1-receptor stimulation)
- Hyperglycemia (particularly with NE and epinephrine)
- Electrolyte disturbances (hyponatremia with vasopressin, hypokalemia with agents with potent β-2-receptor agonistic effects such as dobutamine and isoproterenol, propensity for hyperkalemia possible with agents with strong α-adrenergic activity such as phenylephrine)

Sepsis

The Third International Consensus definition of sepsis (Sepsis-3)

- "Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection," where
- "Organ dysfunction can be identified as an acute change in total Sequential Organ Failure Assessment (SOFA) score ≥2 consequent to the infection."
  - SOFA scoring system is based on respiratory rate, coagulation, liver function, renal function, cardiovascular status, CNS, and Glasgow score.
  - Given the complexity of SOFA scoring, a quick SOFA (qSOFA) for bedside use has been developed, which only includes three factors: (1) respiratory rate ≥22 breaths/minute, (2) altered mental status, and (3) SBP ≤100 mm Hg. Meeting two of three criteria suggests sepsis.
- Septic shock is defined as sepsis with persistent hypotension requiring vasopressors to maintain an MAP ≥65 mm Hg and serum lactate >2 mmol/L despite adequate volume resuscitation.

Management of sepsis

- Early goal-directed therapy (EGDT):
  - There is no clear benefit with the use of early goal-directed resuscitation protocol using IV fluids, vasopressors, inotropes, and blood transfusion.
- Antibiotics:
  - Early antibiotic initiation is associated with improved morbidity and mortality.
- Albumin:

- Possible harm in patients with traumatic brain injury
- Trend for benefit in patients with sepsis

- HES and pentastarch:
  - Associated with higher rates of AKI and death risk
  - *Not* recommended
- Vasopressors for patients with septic shock:
  - NE is the preferred initial agent (5 µg/min).
  - Current data do not demonstrate survival difference between patients with shock treated with either dopamine or NE.
  - Dopamine may be associated with increased adverse events.
  - For patients with impaired cardiac contractility who require inotropic support:
    - Add dobutamine to NE, *or*
    - Use epinephrine as both vasopressor and inotropic agents
- Steroids:
    - Hydrocortisone 50 mg every 6 hours × 5 days followed by taper regimen
    - Data on mortality in septic shock are mixed.
    - Current data do not suggest renal benefits from the use of steroids in septic shock.
- Glycemic control:
  - Control to <180 mg/dl leads to similar outcomes compared with tighter control of 80 to 100 mg/dl and avoids hypoglycemic episodes.
- AKI:
  - Low-dose dopamine does not reduce the incidence of AKI or its associated mortality.
  - Loop diuretics do not reduce the need for RRT, duration on RRT, or mortality.
  - Others:
    - Recombinant-activated protein C (rhAPC): PROWESS-SHOCK trial (randomized controlled trial comparing rhAPC treatment vs. placebo in vasopressor-dependent septic shock patients) revealed no mortality

benefit.

- IV immunoglobulin:
  - Conflicting data; no benefit shown in high-quality trials
  - 2019 network meta-analysis suggested reduction in all-cause mortality of patients with sepsis, with the highest dose range of 1.5 to 2.0 g/kg.
  - Confirmatory study needed. Routine use in septic patients not recommended at this time.
- Extracorporeal blood purification:
  - Rationale: Improve removal of inflammatory mediators.
  - No benefit has been found with higher intensity RRT (i.e., CRRT with dose >20 to 25 mL/kg/h) in septic patients with AKI. However, higher treatment dose may be considered in individuals with hypercatabolism, severe hyperkalemia, or acidemia.
  - Hemoperfusion (removes endotoxins with use of polymyxin-bound fibers) in patients with septic shock plus conventional medical therapy compared with sham treatment plus conventional medical therapy did not reduce mortality at 28 days (EUPHRATES trial, 2018).

HEMODYNAMIC MONITORING

Static Testing for Fluid Responsiveness

Static testing parameters

- CVP via central line (IJ or subclavian vein): estimates right atrial pressure and, in effect, right ventricular end diastolic volume, blood volume, and right ventricular preload
- Pulmonary artery occlusion pressure (PAoP) via PA catheter: estimates left atrial pressure and, in effect, left ventricular diastolic volume
- Left ventricular end diastolic area (LVEDA) via transthoracic or transesophageal echocardiography: Theoretically, an increase in LVEDA corresponds to greater ventricular myocardial stretch, thus presumed greater cardiac output.
- End-expiratory occlusion with echocardiography: This technique involves

holding the patient at end expiration for approximately 15 seconds. A rise in stroke volume suggests fluid responsiveness.

Limitations to static testing

- CVP, PAoP, and LVEDA lack accuracy and precision.
- CVP: invasive, falsely high readings with pulmonary HTN, right ventricular dysfunction, or high PEEP
- PAoP: invasive, falsely high readings with ARDS due to misleadingly high cardiac filling pressure
- LVEDA: cannot predict where in the Frank–Starling curve the myocardial stretch is to accurately determine actual cardiac output

Dynamic Testing for Fluid Responsiveness (Table 11.9)

Table 11.9 Hemodynamic monitoring

	Comments
Clinical examination	Increased capillary refill and cold clammy skin arc consistent with low cardiac output
Diastolic BP	Low DBP suggests low vascular tone (e.g., sepsis)
Arterial pulse pressure	Low PP suggests low stroke volume (e.g., poor ejection fraction, aortic regurgitation, severe hypovolemia)
Passive leg raising	Assess hemodynamic differences with head of bed tilting at 45° up and 45° down; may provide information on fluid responsiveness Limitations: contraindicated in patients with high intracranial pressure or lower extremity amputations or patients who cannot lie flat
Echocardiogram	Clinical utility: Assess cardiac structure and function, inferior vena cava size and collapsibility Limitation: No continuous hemodynamic monitoring
Central venous pressure	Clinical utility: Assess volume status, CVP, $S_{CV}O_2$, $P_{CV}CO_2$, right-sided heart failure, organ perfusion pressure = MAP − CVP Limitation: Docs not predict fluid responsiveness
Pulmonary artery catheterization	Invasive; indicated in patients with refractory shock associated with right ventricular dysfunction and/or with ARDS Limitation: Cannot provide accurate short-term changes in cardiac output due to its noncontinuous monitoring of cardiac output
Arterial line	Clinical utility: Assess arterial BP, PPV, SVV Limitation to PPV and SVV assessments: Only reliable during mechanical ventilation with a tidal volume of >8 mL/kg in sedated patients (without spontaneous breathing activity) and without cardiac arrhythmias
Transpulmonary thermodilution	Clinical utility: Assess CO, PPV, SVV, global end diastolic volume (preload), cardiac function index, global ejection fraction, extravascular lung water

	(pulmonary edema), pulmonary vascular permeability index (pulmonary capillary leak)

Abbreviations: ARDS, acute respiratory distress syndrome; BP, blood pressure; CO, cardiac output; CVP, central venous pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; $P_{CV}CO_2$, CO_2 pressure in central vein; PP, pulse pressure; PPV, pulse pressure variation; $S_{CV}O_2$, oxygen saturation in central vein; SVV, stroke volume variation.

Pulse pressure variation (PPV) and stroke volume variation (SVV)

- Technique is based on the principle of pulsus paradoxus, which is the variation of stroke volume and BP with respiration. Positive-pressure ventilation causes decreased venous return and increased right ventricular afterload, hence reduced stroke volume or pulse pressure. Volume depletion exaggerates SVV and PPV.
- PPV and SVV measurements require that patient is sedated without spontaneous breathing or arrhythmia and mechanically ventilated with tidal volume ≥8 mL/kg.
- PPV = (PP [highest value] – PP [lowest value])/PP (mean value). Variation >12% suggests greater likelihood for fluid responsiveness.
- SVV= (SV [highest value] – SV [lowest value])/SV (mean value). Variation >12% suggests greater likelihood for fluid responsiveness.

IVC diameter

- An IVC diameter <10 mm suggests that fluid is tolerated.
- Subcostal measurement of IVC diameter (below junction with right atrium) changes during respiration by echocardiography: A change of >10% to 18% in IVC diameter between inspiration and expiration (expiration is considered as “baseline”) predicts fluid responsiveness, with sensitivity 50% to 100% and specificity 53% to 100%. This test may be used for both ventilated and spontaneously breathing patients.

Passive leg raising

- Measures changes in various hemodynamic parameters between tilting head of bed down to 45° versus head of bed up at 45%. Tilting of bed is preferred over leg bending to avoid compression of femoral veins.
- Changes in cardiac output, pulse pressure/stroke volume, MAP, or PAoP may be measured. Improvement in hemodynamic parameters suggests

fluid responsiveness. This test is limited to patients who can lie flat and is contraindicated in patients with high ICP or severe peripheral vascular disease.

Hemodynamic Methods for Measuring Cardiac Output and Body Volume Status

- Thermodilution: Requires a PA catheter, where a small volume of cold solution (injectate) is injected into the PA catheter. The change in blood temperature following blood mixing with the injectate can be used to calculate cardiac output.
- Transpulmonary thermodilution: Theory as above. Injectate is injected through a standard central venous catheter and a thermistor that is inserted into the femoral artery. This method is thought to be less invasive compared to the thermodilution technique above.
- Esophageal Doppler:
  - Doppler is positioned in the esophagus to measure aortic diameter and velocity of blood flow through the aorta, where cardiac output is estimated by the equation: velocity = flow/cross-sectional area. Flow (blood flow) reflects cardiac output.
  - Limitations: Measurements may be affected by flow turbulence (e.g., from aneurysm, atherosclerotic disease) and by upward flow from the aortic arch (blood volume that does not reach aortic area of interest leads to falsely low cardiac output).
  - Good correlation with thermodilution method
- Thoracic electrical bioimpedance (TEB):
  - Technique is based on Ohm's Law: Voltage = Current × Resistance.
  - Measures electrical resistance on an applied current, where the resistance is affected by the relative water content in the descending aorta, that is, amount of blood flow through the aorta. A volume-repleted patient will theoretically have a low TEB (i.e., low resistance) compared to that of a volume-depleted patient.
- Pulse contour analysis: measures/calculates cardiac performance based on variations in arterial line tracings with bedside computers/programs

- Pulse oximetry waveform variation: The pulse oximetry curve represents the amount of infrared light absorbed by circulating hemoglobin during a cardiac cycle. Variation in the amplitude of this curve relates to the amount of blood in the capillary bed/volume status.

ETHICS AND PALLIATIVE CARE

- Goals of palliative care in end of life:
  - Reduce patient's symptom burden
  - Reduce caregiver burden
  - Provide emotional and spiritual support for all involved
- Palliative care is underutilized in patients with AKI requiring RRT compared to those with other diagnoses, despite having comparable or higher mortality.
- Current data suggest that palliative care is offered less frequently among African Americans and Hispanics compared with Caucasians, less frequently among rural than urban teaching hospitals, and less frequently in the Northeast compared with Southern, followed by Western region of the United States.
- Factors to consider in providing palliative care/end-of-life care:
  - Patient's characteristics and medical conditions: age, comorbidities, functional status, nutritional status, decision-making capacity
  - Present illness: severity of disease and expected progression
  - Patient's wishes if applicable, otherwise designated/appointed decision maker
  - Prognosis: possibility of getting discharged
  - RRT complications risks: hemodynamic instability, cardiac arrest
  - Limited-time RRT trial may be considered and discussed with all involved, including health care professionals, family, and patient. Discussion and documentation of expected goals for RRT continuation or discontinuation should be done prior to RRT initiation.

Access the eBook for self-assessment questions.

CHAPTER 12

Continuous Renal Replacement Therapy

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BACKGROUND

- Continuous renal replacement therapy (CRRT) is beneficial for hemodynamically unstable patients and generally provides better volume control than intermittent hemodialysis (IHD) in critically ill unstable patients with acute kidney injury (AKI).
- CRRT provides better hemodynamic stability due to slower volume removal and solute removal per unit time as compared to IHD.
- Observational studies demonstrate a trend for improved renal recovery with CRRT compared to IHD, but randomized controlled trials (RCTs) have not shown this.
- Randomized studies have not shown a survival benefit with CRRT as compared to IHD.

Patient Selection

- CRRT is preferred in patients with acute liver failure, cardiogenic shock, septic shock, and multiorgan failure.

Indications for CRRT in patients with kidney failure include the following

- Need for continuous solute control (e.g., tumor lysis syndrome,

rhabdomyolysis)
- Need for continuous volume control (e.g., heart failure, acute respiratory distress syndrome)
- Increased intracranial pressure (ICP)
- Slow correction of severe dysnatremias
- High risk of osmotic disequilibrium with IHD

Disadvantages of CRRT compared with IHD

- Intensive care unit (ICU) level care
- Slower removal of toxins (which means that CRRT is not the RRT of choice for drug intoxications or severe hyperkalemia)
- Patient immobility
- Anticoagulation is often needed.
- Hypothermia
- Nutritional losses
- Increased drug clearance with difficulty in dosing medications
- Increased cost

Timing: Early Versus Late RRT

- The optimal timing of RRT initiation remains undefined.
- A 2019 meta-analysis on the timing of initiation of RRT in AKI involving 18 RCTs from 1997 to 2018, n = 2,856, showed no significant difference in mortality between early initiation and delayed initiation of RRT in both critically ill and community-acquired AKI patients, as well as in a subgroup of patients with sepsis and in cardiac surgery recipients. An early RRT strategy was associated with a significantly higher incidence of the need for RRT for AKI patients (relative risk [RR] 1.24, 95% confidence interval [CI]: 1.13 to 1.36, $p < 0.01$). that is, delayed start avoided rrt altogether in some patients because they were allowed the time to recover adequate kidney function (yi l et al. med (baltimore)).

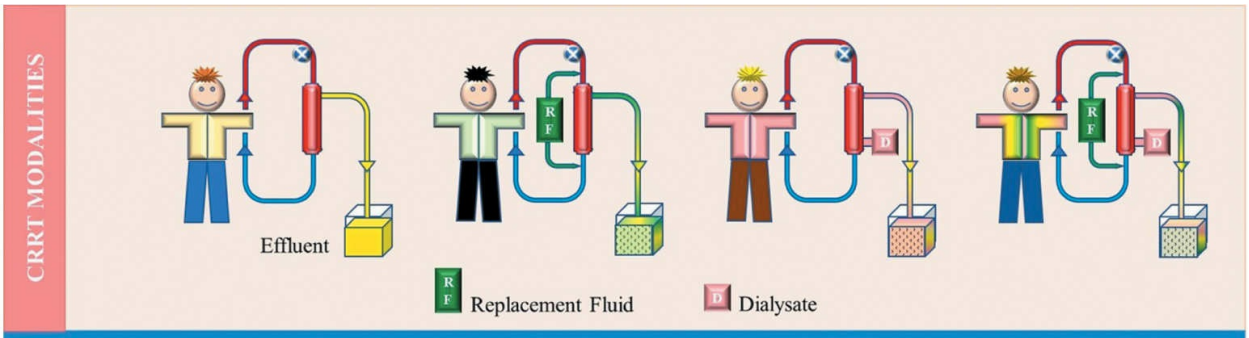
NOTE The international STARRT-AKI (Standard vs. Accelerated Initiation of RRT in Acute Kidney Injury) trial designed to determine whether accelerated initiation of RRT (aRRT, initiation of RRT within 12 hours after meeting eligibility criteria) reduces mortality

compared to a standard strategy of RRT (sRRT, initiation based on conventional indications for AKI lasting >72h) revealed that aRRT was not associated with lower risk of death at 90 days compared with sRRT. Lower rates of adverse events and dependence on RRT were noted in the sRRT group.

CRRT Procedure

- Determinants of the CRRT prescription include modality, dose, hemofilter selection, blood flow, anticoagulation, and fluid removal goals.

CRRT modality (Fig. 12.1)



	SCUF	CVVH	CVVHD	CVVHDF
Goal	Fluid removal	Combined solute & fluid removal		
Mechanism of solute clearance	No solute clearance	Convection	Diffusion	Diffusion & Convection
Operative fluid	None	Pre/post replacement fluid	Dialysate	Dialysate & Replacement Fluid
Effluent	Fluid Removed	Fluid Removed + Replacement Fluid	Fluid Removed + Dialysate	Fluid Removed + Replacement Fluid + Dialysate

FIGURE 12.1 Continuous renal replacement modalities. Abbreviations: CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; SCUF, slow continuous ultrafiltration.

Convective solute clearance

- Continuous venovenous hemofiltration (CVVH)
- Solutes removed: both small and middle molecular weight (MW) molecules up to potential size of 15 to 20,000 Da (e.g., myoglobin, β-2 microglobulin, inulin, B_{12}, interleukin-8 [IL-8], tumor necrosis factor [TNF], IL-10, IL-6)
- Operative fluid: replacement fluid (RF)

Diffusive solute clearance

- Continuous venovenous hemodialysis (CVVHD)
- Solutes removed: electrolytes, uric acid, urea, creatinine (up to molecular size of 500 to 1,000 Da)
- Operative fluid: dialysate

Both convective and diffusive solute clearance

- Continuous venovenous hemodiafiltration (CVVHDF)
- Operative fluids: dialysate and RF
- Placement of the RF for CVVH or CVVHDF can be prefilter or postfilter or both:

Prefilter RF

- RF is infused into the arterial line (prefilter) prior to filtration at the hemofilter.
- Disadvantages: Dilution of solute concentration reduces clearance.
- Advantage: less ultrafiltration (UF) rate limitation and prolonged circuit life

Postfilter RF

- RF is infused into venous line (postfilter) prior to returning blood into patient.
- Disadvantage: UF rate is limited to a certain percentage of blood flow rate to prevent hemoconcentration and minimize the risk of hemofilter clotting.
- Advantage: Clearance is directly related to UF rate.
- All modalities are equally acceptable forms of CRRT.
    - No study has demonstrated a benefit from any specific modality of CRRT.
    - No study has demonstrated a benefit of convective over diffusive therapy.
    - Convective therapy may increase clearance of middle weight molecules but may also shorten filter life.

Slow continuous ultrafiltration (SCUF)

- Modality used for plasma water removal with minimal solute clearance,

blood flow is typically 100 to 250 mL/min.

High-volume hemofiltration (HVHF)

- Using total UF rates >50 mL/kg/h has been suggested to be better in sepsis in observational studies due to removal of cytokines, but data from randomized trials have not shown any change in mortality.
- Concerns with HVHF: loss of nutrients, protective molecules, and antibiotics

CRRT dose

- Current guidelines state an effluent flow rate of 20 to 25 mL/kg/h is sufficient, with care to ensure that the target dose of therapy is actually delivered. Target dose may not be achieved due to intermittent discontinuation of CRRT for procedures, clotting of filter, or any other reason.
- In order to ensure delivery of the target dose, a prescription of a higher dose at 25 to 30 mL/kg/h may be needed.

Hemofilter selection

- All modalities of CRRT use high-permeability, high-flux biocompatible membranes.
- Typical membrane materials used are polyacrylonitrile (AN69), polyarylethersulfone (PAES), and polyethersulfone (PES). There are no data suggesting that one type of membrane is better.
- Because of their negative charge, polyacrylonitrile membranes may allow more adsorption and removal of middle MW solutes, such as cytokines. However, no difference in outcomes has been demonstrated.
- The polyacrylonitrile membranes can cause bradykinin release. An untreated AN69 membrane should not be used in patients with recent or ongoing angiotensin-converting enzyme (ACE) inhibitor use, as this has been reported to cause anaphylaxis.

Blood flow

- Low blood flow rates (<100 to 150 ml/min in adults) can increase

hemofilter clotting due to stasis of blood and an increased filtration fraction (ff) (especially in convective modalities) because the ff is inversely proportional to the blood flow.

- A higher blood flow rate (200 to 350 mL/min) may be required if anticoagulation is not used in order to maintain filter patency.
- If citrate anticoagulation is used, blood flow rates < 150 ml/min are preferred to allow for lower citrate rates and to prevent high systemic citrate levels and associated adverse effects (see complications of citrate below).
- When using CVVHD or CVVHDF, the blood flow rate should be ≥ 2.5 times the dialysate flow rate. This allows for complete saturation of dialysate and preserves the linear relationship of dialysate rate and small solute clearance.
- When using postfilter RF, the blood flow rate should be ≥5 times the RF rate to optimize the FF.
- When using prefilter RF, the blood flow rate should be ≥6 times the RF rate to optimize solute clearance efficiency.
- The blood flow rate does not affect hemodynamic stability because the volume of blood in the circuit at any one time does not change as blood flow rate changes.

Anticoagulation

Types

- None
- Heparin (unfractionated heparin, low MW) or regional heparinization with protamine
- Citrate (see sample of **citrate anticoagulation protocol used at the University of Alabama in Appendix A**)

Citrate versus heparin

- Citrate binds ionized calcium (iCa^{2+}) from the blood and inhibits the coagulation cascade. Infusion of citrate into the CRRT circuit (arterial blood) to achieve levels between 2 and 4 mmol/L reduces iCa^{2+} to <0.35 mmol/l and prolongs bleeding time to infinity. normal plasma citrate level

is ~0.05 mmol/l. the blood returning to the patient from the hemofilter combines with the mixed venous blood in the body and prevents systemic anticoagulation. a separate continuous systemic calcium infusion is required to replace the calcium lost in the effluent and to normalize the systemic ionized calcium (**Fig. 12.2**).

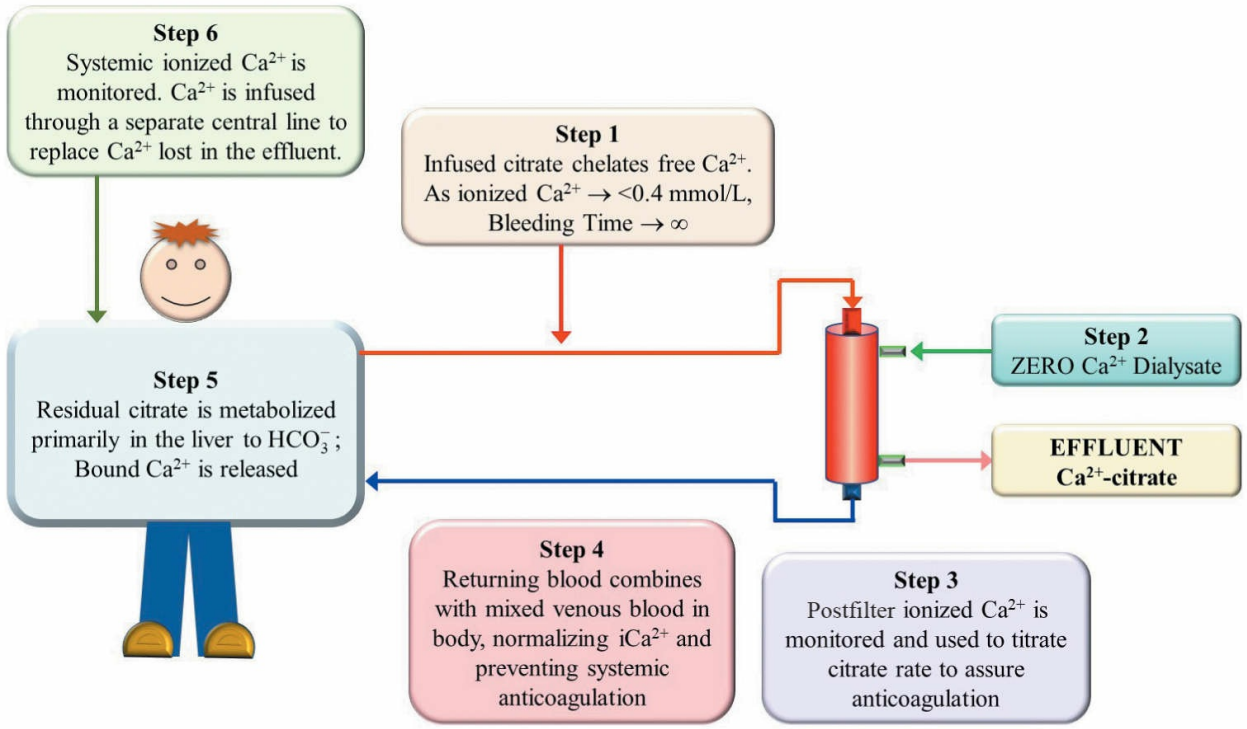


FIGURE 12.2 Citrate anticoagulation during continuous renal replacement therapy.

- Citrate has been shown to confer higher filter life and lower need for blood transfusions (presumably due to lower bleeding complications) compared to heparin in multiple RCTs.
- Citrate is cleared easily because of its small MW.
- Citrate is not recommended with SCUF because minimal total UF rates limit citrate removal, resulting in a large load of citrate directly entering the patient's blood.
- Current Kidney Disease: Improving Global Outcomes Organization (KDIGO) suggests the use of regional anticoagulation with citrate.

Complications of citrate

- Metabolic alkalosis: Citrate is metabolized to HCO_3^- predominantly in the liver. Patients can develop alkalosis from high rates of citrate infusion. This can be corrected by decreasing the blood flow (thus less citrate required to anticoagulate the blood in the hemofilter and less residual citrate entering the systemic circulation), eliminating exogenous sources of bicarbonate, and/or increasing the dialysate rate to increase citrate removal.

- Metabolic acidosis may be a problem among patients with poor tissue perfusion (lactate level >8 mmol/L) or shock liver (transaminases >800 U/L and increasing) due to poor hepatic metabolism of citrate into HCO_3^-.
- Citrate accumulation or toxicity should be suspected with the following:
  - An elevated systemic total calcium to systemic iCa^{2+} ratio: total calcium (mmol/L)/iCa^{2+} (mmol/L) > 2.5 (see **Summary of CRRT Equations** at the end of this chapter)
  - Increasing rates of systemic calcium infusion are needed to maintain normal iCa2+ levels.
  - Increasing plasma anion gap
- Hypernatremia (may be seen with the use of concentrated sodium citrate for anticoagulation such as 2.2% ACD-A and 4% TSC)
- Hypocalcemia: Patients can develop fatal arrhythmias, hypotension, and tetany from severe hypocalcemia. Systemic iCa^{2+} levels must be carefully monitored and the systemic Ca^{2+} infusion rate adjusted accordingly. Patients with systemic iCa^{2+} levels < 0.9 mmol/l should have levels drawn more frequently and the hypocalcemia corrected rapidly.
- Hypercalcemia: Due to inadvertent high calcium infusion rates or exogenous sources of calcium

Vascular access

- Site: KDIGO recommends the following sites in order of preference: right internal jugular (IJ) vein > femoral vein > left IJ vein > subclavian (SC) vein.
- Use large diameter of appropriate length catheter
- Length of catheter:
  - Right IJ: 12 to 15 cm
  - Left IJ: 15 to 20 cm
  - Femoral: 19 to 24 cm (Femoral catheter tip should be in abdominal inferior vena cava [IVC])
  - Bottom line: Right IJ is preferred; SC is the least recommended.
- Catheter tip location:

    - IJ and SC → superior vena cava (SVC) at caval atrial junction
        - Catheter tips ~3 cm caudal of right tracheobronchial angle
        - Approximately 5 cm caudal of carini
    - Femoral → IVC = at least 24 cm catheter
- Do not reduce lumen with smaller gauge connectors/three-way stopcocks.

Circuit monitoring

Access pressure

- Measures pressure as it leaves patient.
- Normal pressure −50 to −150 mm Hg
- Very positive pressure may indicate kinking of access, occlusion in venous return, or access erroneous placement in arterial circulation—Call vascular surgery if the catheter has been placed in arterial circulation. Do not pull line out.
- Very negative pressure: problem with access (clot, kinked, malposition, or very low circulatory volume)
- Fix access: flip catheter, change patient position, switch ports. If nothing works, check for signs of decreased circulatory volume.

Filter pressure

- Normal (100 to 250 mm Hg)
- High filter pressure: clogging of membrane or downstream clotting

Transmembrane pressure (TMP)

- TMP = mean filter pressure − effluent pressure
- High TMP (>150 mm Hg) indicates clogging of filter (protein buildup).
- Clogging risk: high inflammatory state (e.g., disseminated intravascular coagulation)
- To reduce clogging, use citrate anticoagulation.

Pressure drop (across the filter) 徊 prefilter pressure 𠂢 return pressure

Return pressure

- Normal pressures are +50 to 150 mm Hg.
- High return pressure could indicate kinked line, poor patient positioning,

clotted line.

Signs of imminent filter clotting

- High pressure drop (>150 mm Hg) indicates filter clotting (blood clots within hollow fibers).
- Low filtrate (FUN) to blood urea concentration (BUN), FUN/BUN ratio < 0.6 indicates clotting of filter is imminent.
- Darkening of blood in extracorporeal circuit
- Coolness of blood in venous blood line
- Separation of red blood cells and plasma
- Saline infusion can help diagnose imminent clotting: Clots may be seen in transparent parts of hemofilter with saline infusion.
- To reduce clotting: Reduce FF, use anticoagulation.

Special considerations

Brain edema

- KDIGO 2012 AKI guidelines recommend the use of CRRT over IHD in patients with evidence of brain edema or increased ICP.
- Rationale: CRRT minimizes large osmotic changes, thereby minimizing large variations in cerebral perfusion pressure and ICP.
- CRRT may benefit patients with liver failure because they are at risk for developing cerebral edema, presumably due to difficulty in maintaining cerebral autoregulation of blood flow.
- Prescriptions:
  - Use Na >140 mmol/L: Extracellular water shift lowers brain edema. (**Note:** However, in patients with severe hyponatremia, sodium concentration needs to be lower than 140 mmol/L to limit serum sodium correction to within 6 to 8 mmol/L/24 hours.)
  - Consider cooling of dialysate to 32°C to 33°C to reduce cranial oxygen demands in case of severe uncontrolled ICP

Sepsis, multiorgan failure

- The use of CVVH has been theorized to remove proinflammatory factors (TNF-β, thromboxane B2, platelet-activating factor) and anti-inflammatory

mediators (IL-10) compared with CVVHD.

- However, clinical benefits of CVVH over CVVHD have not been shown in RCTs.
- Benefit of using higher dose (≥40 mL/kg/h) has not been shown (possibly due to the loss of beneficial factors and vitamins and/or reduced drug levels [i.e., antibiotics]).

Potential complications with phosphate-containing solutions

- 1.2-mM phosphate has been associated with mild metabolic acidosis and hyperphosphatemia.

Management of Electrolyte Disorders

Severe acidosis

- For severe acidosis (pH < 7.2, bicarbonate < 10 mmol/l, or lactic acid > 8 mmol/L), CRRT solutions with the highest bicarbonate concentrations are recommended if available.
- Higher effluent rates than the recommended dose of 20 to 25 mL/kg/h will likely be needed to allow for more bicarbonate delivery if the acidosis does not substantially improve.

Hyperkalemia

- For patients with K^+ 6.5 mmol/L or lower, CRRT solutions with 4 mmol/L K^+ should be sufficient unless the patient has continuous hemolysis or other reasons to have persistent hyperkalemia.
- For patients with severe hyperkalemia (K^+ > 7.0 mmol/L), CRRT solutions with 0 or 2.0 mmol/L and higher effluent rates than the recommended dose of 20 to 25 mL/kg/h would be used to facilitate faster potassium removal. Patient potassium levels should be measured frequently with adjustment of the CRRT fluid K^+ concentration and rate made accordingly.

Dysnatremias

Hyponatremia

- 5% dextrose water (D5W) can be used as postfilter RF or separate systemic infusion to slowly correct patients who have hyponatremia: Care

must be taken to closely monitor serum total CO2 and potassium with the use of D5W because D5W does not contain bicarbonate or potassium.

- D5W rate = ([140 − target Na]/140) × desired clearance
- For example, using postdilution CVVHDF in a patient with initial sodium of 120 mmol/L with target sodium concentration of 130 mmol/L at a desired clearance of 3 L/h using RF/dialysate with 140 mmol/L of sodium, the D5W infusion rate would be ([140 − 130])/140 × 3 L = 0.214 L/h. The D5W postfilter RF would be 210 mL/h, and the dialysate/prefilter RF would be 3,000 − 214 = 2,786 or ~2,790 mL/h.

Hypernatremia

- In patients with cerebral edema who need 3% saline to maintain serum Na concentration in the range 150 to 155 mmol/L, 3% saline can be delivered as postfilter RF.
- 3% infusion rate = ([target Na − 140]/[513 − 140]) × desired clearance
- For example, in a patient with an initial sodium 140 mmol/L with target sodium concentration of 155 mmol/L at a desired clearance of 3 L/h, the 3% saline infusion rate would be ([155 − 140]/[513 − 140]) × 3 = 0.120 L/h or 120 mL/h. The dialysate/prefilter RF would be 3,000 − 120 = 2,880 mL/h.

Miscellaneous

- Patients can become hypothermic on CRRT due to the continuous blood exposure to room temperature dialysate and/or RF. The use of a warming blanket or blood warmer is recommended.
- If the CRRT solutions do not contain phosphate, aggressive phosphate repletion needs to occur in the form of intravenous phosphate, oral phosphate, or total parenteral nutrition (TPN). Patients should also be on nonrenal or normal-phosphate tube feeds.
- Medications/antibiotics must be dose adjusted when patients are initiated on CRRT, switched to IHD, or taken off RRT completely. Dose adjustments should also be made when patients are temporarily disconnected from CRRT for a prolonged period for procedures and/or circuit failure.

SUMMARY OF CRRT EQUATIONS

Terms/Abbreviations

Q_B is blood flow rate (mL/min). Remember, Q_B is usually recorded in mL/min. For below equations, multiply Q_B by 60 to convert to mL/h.

Q_P is plasma flow rate (mL/h).

Q_R is RF flow rate (mL/h).

Q_D is dialysate flow rate (mL/h).

Q_{UF} is UF rate (mL/h).

Total Q_{UF} is Q_R + net Q_{UF}.

Net Q_{UF} is net fluid removal rate.

Q_{PBP} if PBP fluid rate (mL/h). This is only in CRRT devices with a PBP and is considered a prefilter RF.

Q_E is the effluent flow rate (mL/h).

C_E is the concentration of solute in effluent.

C_P is the concentration of solute in plasma.

K is solute clearance.

Abbreviations: PBP, pre-blood pump; Hct, hematocrit

** For all formulas below, PBP rate only applies if utilizing a CRRT device with PBP.*

CRRT Dose

Recommended minimal effluent dose is 20 to 25 mL/kg/h (consider a target 25 to 30 mL/kg/h to take downtime into account). An acceptable dose has not been established in obese patients. Therefore, in patients weighing >100 kg, consider a total dose of 3,000 mL/h (for example, 1,500 mL/h RF and 1,500 mL/h dialysate). Adjust rate as needed per metabolic demand.

Dose = Effluent rate (mL/h)/Patient weight (kg)

Effluent rate for CVVHDF = Q_R (pre and/or post) + Q_D + net Q_{UF}, where Q_R also includes PBP fluid rate if CRRT device has PBP pump

Effluent Rate (mL/h) Definition per CRRT Modality

Effluent is essentially all fluid "waste" collected from a CRRT treatment.

- Effluent reflects dose and determines solute clearance.
- CVVH: Total UF rate (mL/h) = [1]Replacement fluid rate (mL/h) + [2]Fluid removal rate (mL/h) + *PBP fluid rate (mL/h)
- CVVHD: Dialysate rate (mL/h) + [2]Fluid removal rate (mL/h)
- CVVHDF: Total UF rate (mL/h) + Dialysate rate (mL/h) = ([1]Replacement fluid rate [mL/h] + [2]Fluid removal rate [mL/h] + *PBP fluid rate [mL/h]) + Dialysate rate (mL/h)

[1]Replacement fluid = Prefilter replacement fluid + Postfilter replacement fluid.

[2]Fluid removal is also termed net UF.

CRRT Dose Dilution Factor

- When using prefilter RF and/or PBP fluid, the CRRT dose is diluted and, therefore, decreased. CRRT effluent rate is multiplied by the **dilution factor** and then divided by patient weight to reflect actual CRRT dose in mL/kg/h; this takes the dilution effect into account. See example in **Clearance (K)** section.

  Dilution factor = Plasma flow rate (mL/h)/(Plasma flow rate [mL/h] + Prefilter replacement fluid rate [mL/h] + *PBP fluid rate [mL/h]), denoted as:

  Dilution factor = Q_P (mL/h)/(Q_P [mL/h] + prefilter Q_R [mL/h] + *Q_{PBP} [mL/h])

  where Q_P = Blood flow rate mL/min (Q_B) × 60 min/h × (1 − Hct)

Clearance (K)

- Clearance (K) = Mass removal rate/Blood concentration

  K = Effluent flow rate × solute concentration in effluent/solute concentration in plasma

  $K = Q_E \times C_E/C_P$

- For small solutes such as urea, effluent flow rate (17 to 50 mL/min) is

much slower than the blood flood flow rate (100 to 250 mL/min); at equilibrium, $C_E = C_P$.

- Thus, for urea, $K = Q_E \times (C_E/C_P) = Q_E \times 1$, or $K = Q_E$.
- C_E/C_P defines the *sieving coefficient* (SC), denoted as σ. This is 1 for urea.

Example:

Calculate K and CRRT dose for CVVHD in 70-kg patient: Q_D = 1,500 mL/h, net UF = 0, blood urea nitrogen concentration 60 mg/dL, effluent urea nitrogen concentration 60 mg/dL.

$K = Q_E \times C_E/C_P = Q_E$ for urea

In this case, $Q_E = Q_D$.

K = 1,500 × 60/60 = 1,500 mL/h or 25 mL/min

CRRT dose for this 70-kg patient would be 1,500 (mL/h)/70 kg = 21 mL/kg/h.

- Effect of prefilter RF on clearance K:
  - The use of pre-RF dilutes the blood that reaches the hemofilter, thereby reduces solute clearance.

    $K = Q_E \times (C_E/C_P) \times$ dilution factor

    $= Q_E \times \sigma \times (Q_P/[Q_P +$ prefilter $Q_R + *Q_{PBP}])$, where σ is the sieving coefficient of the solute of interest.

    For urea, $\mathbf{C}_{E =} \mathbf{C}_P$ or σ = 1, which simplifies K as:

    $K = Q_E \times (Q_P/[Q_P +$ prefilter $Q_R + *Q_{PBP}])$

    Example: 70 kg, net UF = 0, Hct 30%, prefilter Q_R = 1,500 mL/h, Q_B = 100 mL/min, blood urea nitrogen concentration 60 mg/dL, effluent urea concentration 60 mg/dL.

    $K = Q_E \times (Q_P/[Q_P +$ prefilter $Q_R])$,

    where Q_P = 100 mL/min × 60 min/h × (1 − 0.3) = 4,200 mL/h

    K = 1,500 mL/h × (4,200 mL/h/[4,200 + 1,500 mL/h]) = 1,500 × 0.74

= 1.1 L/h or 18 mL/min.

CRRT dose for this patient can be calculated as K (mL/h) ÷ weight (kg) = 1,100 mL/h ÷ 70 kg = ~16 mL/kg/h.

If the 1,500 mL is used as post-RF instead of pre-RF, use K formula without the dilution factor:

$K = Q_E \times C_E/C_P$ = 1,500 mL/h × (60/60) = 1,500 mL/h = 25 mL/min

Dose = K (mL/h) ÷ Wt (kg) = 1,500 ÷ 70 = 21 mL/kg/h

The change in clearance in placing RF in postfilter versus prefilter would be 25 − 19 mL/min = 6 mL/min, or a reduction in clearance of 6 ÷ 25 × 100% = 24%.

- For small solutes, clearance for CVVH with postfilter RF is similar to that for CVVHD if using the same effluent rates for both. That is, K(CVVH) with postfilter RF = K(CVVHD), given the same Q_E.

CRRT Filtration Fraction

- Filter clotting occurs with FF > 20% to 25%.
- Filtration fraction (FF) = Total ultrafiltration rate/(Plasma flow rate + Prefilter replacement fluid rate + *PBP fluid rate)
- Total ultrafiltration rate (mL/h) = Prefilter replacement fluid rate (mL/h) + Postfilter replacement fluid rate (mL/h) + Fluid removal rate (mL/h) + *PBP fluid rate (mL/h)
- Plasma flow rate (mL/h) = Blood flow rate (Q_B mL/min) × 60 (min/h) × (1 − Hct)
- **Note:** Dialysate rate does *not* factor into the FF equation.
- FF can be reduced by increasing Q_B, increasing the proportion of prefilter Q_R relative to total RF used, or reducing net UF. The last option is usually not a good option because patient needs the UF. It must be noted, however, that increasing prefilter Q_R reduces clearance.

  Example:

  Calculate K and FF for a CVVHDF in 70-kg patient: Q_B 100 mL/min, Hct 30%, prefilter Q_R 1,500 mL/h, Q_D 1,500 mL/h, net UF = 0.

In this particular case:

$$Q_E = Q_D + \text{prefilter } Q_R = 3{,}000 \text{ mL/h}$$

$$\text{Prefilter } Q_R = 1{,}500 \text{ mL/h} = \text{Total } Q_{UF}$$

$$K = Q_E \times \text{dilution factor} = Q_E \times (Q_P/[Q_P + \text{prefilter } Q_R])$$

$$= 3{,}000 \text{ mL/h} \times (100 \text{ mL/min} \times 60 \text{ min/h} \times [1 - 0.3])/(100 \times 60 \times [1 - 0.3] + 1{,}500 \text{ mL/h})$$

$$= 2{,}211 \text{ mL/h}/70 \text{ kg} = 32 \text{ mL/kg/h}$$

$FF = \text{Total } Q_{UF}/(Q_P + \text{prefilter } Q_R) = 1{,}500/(6{,}000 \times [1 - 0.3] + 1{,}500) = 0.26$ (26%)

Example:

100-kg patient on CVVH: Q_B 100 mL/min, postfilter Q_R 1,500 mL/h, fluid removal 200 mL/h, no anticoagulation, Hct 30%.

What are your thoughts on prescription in terms of dose and FF?

Effluent rate Q_E = 1,500 mL/h + 200 mL/h = 1,700 mL/h

Dose = 1,700 mL/h ÷ 100 kg = 17 mL/kg/h

Thoughts: This is lower than the recommended dose of 20 to 25 mL/kg/h.

FF = 1,700 mL/h/(100 mL/min × 60 min/h × [1 − 0.3]) = 0.4 (40%).

Thoughts: This is much greater than 25% to 30%. Clotting risk is much increased with this prescription.

Example:

120-kg patient placed on postdilution CVVH, Q_B 200 mL/min, desired CVVH dose 25 mL/kg/h, Hct 30%.

Total Q_{UF} = 3,000 mL/h (120 kg × 25 mL/kg/h), no anticoagulation.

What is the FF?

FF = 3,000 mL/h/([200 mL/min × 60 mL/min] × [1 − 0.3]) = 36%

Which of the following options will decrease the effect of FF on clotting of

the circuit?

A. Add anticoagulation (along with reduction in Q_b to reduce citrate accumulation)
B. Change to a diffusive therapy (CVVHD)
C. Increase blood flow rate
D. Change to prefilter RF
E. All of the above

Answer: E

Adding anticoagulation will mitigate the effects of clotting; changing to a diffusive therapy and delivering most of the dose by a dialysate in CVVHD will decrease the FF; increasing the blood flow rate will decrease FF; changing to prefilter RF will decrease FF.

Citrate Toxicity Detection

- Rising anion gap, worsening metabolic acidosis
- Falling systemic ionized calcium (iCa^{2+})
- Escalating Ca^{2+} infusion requirements
- **Total Ca^{2+}/Systemic iCa^{2+} ratio > 2.5:1. A ratio > 2.5:1 is referred to as "an increased Ca^{2+} gap."
- ***To convert total calcium measured in mg/dL to mmol/L, multiply total calcium by 0.25.*

Drug Dosing With CRRT

Determinants of drug removal with CRRT

- Drug-dependent factors include protein binding, volume of distribution, MW, and drug charge.
- Therapy-dependent factors include type of CRRT modality, effluent flow rate, blood flow rate, RF placement (pre/post), and type of hemofilter.

Protein binding is the single most important determinant of drug removal by CRRT.

- Only unbound drugs can be removed by CRRT.
- Protein binding > 90% indicates the drug is less likely to be removed by

CRRT. Examples are ceftriaxone and warfarin.

- The sieving coefficient (SC) measures the ability of a drug to pass through the hemofilter:
  - SC measured = (drug effluent)/(drug plasma)
  - SC estimate = 1 − PB (PB, protein binding)

Volume of distribution (V_d) is the theoretical volume of water the drug would occupy if the body were a single homogeneous reservoir whose concentration is equal to the plasma concentration. Drugs that are lipid soluble or highly tissue bound have a large volume of distribution.

- Drugs with a large distribution volume (>1 L/kg body weight) are removed less efficiently by CRRT.
- Drugs that are limited to intravascular compartment have a small volume of distribution (<0.3 l/kg) and are efficiently removed by crrt.

Drug size

- Drugs ≤ 2,000 Da (which are most drugs) readily cross the membrane and are small enough to be removed equally by all CRRT modalities.
- Drugs >15,000 Da are not removed by any CRRT modality, as they do not cross the membrane.

Drug dosing considerations

- The sum of intrinsic renal creatinine clearance (CrCl) and CRRT effluent rate normalized for drug protein binding provides a starting point for maintenance drug dosing in CRRT.
- The CrCl or eGFR for the CRRT device is the effluent rate in mL/h divided by 60 to convert rate into mL/min. This effluent rate is then multiplied by the SC of the drug which is (1 − PB).
- Calculation of CRRT drug clearance must correct for the rate of prefilter replacement relative to blood flow.
  - CRRT drug clearance = Effluent rate (mL/min) × dilution factor × SC.
  - If prefilter RF is used, dilution factor = (Q_B [1 − Hct]/[Q_B (1 − Hct) + prefilter Q_R]); if no dilution factor is used, dilution factor = 1.
  - This final value should be added to the patient's renal CrCl if the patient

is making urine on CRRT. Once the CRRT clearance (plus residual renal function, if any) is estimated in mL/min, administer the maintenance dose that is recommended for patients with an equivalent level of renal function.

Example:

Patient is on CVVHDF with Q_B 100 mL/min, Q_D 1,000 mL/h, Q_{PBP} of 1,000 mL/h, postfilter Q_R 200 mL/h, and net Q_{UF} 100 mL/h. The patient is being dosed with vancomycin which has SC of 0.8.

What is the equivalent CrCl that may be used for dosing of this drug?

The effluent rate is 1,000 (Q_D) + 1,000 (Q_{PBP}) + 200 (Q_R) + 100 (net Q_{UF}) = 2,300 mL/h. To convert to mL/min, divide by 60. CRRT eGFR or CrCl is 2,300/60 or 38 mL/min.

However, since 1,000 mL/h is given prefilter, the dilution factor must be considered.

For this patient with an Hct of 30% or 0.3, the dilution factor is = (100 mL/min × 60 × [1 − 0.3])/([100 × 60 × (1 − 0.3)] + 1,000 mL/h) = 0.8.

The estimated CRRT clearance is therefore = 38 mL/min × 0.8 = 30 mL/min.

The estimated CRRT clearance has to be multiplied by the SC for vancomycin which is 0.8. Thus, the estimated clearance for vancomycin = 30 mL/min × 0.8 = 24 mL/min.

Answer: The maintenance vancomycin dosing should be based on an estimated CrCl of 24 mL/min.

APPENDIX A: Facts, Formulas, and Protocols

CHAPTER 1: SODIUM/WATER

Protocol for Water Loading Test

- Purpose: Water loading test may be used in equivocal cases of SIADH (syndrome of inappropriate secretion of antidiuretic hormone). This test should only be performed in patients with mild hyponatremia and *not* in moderate or severe hyponatremia. This test is not valid in patients with poor kidney function.
- Two hours after a light breakfast:
  - Measure baseline S_{OSM} and U_{OSM}
  - Give patient water to drink (20 mL/kg) over 15 to 30 minutes
- Patient should remain recumbent during test:
  - Collect hourly S_{OSM} and U_{OSM} over the next 4 hours
  - Measure total urine output over the 4-hour duration
- Interpretation of results:
  - For all patients, S_{OSM} will acutely drop by > 5 mOsm/kg.
  - Normal individuals: Urine *will* be appropriately diluted to U_{OSM} < 100 mosm/kg. ninety percent of water load is typically excreted by 4 hours.
  - Patients with SIADH: Urine *will not* appropriately dilute to U_{OSM} < 100 mosm/kg and urine output will be <90% of water load.

Water Deprivation Test

- Purpose: Water deprivation test with the use of DDAVP may be used to evaluate the underlying etiology of polyuria with or without hypernatremia. Conditions such as central and nephrogenic diabetes insipidus may be diagnosed with this test.

- See “Diagnosis of Polyuria” in Chapter 1.

Calculations for the Correction of Hyponatremia in Patients Receiving Intermittent Hemodialysis Patient

- Correction rates of hyponatremia in the hemodialysis (HD) patient:
  - Uremic patients are thought to be protected from osmotic demyelinating syndrome (ODS) with overly rapid correction of hyponatremia during dialysis because of the simultaneous removal of uremic solutes.
  - However, ODS has been reported in patients with rapid sodium correction with dialysis.
  - Correction rates should, therefore, follow the same guidelines for nonuremic patients.
- Calculations of blood flow for intermittent hemodialysis (IHD): Minimization of sodium correction may be achieved by using the dialysate with the lowest sodium concentration appropriate for patient’s S[Na^+] level (lowest dialysate [Na^+] is typically 130 mmol/L) and lowest blood flow rate (BFR).
  1. *One can assume that 100% of the [Na^+] difference from the dialysate will transfer to the blood if the blood is allowed to flow very slowly against a high dialysate flow rate of 800 mL/min.*
  2. *Consider a patient with S[Na^+] of 120 mmol/L; goal correction of 6 mmol/L over a 3-hour dialysis session using a dialysate with [Na^+] of 130 mmol/L.*
  3. *Assuming 100% Na^+ transfer from the dialysate, every 1 L of blood that passes through the dialyzer will gain 10 mmol of Na^+.*
  4. *If goal S[Na^+] is 126 mmol/L and patient has total body volume of 30 L, the total amount of Na^+ needed is 6 mmol/L × 30 L = 180 mmol. Since every 1 L of blood that passes through the dialyzer picks up 10 mmol of Na^+ from the dialysate, a total blood volume of 18 L (180 mmol/10 mmol/L) would need to pass through the dialyzer over 3 hours. The BFR would thus be 18 L/3 hours or 100 mL/min. This may be achieved using the pediatric mode on the dialyzer.*

Essentially, to correct hyponatremia with IHD using a dialysate flow of

800 mL/min, the BFR (mL/min) may be estimated as:

$$BFR = \frac{(Total\ body\ volume)^{*}(\Delta S[Na^{+}]) \times 1{,}000}{(Dialysate\ [Na^{+}] - S[Na^{+}]) \times Duration\ of\ dialysis\ treatment\ (minutes)}$$

where $\Delta S[Na^{+}]$ = goal $S[Na^{+}]$ at end of dialysis − presenting $S[Na^{+}]$. The unit for total body volume above is in liter.

If slow correction rate is limited by lowest blood flow possible with IHD, consider lowering dialysate flow or switch to continuous renal replacement therapy.

Calculations for the Correction of Dysnatremias in Patients Receiving Continuous Renal Replacement Therapy

See **Chapter 12 Continuous Renal Replacement Therapy**.

CHAPTER 2: ACID–BASE AND POTASSIUM DISORDERS

Diagnosis of Acid–Base Disorders

- In determining acid–base disorders from a blood gas and chemistry, the following are defined as normal values: pH = 7.4, Pco_2 = 40 mm Hg, total CO_2 (herein referred to as $[HCO_3^-]$ to avoid confusion with Pco_2) = 24 mmol/L, serum anion gap (SAG) = 12 mmol/L
- Four *basic steps* in the assessment of acid–base disorders:
- **Step 1:** Check serum $[HCO_3^-]$ to determine two different acid–base disorder possibilities.
  - Example:
  - If $[HCO_3^-] < 24 \rightarrow$ either (a) metabolic acidosis *or* (b) respiratory alkalosis (acute or chronic)
  - If $[HCO_3^-] > 24 \rightarrow$ either (a) metabolic alkalosis *or (*b) respiratory acidosis (acute or chronic)
- **Step 2:** Check pH to determine which of two possibilities (a or b) in Step 1 is most likely. Essentially, steps 1 and 2 determine the *first* acid–base disturbance.
  - Example: If a patient has $[HCO_3^-]$ 16 mmol/L, he can have either a

metabolic acidosis or respiratory alkalosis. If his pH is 7.2, it would be more likely that he has metabolic acidosis rather than respiratory alkalosis. If, however, this same patient's pH is 7.45, then it is more likely that he has respiratory alkalosis.

- **Step 3:** Calculate expected compensation for the first acid–base disturbance above, then compare expected to actual value. A mismatch indicates the presence of a *second* acid–base disturbance:

COMPENSATION FACTORS:

	$\Delta[HCO_3^-]$	ΔPco_2
Metabolic acidosis[a]	↓**1**	↓1
Metabolic alkalosis	↑**1**	↑0.7
Respiratory acidosis (acute)	↑0.1	↑**1**
Respiratory acidosis (chronic)[b]	↑0.3	↑**1**
Respiratory alkalosis (acute)[b]	↓0.1	↓**1**
Respiratory alkalosis (chronic)[b]	↓0.4	↓**1**

[a]For severe metabolic acidosis, that is, serum HCO_3^- <10 mmol/l, use winter's formula to calculate expected pco_2. winter's formula calculates the "expected pco_2" and *not* ΔPco_2.
Winter's formula: Expected Pco_2 = (1.5 × serum $[HCO_3^-]$) + 8 ± 2 mm Hg
Applying Winter's formula: For a patient with metabolic acidosis, serum $[HCO_3^-]$ of 12 mmol/L would have an expected Pco_2 of 26 ± 2 mm Hg.
[b]Compensation factors vary slightly in the literature. Overall, however, if a margin of error of ±2 mmol/L for HCO_3^- and ±3 mm Hg for Pco_2 are allowed, acid–base disorders calculated will all be relatively similar.

- ***Example 1:*** *Patient with $[HCO_3^-]$ 37 mmol/L, pH 7.5, Pco_2 34 mm Hg. What are the acid–base disorders?*
  - *Steps 1 and 2: Check $[HCO_3^-]$ and pH: Based on the high $[HCO_3^-]$ and pH, the "first" acid–base disturbance is metabolic alkalosis.*
  - *Step 3: Calculate compensation. Compare expected to actual value to determine the presence of second acid–base disturbance.*
    - *Expected compensation for metabolic alkalosis: For every 1 increase in $[HCO_3^-]$, there is a 0.7 increase in Pco_2.*
    - *Since there is a 13 increase in $[HCO_3^-]$ in current patient, there should be a 0.7 × 13 = 9.1 increase in Pco_2.*
    - *The expected Pco_2 should be 40 + 9.1 or ~49 ± 3 mm Hg.*
    - *Compare to actual value: The actual Pco_2 is 34 mm Hg, a value*

much lower than the expected 49.

- *This means patient also has a respiratory alkalosis as a "second" acid–base disturbance.*

- ***Example 2:*** *Patient with [HCO_3^-] 18 mmol/L, pH 7.5, Pco_2 26 mm Hg.*
  - *Steps 1 and 2: Check [HCO_3^-] and pH: Based on the low [HCO_3^-] and high pH, the "first" acid–base disturbance is respiratory alkalosis.*
  - *Step 3: Calculate compensation. Compare expected to actual value to determine the presence of second acid–base disturbance:*
    - *Expected compensation for respiratory alkalosis (acute): For every 1 decrease in Pco_2, there is a 0.1 decrease in [HCO_3^-].*
    - *Since there is a decrease of 14 in Pco_2, there should be a decrease in [HCO_3^-] of 0.1 × 14 = 1.4 or ~1. The expected [HCO_3^-] for acute respiratory alkalosis is 24 − 1 = 23 ± 2 mm Hg.*
    - *Expected compensation for respiratory alkalosis (chronic): For every 1 decrease in Pco_2, there is a decrease of 0.4 in [HCO_3^-].*
    - *Since there is a decrease of 14 in Pco_2, there should be a decrease in [HCO_3^-] of 0.4 × 14 = 5.6 or ~6.0. The expected [HCO_3^-] for chronic respiratory alkalosis is 24 − 6 = 18 ± 2 mmol/L.*
    - *Since the actual [HCO_3^-] is 18, it is likely that the patient just has a chronic respiratory alkalosis and no "second" acid–base disturbance.*

- **Step 4:** Check SAG to determine the presence of *third* acid–base disorder:
  - Derivation and definition of SAG:

Total positive charges = Total negative charges

Na^+ + unmeasured $Cations^+$ = Cl^- + [HCO_3^-] + unmeasured $Anions^-$

Rearranging the equation above,

[Na^+] − [Cl^-] − [HCO_3^-] = [unmeasured $Anions^-$ − unmeasured $Cations^+$] = SAG

A normal SAG is approximately 12 (may vary slightly from institution to institution).

NOTE

- **Conditions with *high SAG metabolic acidosis*:**
  - ↑SAG = [↑unmeasured $Anions^-$ − unmeasured $Cations^+$] > 12
  - Unmeasured anions from: methanol (converts to formic acid; formic acid, in turn,

inhibits mitochondrial function, which could lead to lactic acid accumulation), uremia (accumulation of sulfates, phosphates, urates, etc.), diabetic ketoacidosis (ketone bodies), paraldehyde (causes hypotension and lactic acidosis), pyroglutamate (i.e., oxoproline), propylene glycol (converts to lactate), isoniazid (inhibits lactate dehydrogenase, causes lactic acidosis), metformin and iron (inhibit mitochondrial function, hence lactic acid accumulation), bacteria-producing D-lactic acidosis seen in short-bowel or malabsorption syndromes (may be associated with elevated or normal SAG depending on severity and kidney function; D-lactic acid is filtered and easily excreted, which may leave a normal SAG. If patient has poor kidney function, D-lactate accumulates and results in elevated SAG. Renal tubular reabsorption of L-lactate is greater than that for D-lactate), L-lactic acidosis, salicylates, ethylene glycol (lactic acid, oxalate); A small elevation in lactic acid can be seen with ethylene glycol (EG) intoxication. However, erroneously markedly increase in lactic acid levels has been reported with the use of analyzers that cannot differentiate between lactate and glycolate, an EG metabolite.

- **Conditions with *normal SAG metabolic acidosis:***
  - SAG = [unmeasured $Anions^-$ − unmeasured $Cations^+$] ~− 12
  - Diarrhea, poor kidney function but with estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2, ureterosigmoid anastomosis > ileal conduit, enteric fistulas, drainage of biliary, pancreatic, or enteric secretions, renal tubular acidosis, D-lactic acidosis with good kidney function, ingestion of NH_4Cl and/or acidic amino acids (e.g., with total parenteral nutrition), large volume normal saline infusion, toluene ingestion (if good kidney function due to rapid excretion of hippurate acid), post**hypo**capnic state (i.e., posthyperventilated state with residual compensatory loss of [HCO_3^-]), drug-induced: acetazolamide, topiramate, zonisamide, amphotericin B, K-sparing diuretics, trimethoprim, pentamidine, $CaCl_2$, $MgSO_4$, ($CaCl_2$ and $MgSO_4$ may cause metabolic acidosis because of intestinal calcium carbonate formation and elimination in the stool), cholestyramine (Cholestyramine [cationic resin given as a chloride salt] may form a bicarbonate salt that is eliminated in the stool), renal tubular acidosis
- **Conditions with *high SAG but without metabolic acidosis:*** severe metabolic alkalosis (pH > 7.5), cellular phosphate/anion leaks in nonketotic hyperglycemia
- **Conditions with *low SAG that has no associated acid–base disorder:***
  - Hypoalbuminemia: For every drop of 1 g/dL of albumin, there is an expected drop of 2.5 in SAG. Albumin is an unmeasured anion. If albumin is low, the quantity [↓unmeasured $Anions^-$ − unmeasured $Cations^+$], SAG, is reduced. It is important to always correct SAG for hypoalbuminemia to unmask any high SAG acid–base disturbances.

    Example: Patient with SAG of 10, serum albumin 1.5 g/dL.
    Assuming normal serum albumin level of 4.5 g/dL for the general population,
    Corrected SAG = 10 + (4.5 − 1.5) × 2.5 = 17.5. Patient does have an ↑SAG.

  - Presence of positively charged immunoglobulins (Igs): In the presence of positively charged Igs (e.g., multiple myeloma, intravenous [IV] infusion of high-dose Igs), the quantity [unmeasured $Anions^-$ − ↑unmeasured $Cations^+$], SAG, is reduced.
  - Primary hyperparathyroidism with elevated Ca^{2+} and low PO_4^{2-}: The quantity [↓unmeasured $Anions^-$ − ↑unmeasured $Cations^+$], SAG, is reduced. In hypercalcemic conditions with high PO_4^{2-} levels (e.g., increased bone resorption), SAG [↑unmeasured $Anions^-$ − ↑unmeasured $Cations^+$] is likely normal.
  - Falsely low measurements of S[Na^+] in the case of severe hypernatremia. When S[Na^+]

is greater than 170 mmol/L, S[Na^+] measurement may not be accurate and may be falsely low. [Na^+] − [Cl^-] − [HCO_3^-] would thus be falsely low.

- Falsely high measurements of Cl^- (may occur with fluoride/bromide intoxication, hyperlipidemia); [Na^+] − [Cl^-] − [HCO_3^-] would thus be falsely low.

- Interpretation of increased SAG:
  - Imagine a patient with an SAG = 27. This may be interpreted as having 12 normal SAG and 15 excess Anions$^-$ (A^-):
    - 27 = 12 normal AG + 15 A^-
    - One can assume that the excess 15 Anions$^-$ detected is accompanied by 15 acid H^+.
    - 15 HA ↔ 15 H^+ + 15 Anions$^-$
    - Assume that for every H^+, one HCO_3^- will be consumed.
    - Expected [HCO_3^-] would thus be = 24 − 15 = 9 mmol/L. This is the *expected* [HCO_3^-] based on the detected excess Anions$^-$.
    - Compare the calculated *expected* [HCO_3^-] to the measured *actual* serum [HCO_3^-]:
      - If the actual serum [HCO_3^-] = expected [HCO_3^-] ± 2, there is no other acid–base process.
      - If the actual serum [HCO_3^-] > expected [HCO_3^-], there are more [HCO_3^-] than expected, which implies patient **also** has metabolic alkalosis.
      - If the actual serum [HCO_3^-] < expected [hco_3^-], there are less [HCO_3^-] than expected, which implies there is “some other process” that is consuming [HCO_3^-], but is not contributing any anions for detection on SAG. This implies patient **also** has a non-AG metabolic acidosis.
  - Imagine another patient with an SAG = 25. This may be interpreted as having 12 normal SAG and 13 excess Anions$^-$ (A^-):
    - 25 = 12 normal AG + 13 A^-
    - One can assume that the excess 13 Anions$^-$ detected is associated with 13 acid H^+.
    - 13 HA ↔ 13 H^+ + 13 Anions$^-$
    - Assume that for every H^+, one HCO_3^- will be consumed.

- Expected [HCO_3^-] is calculated to be = 24 − 13 = 11 mmol/L. This is the *expected* [HCO_3^-] based on the detected excess Anions$^-$.
- Compare the calculated *expected* [HCO_3^-] of 11 mmol/L to the measured *actual* serum [HCO_3^-].
  - If patient's actual serum [HCO_3^-] = 25 mmol/L, it would mean patient **also** has a metabolic alkalosis in addition to the high AG metabolic acidosis.
  - If patient's actual [HCO_3^-] = 5 mmol/L, it would imply that patient has another metabolic acidosis process that is using up the HCO_3^- but did not show up in the elevated AG. This implies that patient **also** has a **non-AG** metabolic acidosis in addition to the high AG metabolic acidosis.

NOTE Although we typically assume a 1:1 ratio of acid consumption of HCO_3^-, this ratio is slightly higher for organic acids. For lactic acidosis, this ratio is 1.6 lactate:1.0 HCO_3^- due to the buffering of lactic acid by molecules other than [HCO_3^-]. That is, for every 1.6 mmol of lactate, only one HCO_3^- will be consumed, not 1.6 HCO_3^-.

Example: In a patient with an increased SAG of 29 due to lactate acidosis, one would expect the HCO_3^- to drop by (29 − 12)/1.6 = 11 instead of (29 − 12) = 17. The expected HCO_3^- would be 24 − 11= 13, not 24 − 17 = 7.

Practice Acid–Base Problems

- Unless otherwise specified, units for electrolytes are mmol/L.

Case

- A 78-year-old fragile female with recent weight gain due to edema and loss of appetite:

Blood chemistry: [Na^+] 132, [K^+] 4.2, [Cl^-] 95, [HCO_3^-] 15, blood urea nitrogen (BUN) 69 mg/dL, serum creatinine (SCr) 8.2 mg/dL. Blood gas: pH 7.33, Pco_2 29 mm Hg. What is/are the acid–base disturbance(s)?

Steps 1 and 2: Low **[HCO^{3-}] and** low **pH** → "First" process is metabolic acidosis.

Step 3: Compensation:	Δ[HCO_3^-]	ΔPco_2
Metabolic acidosis	↓1	↓1

For current case, ↓[HCO_3^-] by 9, Pco_2 thus ↓ by 9 × 1 = 9 → expected

Pco_2 = 40 − 9 = 31 ± 3, which is within range of actual Pco_2 of 29 → no "second" process.

Step 4: SAG = 22 → 12 normal AG + 10 anions → 10 anions must have accompanied 10 H^+ ions, which are expected to consume 10 [HCO_3^-] → expected [HCO_3^-] = 24 − 10 = 14 ± 2, which is within range of the actual [HCO_3^-] of 13 → No "third" process.

Answer: High SAG metabolic acidosis, likely due to kidney failure. The high SAG is likely due to the accumulation of organic anions such as sulfates, phosphates, and urates seen with reduced glomerular filtration.

Case

- A 75-year-old fragile male who presents with chronic aches and pains:

Blood chemistry: [Na^+] 137, [K^+] 4.8, [Cl^-] 101, [HCO_3^-] 12, BUN 19 mg/dL, SCr 1.2 mg/dL. Blood gas: pH 7.36, Pco_2 23 mm Hg. What is/are the acid–base disturbance(s)?

Steps 1 and 2: Low **[HCO^{3-}] and** low **pH** → "First" process is metabolic acidosis.

Step 3: Compensation:	Δ[HCO_3^-]	ΔPco_2
Metabolic acidosis	↓1	↓1

For current case, ↓[HCO_3^-] by 12, Pco_2 thus ↓ by 12 × 1= 12 → expected Pco_2 = 40 − 12 = 28 ± 3, which is higher than the actual Pco_2 of 23 → "second" process: respiratory alkalosis.

Step 4: SAG = 24 → 12 normal AG + 12 anions → 12 anions must have accompanied 12 H^+ → These 12 H^+ ions are expected to consume 12 [HCO_3^-] → expected [HCO_3^-] = 24 − 12 = 12 ± 2, which is within range of actual [HCO_3^-] of 12 → No "third" process.

Answer: High SAG metabolic acidosis and respiratory alkalosis, likely due to excess salicylate ingestion. Other possible scenarios: respiratory alkalosis from acute pulmonary embolism or pneumonia and concurrent high SAG from chronic acetaminophen use (accumulation of oxoproline, i.e., pyroglutamic acid), and so on.

Case

- A 37-year-old male found down at the bus station:

Blood chemistry: [Na^+] 129, [K^+] 3.1, [Cl^-] 80, [HCO_3^-] 24, BUN 15 mg/dL, SCr 1.7 mg/dL. Blood gas: pH 7.40, Pco_2 40 mm Hg. What is/are the acid–base disturbance(s)?

Steps 1 and 2: Normal [HCO^{3-}] **and** normal **pH** → "first" process: not clearly detectable		
Step 3: Compensation:	Δ[HCO_3^-]	ΔPco_2
Unknown process	?	?

For current case, there is no obvious "first" process, thus no compensation can be calculated → No calculable "second" process.

Step 4: SAG = 25 → 12 normal AG + 13 anions → *13 anions must have accompanied 13 H^+. This implies the presence of a high SAG metabolic acidosis. The 13 H^+ is expected to consume 13 [HCO_3^-] → expected [HCO_3^-] = 24 − 13 = 11 ± 2, which is much lower than the actual [HCO_3^-] of 24. The higher actual [HCO_3^-] compared to expected [HCO_3^-] suggests that the "third" process is metabolic alkalosis.

Answer: High SAG metabolic acidosis and metabolic alkalosis. A possible scenario would be combined volume depletion, vomiting, and lactic acidosis with hypotension. Alternatively, this could be due to methanol intoxication and vomiting, and so on.

NOTE

- If lactic acid and ethanol levels are negative in a patient with high suspicion for ingestion, serum osmolality measurement is warranted to evaluate for serum osmolality gap as evidence for other ingestion.
- While a high SAG is typically associated with metabolic acidosis, a high SAG may also occur in severe metabolic alkalosis, that is, blood pH >7.5. This is thought to be due to the conversion of previously neutral molecules to anions with severe metabolic alkalosis.

Case

- A 46-year-old morbidly obese male with obstructive sleep apnea and heart failure, status post respiratory arrest requiring mechanical ventilation 12 hours prior:

Blood chemistry: [Na^+] 145, [K^+] 3.5, [Cl^-] 100, [HCO_3^-] 32, BUN 15 mg/dL, SCr 1.5 mg/dL. Blood gas: pH 7.49, Pco_2 45 mm Hg. Urine Cl^- 14. What is/are the acid–base disturbance(s)?

Steps 1 and 2: High **[HCO^{3-}] and** high **pH** → "First" process is metabolic alkalosis.

Step 3: Compensation:	Δ[HCO_3^-]	ΔPco_2
Metabolic alkalosis	↑1	↑0.7

For current case, [HCO_3^-] ↑ by 8, Pco_2 thus ↑ by 8 × 0.7 = 5.6 or ~6 → expected Pco_2 = 40 + 6 = 46 ± 3, which is within range of actual Pco_2 of 45 → no "second" process.

Step 4: SAG = 13, which is within ±2 of normal AG of 12. → No "third" process.

Answer: Metabolic alkalosis, with urine Cl^- < 20 mmol/l, suggesting chloride-sensitive metabolic alkalosis. posthypercapnic (i.e., recovery from chronic co_2 retention with mechanical ventilation) metabolic alkalosis is the likely diagnosis.

Case

- A 27-year-old male with a 2- to 3-month history of back and abdominal pain, and left lower extremity deep venous thrombosis who presents with shortness of breath.

Blood chemistry: [Na^+] 137, [K^+] 4.4, [Cl^-] 100, [HCO_3^-] 12, BUN 65 mg/dL, SCr 7.2 mg/dL. Blood gas: pH 7.44, Pco_2 26 mm Hg.

Steps 1 and 2: Low **[HCO^{3-}] and** high **pH** → "First" process is respiratory alkalosis.

Step 3: Compensation:	Δ[HCO_3^-]	ΔPco_2
Respiratory alkalosis (acute − chronic range)	↓0.1 − 0.4	↓1

For current case, ↓Pco_2 by 14, range of Δ[HCO_3^-] would be 14 × 0.1 = 1.4 or ~1 ± 2 for acute respiratory alkalosis and 14 × 0.4 = 5.6 or ~6 ± 2 for chronic respiratory alkalosis. The expected [HCO_3^-] would thus be 24 − 1 to 24 − 6 = 23 to 18 ± 2 range or 18 to 23. Since actual [HCO_3^-] is 12 and lower than the expected range of 18 to 23, there is also a metabolic acidosis → "Second" process is metabolic acidosis.

Step 4: SAG = 25 → 12 normal AG + 13 anions → 13 anions must have accompanied 13 H^+ → 13 H^+ is expected to consume 13 [HCO_3^-] → expected [HCO_3^-] = 24 − 13 = 11 ± 2, which is within range of the actual [HCO_3^-] of 12. There is no "third" acid-base process.

Answer: Respiratory alkalosis and high SAG metabolic acidosis. This was the case of a patient with immunoglobulin G4 (IgG4)–related retroperitoneal fibrosis who presented with pulmonary embolism as a complication of lower extremity deep venous thrombosis and kidney failure from obstructive uropathy.

Case

- A 89-year-old thin female with nonspecific fatigue and weight loss:

Admitting arterial blood gas: pH 7.29, Pco_2 60 mm Hg, Po_2 70 mm Hg on 2 L of O_2. After achieving a net negative fluid balance of 7 L over 2 days on a bumetanide drip, patient eats less and sleeps more. Repeat blood gas: pH 7.34, Pco_2 85 mm Hg. Patient is still volume overloaded, and kidney function is still adequate with good response to diuretics.

Which *one* of the following would be the best treatment for her worsening hypercapnia?

A. Replace fluid loss with normal saline
B. Correct diuretic-induced metabolic alkalosis with IV 100 mM HCl
C. Initiate HD with ultrafiltration (UF)
D. Initiate noninvasive positive pressure support, add acetazolamide, and reduce bumetanide dose

Answer: D. The rise in Pco_2 is likely a compensatory response to loop-induced volume loss and metabolic alkalosis. Since patient is still volume overloaded, more fluid needs to be removed. Since patient still responds to diuretics, HD/UF is not yet necessary. Acetazolamide is a diuretic that induces bicarbonaturia. This may be added transiently to reduce the severity of bumetanide-induced metabolic alkalosis while continuing medical diuresis.

- True or false: A person walking in the street with [HCO_3^-] 34 can have either a metabolic alkalosis or acute respiratory acidosis as the *only* acid–base disorder.

For acute respiratory acidosis, the compensation is ↑0.1 HCO_3^- for every 1 increase in Pco_2.

An increase in HCO_3^- of 10 (from 24) would imply an increase in Pco_2 of 100 mm Hg. The expected Pco_2 would be 100 + 40 = 140 mm Hg.

Answer: False. Although a pure metabolic alkalosis is possible, a pure acute respiratory acidosis that would give a [HCO_3^-] of 34 implies that this individual would have to retain a Pco_2 of 140 mm Hg acutely. It is highly unlikely for an individual to have this acute rise in Pco_2 and still well enough to be walking in the street.

Similarly, an individual with a [HCO_3^-] of 14 unlikely has this value from pure acute respiratory alkalosis. A drop in [HCO_3^-] of 10 would imply a drop in Pco_2 of 10/0.1 = 100 (for every drop of 1 in Pco_2, there is a drop of 0.1 in [HCO_3^-]). The expected Pco_2 would thus be 40 − 100 = −60. This is physiologically impossible.

Bicarbonate Generation from the Combined Use of Polystyrene Sulfonate (Kayexalate) and Either Aluminum or Magnesium Hydroxide or Calcium Carbonate

Without Resin	Antacid Ingestion	With Resin
X$(OH)_2$	$Mg(OH)_2$ or any X-hydroxide salt, **X**$(OH)_2$	**X**$(OH)_2$ + Na-**Resin**
↓		↓
X$Cl_2 + 2H_2O$ ←	STOMACH 2HCl	→ **X**Cl_2 + 2Na-**Resin** + $2H_2O$
↓		↓
X$CO_3 + 2NaCl + H_2O + CO_2$ ←	DUODENUM $2NaHCO_3$	→ **X**-$(Resin)_2$ + 2NaCl
(2$NaHCO_3$ lost in reaction)		*+ 2$NaHCO_3$ (reabsorbed)*
CaCO$_3$	Calcium carbonate **CaCO$_3$**	$CaCO_3$ + Na-**Resin**
↓		↓
$CaCl_2 + CO_2 + H_2O$ ←	STOMACH 2HCl	→ $CaCl_2$ + 2Na-**Resin** + $CO_2 + H_2O$
↓		↓
$CaCO_3 + 2NaCl + H_2O + CO_2$ ←	DUODENUM $2NaHCO_3$	→ Ca-(**Resin**)$_2$ + 2NaCl
(2$NaHCO_3$ lost in reaction)		*+ 2$NaHCO_3$ (reabsorbed)*

- Similar reactions with newer resins are not yet known. However, patiromer may be expected to be at higher risk than sodium zirconium cyclosilicate, as the former has nonspecific cation binding while the latter has selectivity for potassium.

Reference: Dad T, Garimella PS, Strom JA. An unusual case of metabolic

alkalosis in a patient with CKD. *Am J Kidney Dis*. 2017;69(1):xiii–xvi.

CHAPTER 4: CHRONIC KIDNEY DISEASE

U.S. Policies in the Care of Patients with End-Stage Kidney Disease

U.S. prospective payment system for end-stage kidney disease

- In 2011, the U.S. Centers for Medicare & Medicaid Services (CMS) launched the prospective payment system (PPS) for end-stage kidney disease (ESKD) care, when the "bundled" payment system was created.
- This policy:
  - Limits the use of some medications and services in ESKD patients
  - Increases monthly margin payment per peritoneal dialysis (PD) compared with HD patient. Prior to this policy, payments favored adding an HD over PD patient.
  - The Study to Evaluate the Prospective Payment System Impact on Small Dialysis Organizations (STEPPS) revealed:
    - A decline in erythropoiesis-stimulating agent (ESA) doses and mean hemoglobin (Hb) levels that coincided with the transition to PPS
    - African American patients who tend to have higher ESA requirement to achieve target Hb were noted to have greater reductions in ESA doses in association with a greater proportion of patients with Hb < 10 g/dl, and greater need for transfusions, compared to other groups. long-term patient outcomes of pps are needed.
    - Decrease in IV vitamin D analogs and an increase in oral therapies
    - Increase in serum parathyroid levels from 273 to 324 pg/dL (acceptable parathyroid hormone [PTH] level 150 to 9 times the normal levels or 600 pg/dL)

Advancing American Kidney Care

- In July 2019, CMS Advancing American Kidney Care aimed to improve chronic kidney disease (CKD) and ESKD outcomes. The proposed initiatives are as follows:
  - CMS initiated a mandatory participation by 50% of dialysis units to enter the End-stage Renal Disease Treatment Choices (ETC) model in

2020, which encourages greater use of home dialysis and kidney transplants for Medicare beneficiaries with ESKD, while reducing Medicare expenditures.

- Four voluntary kidney models include the Kidney Care First (KCF) and Comprehensive Kidney Care Contracting (CKCC) graduated, professional, and global models.
- KCF, available to participating nephrologists and nephrology practices, will receive adjusted fixed capitated payments for managing care of aligned beneficiaries with CKD stage 4 or 5 and those on dialysis. A bonus payment will be added for every patient who receives a kidney transplant (if functional up to 3 years).
- CKCC model, available to nephrologist, transplant providers, and dialysis facilities, will take responsibility for the total cost and quality of care for the patient and, in exchange, can receive a portion of the Medicare savings they achieve.
- CKCC Graduated Model, based on the existing Comprehensive ESKD Care (CEC) model one-sided risk, begins under a lower reward one-sided model and incrementally phase in to higher risk and greater potential reward.
- CKCC professional, based on the Professional Population-Based Payment option of the Direct Contracting Model, allows opportunities to earn 50% of shared savings or be liable for 50% of shared losses based on the total cost of care for Part A and B services.
- CKCC Global Model, based on the Global Population-Based Payment option of the Direct Contracting Model, allows providers to risk 100% of the total cost of care for all Parts A and B services for aligned beneficiaries.
- By 2025, 80% of new ESKD starts will be receiving home dialysis or kidney transplant and was outlined in an Executive Order.

Peritoneal Equilibrium Testing (PET) Protocol

1. Drain peritoneal cavity, ideally after an 8 to 12 hours overnight dwell using 2 L of 2.5% dextrose dialysate.

2. Weigh a 2-L bag of warmed 2.5% dextrose dialysate.
3. Infuse bag and have patient roll from side to side after each 400 mL of dialysate.
4. Blood and dialysate samples are taken at 4 hours for urea, creatinine, glucose, and sodium for calculations of dialysate-to-plasma concentration ratios of respective solutes (D/P) to determine patient's transporter type. For glucose, calculation of the ratio D/D_0 is used to determine patient's transporter type, where D is the dialysate glucose at 4 hours of dwell, and D_0 is the dialysate glucose at the start of dwell.
5. At 4 hours, dialysate is drained, and whole bag reweighed. Difference in weight is UF volume.

Guest S. Handbook of Peritoneal Dialysis. 2nd ed. Createspace Independent Pub; 2014.

Kt/V

- Kt/V of a solute is the *proportion of volume V that has undergone clearance of that specific solute over duration of time t*, where
  - K represents the clearance capacity
  - t = the duration over which the clearance process takes place
  - V = the entire volume that is subjected to the clearance process.
- Interpretations of Kt/V for solute A:
  - *Kt/V = 1 means that the total volume V has been completely cleared of solute A over time t.
  - *Kt/V = 0.6 means that 60% of V has been cleared of solute A.

*Assuming no mixing of cleaned volume with "dirty" volume.

  - If there is mixing of cleaned volume back into the "dirty" volume, a Kt/V of 1 does not necessarily mean that all of solutes A have been cleared out. Clinically, when 250 mL of blood from a patient has been dialyzed, it is returned back into circulation, "mixed" with nondialyzed blood, then undergoes further dialysis. The remixing process does not allow for complete clearance of urea despite having passed an amount of blood equivalent to the patient's total body volume through the dialyzer.

This explains why a patient with a urea Kt/V of 1.5 or 2.0, and so on, which technically means that 1.5 or 2.0 times the patient's total body volumes V have gone through the dialyzer, still does not achieve a BUN level of 0 mg/dL.

- Currently, creatinine and urea clearances are commonly used as surrogates for all other (toxic) metabolite clearance.

Urea Clearance

Conventional indices for urea clearance

- Urea reduction ratio (URR)
  - URR = (pre − post)/pre = (1 − post/pre), which may also be expressed as %
  - Example: predialysis BUN 100 mg/dL, postdialysis BUN 66 mg/dL
  - URR = (100 − 66)/100 = 0.34 or 34%.
- Single-pool Kt/V (spKt/V) of urea
  - This is a dimensionless ratio that represents the fractional clearance of urea from a single pool, where
    - K = dialyzer blood water urea clearance (L/h)
    - t = dialysis duration (hours)
    - V = volume of distribution of urea (L). Since we cannot "drain" the entire patient's body volume V to pass through the dialyzer at any single time point, the volume that passes through the dialyzer is from a continuous mixture of dialyzed and nondialyzed volumes. Clearance of any solute thus follows a natural logarithmic (decay) pattern; hence,
    - spKt/V = −ln (1 − URR)
- What would URR be when spKt/V = 1 (i.e., the whole tank volume has gone through dialysis)?
  - 1 = −ln (1 − URR), solving for URR:

With the continuous remixing of dialyzed to nondialyzed volumes, the *maximum portion of the total body volume V* that is completely cleared of urea after running the entire body volume sequentially through the dialyzer is 0.63.

- Note that the spKt/V equation above does not take other factors into account:
  - Continuing urea generation (while dialysis is going on)
  - UF alters the volume V, thus Kt/V
  - With corrections for above factors, spKt/V becomes
  - $spKt/V = -\ln(R - 0.008 \times t) + (4 - 3.5 \times R) \times 0.55 \times UF/V$, where
    - $0.008 \times t$ takes into account the continuing urea generation
    - $(4 - 3.5 \times R) \times 0.55 \times UF/V$ takes into account UF
    - $R = 1 - URR$

Inbound versus rebound (multipool model)

- A solute such as urea is sequestered into other compartments (not just single pool).
- *Inbound* refers to the sequestration/movement of urea (solutes) into other compartments during dialysis.
- *Rebound* refers to the release of urea (solutes) from other compartments into the blood volume that is accessible to dialysis.
- These occurrences lead to the concept of equilibrated Kt/V, or eKt/V. This is measured 30 to 60 minutes postdialysis.
- In general, eKt/V = spKt/V − rebound. To measure rebound, blood sampling is measured 30 to 60 minutes postdialysis. To avoid waiting, eKt/V may be estimated to be ~0.8 × Kt/V (i.e., eKt/V is typically 20% less than Kt/V).
- What is the difference between whole blood versus plasma clearance? Solute clearance per 1 L of whole blood is lower than that for 1 L of plasma volume. Whereas solutes dissolved in plasma are accessible to dialysis, solutes inside red blood cells are not accessible to dialysis.
- How does increasing Hb level affect dialysis clearance? Correction of anemia does lead to reduced solute clearance due to reduced plasma volume available for solute clearance given the same blood flow through the dialyzer. More dialysis may be needed to achieve the same goal Kt/V.

Common Terms Used in Dialysis

UF coefficient, K_{UF}

- K_{UF} is the ultrafilterability of the membrane, expressed as mL/h/mm Hg of transmembrane pressure (TMP) applied.
- Example: K_{UF} of 10 mL/h/mm Hg implies that in order to ultrafiltrate 500 mL/h, a TMP of 50 mm Hg would have to be applied.
- TMP = Desired UF/K_{UF}

Dialyzer clearance, KoA

- KoA is the maximum theoretical clearance of any dialyzer. True solute removal is typically 5% to 30% less than published KoA.
- Choosing a dialysis KoA for a patient depends on blood flow, dialysate flow, and desired urea clearance to meet a specified Kt/V.

Standardized Kt/V (Std Kt/V)

- Std Kt/V is a continuous clearance equivalent that takes into account the continuing generation of the solute being cleared. Std Kt/V may be used to compare any form of dialysis (home, daily, conventional dialyses, and PD).

Membrane efficiency versus flux

- Efficiency implies amount of solute removed. High efficiency may be obtained with large surface area membranes.
- High flux implies great ability to remove larger molecules such as β2-microglobulins. High-flux dialyzer membranes have larger pores.

For a comprehensive review of all renal replacement modalities, see Daugirdas JT, Blake PG, Ing TS, eds. Handbook of Dialysis. 5th ed. Philadelphia, PA: Wolters Kluwer, 2014.

CHAPTER 7: GLOMERULAR AND VASCULAR DISORDERS

Pathogenesis of Lupus Nephritis

Production of autoantibodies

- *Production of autoantibodies* by mature B cells (plasma cells) against nuclear antigens (e.g., double-stranded DNA [dsDNA]), ribonucleoproteins, complement factors (e.g., C1q). This process may be

driven by:

- Antigenic mimicry: antibodies against bacterial or viral peptides cross-react to self-antigens
- Impaired clearance of apoptotic bodies
- Polyclonal hyperactivity of the B-cell system or defects of T-cell autoregulation leading to high antibody production
- Anti-dsDNA antibody response driven by histone-specific T-helper cells

Immune-complex (IC) deposition

- Deposition of circulating ICs in glomerular basement membrane (GBM) or direct binding of nucleosomal antigens to GBM followed by in situ autoantibody binding activates both complement-dependent and complement-independent inflammatory cascades.

Immune-complex clearance

- ICs are normally cleared by the C1 complement complex. Binding of C1 complex to IC leads to downstream complement activation and opsonization of the IC for phagocytosis.
- C1q is a component of the C1 complex. Upon binding of C1 complex to IC, C1 complex undergoes conformational change, exposing antigenic sites of C1q, which then leads to autoantibody formation against C1q. High autoantibody titers against C1q have been suggested to correlate with active lupus. Additionally high C1q autoantibody levels have also been shown to negatively correlate with C1q antigen serum concentrations.

Inflammatory effects

- **Inflammatory effects** following impaired apoptotic bodies clearance and/or IC formations and roles of other inflammatory cells:
  - Neutrophils:
    - NETosis: a process whereby upon exposure to microorganisms, neutrophils release nuclear components, granule proteins, and chromatin to form an extracellular matrix, referred to as “neutrophil extracellular traps” (NETs) to “trap,” destroy, and clear the invading microorganisms. NETs are comprised of DNA and histones along with various peptides and proteinases, such as high mobility group

protein box-1, cathelicidin, myeloperoxidase, neutrophil elastase, matrix metalloproteinase 9, and proteoglycan recognition protein short. NETs may serve as a source of autoantigens in systemic lupus erythematosus (SLE).
    - There are data to suggest that NETs are complement activators and can play a role in increasing C1q deposition.
- Basophils:
    - Cross-linking of IgE to its receptors (FcεRI) on basophil surface leads to the secretion of histamine and proinflammatory cytokines by basophils.
    - There are data to suggest that increased titers of both dsDNA-IgE and dsDNA-IgG predict SLE disease activity better than dsDNA-IgG titers alone.
    - Activated basophils secrete cytokines (interleukin-4 [IL-4] and IL-6) and express the MHC-II and B-cell–activating factor BAFF (also known as B-Lys), which can enhance plasma cell survival and autoantibody production amplification loop.
    - Other functions of activated basophils: promotion and regulation of TH2 adaptive immune responses, antigen presentation to T cells, plasma cell differentiation and support, monocyte polarization and recruitment, and inflammatory site organization
- Macrophages/monocytes:
    - NETs containing LL37 stimulate NLRP3 inflammasome in monocytes and result in IL-1β and IL-18 release, NETosis, and amplification of the proinflammatory state.
    - Polymorphism in the IL-18 gene promoter with associated increased IL-18 production may promote SLE susceptibility.
- Autoreactive B cells and T cells due to defective regulatory mechanisms

Testing Options for Monoclonal Gammopathy

- Serum (or urine) protein electrophoresis (SPEP or UPEP): SPEP separates serum proteins into five general regions in the order of albumin, α-1, α-2, β, and γ based on their charge and size. The various Ig classes (IgG, IgA,

IgM, IgD, and IgE) are usually of γ mobility, but they may also be found in the β-γ and β regions and, occasionally, extend into the α-2 globulin area.

- An "M"-spike indicates the presence of an "M" onoclonal protein. Each M-protein consists of two heavy polypeptide chains of the same class: γ (IgG: IgG1–IgG4), α (IgA: IgA1, IgA2), μ (IgM), δ (IgD), ε (IgE). The paired heavy chains are associated with two light chains of the same type (κ or λ), not both.
- "Polyclonal γ range" on SPEP indicates polyclonal Ig production in response to various conditions, including liver disease, connective tissue, and nonspecific inflammatory disorders.
- SPEP is a useful screening procedure, but it may miss a small M-protein spike or falsely identify a polyclonal increase in Ig or non-Ig as an M-protein spike. Identification of the actual makeup of the M-protein requires immunofixation. In serum (or urine) protein immunofixation electrophoresis (IFE), antibodies directed against the heavy and light chains (anti-γ, anti-μ, anti-α [IgG, IgM, IgA] and anti-κ and anti-λ) are added following the initial electrophoresis procedure to identify overproduction of any corresponding chain.
- Direct assay for serum free light chain (FLC) (Bence Jones) is more sensitive in establishing the diagnosis of monoclonal gammopathy than either SPEP or IFE. However, it must be noted that the quantity of both κ and λ light chains may be increased with poor kidney function due to reduced renal excretion. The abnormal ratio of κ to λ light chains (i.e., outside the range of 0.26 to 1.65 for normal kidney function and 0.37 to 3.1 for poor kidney function) in addition to the absolute values of the κ and λ light changes may better serve as an indicator of a monoclonal gammopathy in patients with advanced CKD.
- Serum FLC assay is particularly important in the diagnosis of nonsecretory myeloma, AL amyloidosis (patients with amyloidosis may not have active myeloma), and light-chain–only myeloma.

Data Regarding the Effect of Glycemic Control and Albuminuria and Cardiovascular Outcomes

Studies indicating that strict glycemic control decreased risk for

microalbuminuria

- Diabetes Control and Complications Trial (DCCT) (diabetes mellitus [DM] type 1): 9-year follow-up, intensive therapy group with mean A1C of 7% had a 35% to 45% lower risk for development of microalbuminuria compared with control group (mean A1C 9%); renoprotection persists even after return to less intensive therapy, a phenomenon known as "legacy effect." This is presumably due to the effect of euglycemia on long-lasting modification of transcription of genes responsible for diabetic kidney disease (DKD).
- Kumamoto study, DM type 2: 60% rate reduction of microalbuminuria in relatively young nonobese DM type 2 patients in intensive group (mean A1C 7%) compared with conventional therapy group (mean A1C 9.4%)
- U.K. Prospective Diabetes Study (UKPDS), DM type 2: A1C ~7.0% versus 7.9%
  - Relative risk reduction for development of microalbuminuria
  - 10-year follow-up after study ended still revealed 24% lower risk of microvascular disease and myocardial infarction. All-cause mortality also remained reduced and attributed to "legacy effect."

Strict glycemic control: effects on cardiovascular disease (CVD)

- Action in Diabetes and Vascular Disease, Perindopril and Indapamide Controlled Evaluation (ADVANCE): intensive control (A1C 6.5% vs. 7.3%) resulted in a *10% relative reduction in combined outcome of major macrovascular and microvascularly events*, primarily as a consequence of a 21% relative reduction in nephropathy.
- Action to Control Cardiovascular Risk in Diabetes (ACCORD): very tight control (A1C 6.5% vs. 7.5%) had *higher mortality*, up by 22%, $p = 0.04$.
- Veterans Affairs Diabetes Trial (VADT): A1C 6.9% versus 8.4%: *no difference in reduction in cardiovascular deaths or events* at 7.5-year follow-up.

The Use Angiotensin-Converting Enzyme Inhibitor Versus Angiotensin-Receptor Blocker in Diabetic Kidney Disease (DKD)

- Renin–angiotensin–aldosterone system (RAAS) inhibition with either

angiotensin- converting enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB) confers renoprotection in patients with DKD, independent of blood pressure control via both intraglomerular hemodynamic and nonhemodynamic (i.e., antiproliferative and antifibrotic) effects against angiotensin II (AII).

- RAAS inhibition also blocks aldosterone, which, in turn, increases sodium excretion and potassium and magnesium wasting and reduces tissue inflammation and fibrosis. Forty percent to 50% of patients on ACEI or ARB develop an "aldosterone escape" by 12 months of therapy. Addition of aldosterone antagonism may be considered if indicated and safely tolerated.
- **Data on DM type 1:**
  - RAAS inhibition does not reduce the progression from normoalbuminuria to microalbuminuria.
  - ACEI reduces the risk of progression from microalbuminuria to overt nephropathy.
  - In *normotensives* with microalbuminuria, ACEI leads to a 60% reduction in progression to macroalbuminuria and three times likelihood in regression to normoalbuminuria.
  - Captopril treatment in patients with macroalbuminuria or overt nephropathy reduces albuminuria and GFR decline and delays the onset of kidney failure.
  - Similar data for ARB are not as robust as those for ACEI, but their clinical effects are expected to be similar to ACEI.
- **Data on DM type 2:**
  - Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria study (IRMA 2) trial: Irbesartan reduces progression to overt DKD by 70% in hypertensive type 2 patients over 2-year follow-up.
  - Microalbuminuria Reduction with Valsartan in Patients with Type 2 DM (MARVAL) trial: Daily valsartan 80 mg reduces urinary albumin excretion better than amlodipine (44% vs. 8%).
  - Irbesartan Diabetic Nephropathy T (IDNT) and Reduction in Endpoints in NIDDM with the AII Antagonist Losartan (RENAAL) trials: DM

type 2 with macroalbuminuria and reduced GFR, ARBs reduce proteinuria and composite end points of death, dialysis, and doubling of SCr.

Note: In contrast to DM type 1, data on efficacy of ACEI in type 2 DKD are not as robust.

CHAPTER 9: KIDNEY TRANSPLANTATION

Breastfeeding in Kidney Transplantation

- Currently available safety data suggest that breastfeeding while on azathioprine, cyclosporine, or tacrolimus is generally safe. However, exclusively breastfed infants should be monitored closely and cyclosporine (or tacrolimus) drug levels should be measured if there is a concern for toxicity. Consultation with LACTMED database website is recommended (see reference **LACTMED: A TOXNET Database** in **Chapter 9 Kidney Transplantation**).
- Breastfeeding is *not* recommended while on mycophenolic acid derivatives, sirolimus, everolimus, or belatacept due to lack of data on drug excretion in breast milk and lack of clinical safety data.

De Novo Glomerular Diseases After Transplantation

De Novo Disease	Incidence	Risk of Graft Loss	Comments
Diabetic glomerulosclerosis	20%–50%	20%	Of those with posttransplantation diabetes mellitus
FSGS	2%–5%	24%–40%	Months to years after transplantation
Membranous nephropathy	2%–9%	NA	Usually anti-PLA2R negative. IgG1 dominant, may be associated with ABMR or HCV, more common in children
IgA nephropathy	1%–2%	NA	May be transplanted IgA deposits Poor outcome associated with crescents
C1q nephropathy	<1%	NA	Usually > 1 y after transplantation with no clinical significance
Anti-GBM antibody nephritis	3%–12%	Rare	Associated with primary Alport syndrome, may be asymptomatic linear IgG
Immune-complex–	3%	NA	Associated with HCV

mediated MPGN			

Abbreviations: ABMR, antibody-mediated rejection; FSGS, focal segmental glomerulosclerosis; HCV, hepatitis C; MPGN, membranoproliferative glomerulonephritis pattern of injury; NA, not available; PLA2R, phospholipase A2 receptor; GBM, glomerular basement membrane; IgA, immunoglobulin A.

CHAPTER 11: ACUTE KIDNEY INJURY/INTENSIVE CARE UNIT NEPHROLOGY

United Network of Organ Sharing Model for End-Stage Liver Disease

Risk score = 10 × ((0.957 × ln[SCr]) + (0.378 × ln[Bilirubin]) + (1.12 × ln[INR])) + 6.43

If a patient is on HD, SCr is set to 4, the maximum creatinine level allowed in the model. INR: prothrombin time/international normalized ratio. Model for end-stage liver disease (MELD) score can range from 6 to 40 (anything > 40 is grouped into 40 maximum), where a higher range indicates higher urgency for liver transplantation (higher mortality risk).

CHAPTER 12: CONTINUOUS RENAL REPLACEMENT THERAPY

Sample of Citrate Anticoagulation Protocol (University of Alabama)

Initial setup

1. Prefilter replacement fluid (preblood pump): Use 0.5% trisodium citrate solution (Na^+ 140 mmol/L, $citrate^{3-}$ 17 mmol/L); run at 1,000 to 2,000 mL/h. **Note:** This solution does contain any potassium. If this solution is infused at the same rate as that for the standard dialysate solution, the effective K^+ concentration is 2 mmol/L. Hypokalemia may be a problem, in which case IV peripheral potassium supplement may be necessary.
2. Dialysate: Use standard bicarbonate solution (Na^+ 140 mmol/L, HCO_3^- 25 mmol/L, K^+ 4.0 mmol/L, Mg^{2+} 0.75 mmol/L, glucose 100 mg/dL; infuse at 1,500 to 2,500 mL/h).
3. Postfilter fluid: Use standard bicarbonate fluid (25 mmol/L), run at 200 mL/h. The use of postfilter replacement fluid is required for the deaeration chamber of Prismaflex.

4. Peripheral calcium gluconate 66.5 mmol/L: Infuse at initial rate of 60 mL/h.

Follow-up/monitoring

1. Check chemistry panel q6h (including sodium, potassium, total CO_2 [bicarbonate], total serum calcium, phosphorus, and magnesium). All blood drawn from patient must be away from calcium infusion line and the site of the dialysis catheter.
2. Check ionized calcium (iCa^{2+}) q6h from the venous port (blood returning to patient—blue port in Prismaflex). **For optimal anticoagulation, venous port iCa^{2+} goal is 0.25 to 0.4 mmol/L.**
3. Nephrologist must be notified if iCa^{2+} from the venous port (blue port) is >0.5 mmol/L.
4. Check systemic iCa^{2+} from the patient 1 hour after start and then q6h.
5. Nephrologist must be notified if the systemic iCa^{2+} is < 0.9 mmol/l or >1.3 mmol/L.
6. After 48 hours, postfilter ionized calcium level checks may be stopped.

Titration of calcium gluconate drip 66.5 mmol/L

1. Check patient systemic ionized calcium q6h.
2. iCa^{2+} > 1.35 mmol/L → decrease flow by 10 mL/h
3. iCa^{2+} 0.9 to 1.3 mmol/L → no change
4. iCa^{2+} < 0.8 to 0.9 mmol/l → increase drip by 10 ml/h
5. iCa^{2+} < 0.8 mmol/l → increase drip by 20 ml/h—monitor ica^{2+} more frequently (e.g., q4h or more frequently instead of q6h depending on severity). nephrologist must be notified at this ica^{2+} level.

- Troubleshoot for abnormally low systemic iCa^{2+}:
  1. Erroneous source of blood sampling: Systemic ionized calcium sampling must not be drawn from pigtail of the dialysis catheter (falsely low) or calcium infusion line (falsely high).
  2. Erroneous placement of citrate fluid into dialysate line. Citrate fluid should be hung only on the preblood pump line (white line on Prismaflex).
  3. Erroneous rate of infusion of 0.5% trisodium citrate. The rate of this

solution should range between 1,000 and 2,000 mL/h.

4. Erroneous rate and placement of infusion of calcium drip. Calcium drip must be infused while citrate is used and may be stopped when the Prismaflex machine is disconnected. Typical rates are 60 to 100 mL/h. **Note:** The calcium drip should be infused back into the patient through a separate IV pump and Y-connector attached to the venous return line of the continuous renal replacement therapy (CRRT) circuit. It is important that the venous and arterial ports of the catheter are not switched (sometimes, this is done when the access does not work well).
5. Check if patient has received any citrate-containing blood products.
6. If there is no obvious reason for systemically low ionized calcium, repeat level. In the case of severely low iCa^{2+}, administer 1 to 2 ampules of calcium gluconate, increase the calcium infusion rate, and repeat the iCa^{2+} in 1 hour. If systemic iCa^{2+} level remains <0.9 mmol/l, repeat the above steps until ica^{2+} level is within range and evaluate for citrate toxicity.

Points to remember regarding citrate anticoagulation

- Citrate anticoagulation should not be used with slow continuous ultrafiltration (SCUF) because citrate removal is very minimal with SCUF.
- A lower blood flow should be used with citrate anticoagulation to reduce citrate dose.

APPENDIX B: Core Resources and Selected Readings

CORE TEXTBOOKS

Danovitch GM, ed. *Handbook of Kidney Transplantation*. 6th ed. Philadelphia, PA: Wolters Kluwer; 2017.

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Rose B, ed. *Clinical Physiology of Acid-Base and Electrolyte Disorders*. 5th ed. New York, NY: McGraw-Hill Companies, Inc.; 2001.

ONLINE RESOURCES

Asn-online.org//education/brcu

Kdigo.org/home/guidelines

Medscape.com

UptoDate.com

SELF-ASSESSMENT SERIES

Kidney Self-Assessment Program (KSAP), American Society of Nephrology

Nephrology Self-Assessment Program (NephSAP), American Society of Nephrology

CHAPTER-SPECIFIC SELECTED READINGS

Chapter 1

Sodium/Water

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Acid–Base and Potassium Disorders

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APPENDIX C: Normal Laboratory Values

HEMATOLOGY

White blood cell count	4–10 × 10^3/μL
Hemoglobin	Male: 14–17 g/dL Female: 12–16 g/dL
Hematocrit	Male: 45%–52% Female: 37%–48%
Platelet count	150–350 × 10^3/μL
Mean corpuscular volume	80–100 fL
Reticulocyte count	0.5%–1.5% of erythrocytes
Haptoglobin	50–220 mg/dL

COAGULATION STUDIES/COAGULANT FACTORS

Activated partial thromboplastin time	25–35 s
Prothrombin time	11–13 s
Plasma fibrinogen	150–350 mg/dL
D-Dimer	<0.5 μg/mL

ANEMIA EVALUATION STUDIES

Iron	60–160 mg/dL
Iron-binding capacity, total	250–460 mg/dL
Transferrin saturation	20%–50%
Ferritin	15–200 mg/dL
Folate, serum	2.5–20 ng/mL
Folate, red cell	160–855 ng/mL
Vitamin B_{12}, serum	200–800 pg/mL

SERUM CHEMISTRY, COMMON BLOOD, AND PLASMA

STUDIES

Sodium	136–145 mmol/L
Potassium	3.5–5.0 mmol/L
Chloride	98–106 mmol/L
Total CO_2 (bicarbonate)	23–28 mmol/L
Blood urea nitrogen	8–20 mg/dL
Creatinine	0.7–1.3 mg/dL
Glucose (fasting)	70–100 mg/dL
Calcium	9–10.5 mg/dL
Phosphorus	3–4.5 mg/dL
Magnesium	1.5–2.4 mg/dL
Uric acid	2.5–8 mg/dL
Plasma osmolality	275–295 mOsm/kg H_2O
Lactate dehydrogenase	60–100 U/L
Lactic acid (venous)	0.67–1.8 mmol/L
Creatine phosphokinase	30–170 U/L
Complements, C3	55–120 mg/dL
Complements, C4	16–48 mg/dL
Complements, total (CH50)	37–55 U/mL

ENDOCRINE

Parathyroid hormone	10–65 pg/mL
Vitamin D: 1,25-dihydroxy	25–65 pg/mL
Vitamin D: 25-hydroxy	15–80 ng/mL
Aldosterone, supine	2–5 ng/dL
Aldosterone, standing	7–20 ng/dL
Plasma renin activity	0.6–4.3 µg/L/h

LIVER FUNCTION TESTS

Total protein	6.0–7.8 g/dL
Globulins	2.5–3.5 g/dL
Albumin	3.5–5.5 g/dL
Aminotransferase, alanine (ALT)	0–35 U/L
Aminotransferase, aspartate (AST)	0–35 U/L
Alkaline phosphatase	36–92 U/L
γ-Glutamyltransferase (GGT)	0–30 U/L

Total bilirubin	0.3–1.2 mg/dL
Direct bilirubin	0–0.3 mg/dL

URINE

Albumin to creatinine ratio	<30 mg/g
Protein to creatinine ratio	≤0.2 g/g
Catecholamines	<100 µg/m^2/24 h
Cortisol, free	<90 µg/24 h

24-HOUR URINE METABOLIC PROFILE FOR KIDNEY STONES

Collection adequacy for lean patients ≤ 50 years	Women: 15–20 mg/kg/24 h Men: 20–25 mg/kg/24 h
Calcium	Women: <200 mg/24 h Men: <250 mg/24 h
Uric acid	Women: <750 mg/24 h Men: <800 mg/24 h
Oxalate	<40 mg/24 h
Citrate	≥450 mg/24 h

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