303 Cellular and Molecular Biology of the Kidney

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

EMBRYOLOGIC DEVELOPMENT

Kidneys develop from intermediate mesoderm under the timed or sequential control of a growing number of genes, described in Fig. 303-1. The transcription of these genes is guided by morphogenic cues that invite two ureteric buds to each penetrate bilateral metanephric blastema, where they induce primary mesenchymal cells to form early nephrons. The two ureteric buds emerge from posterior nephric ducts and mature into separate collecting systems that eventually form a renal pelvis and ureter. Induced mesenchyme undergoes mesenchymal epithelial transitions to form comma-shaped bodies at the proximal end of each ureteric bud leading to the formation of S-shaped nephrons that cleft and enjoin with penetrating endothelial cells derived from sprouting angioblasts. Under the influence of vascular endothelial growth factor A (VEGF-A), these penetrating cells form capillaries with surrounding mesangial cells that differentiate into a glomerular filter for plasma water and solute. The ureteric buds branch and each branch produce a new set of nephrons. The number of branching events ultimately determines the total number of nephrons in each kidney. There are ~900,000 glomeruli in each kidney in normal birth weight adults and as few as 225,000 in low-birth-weight adults, with the latter producing numerous comorbid risks.

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

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

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

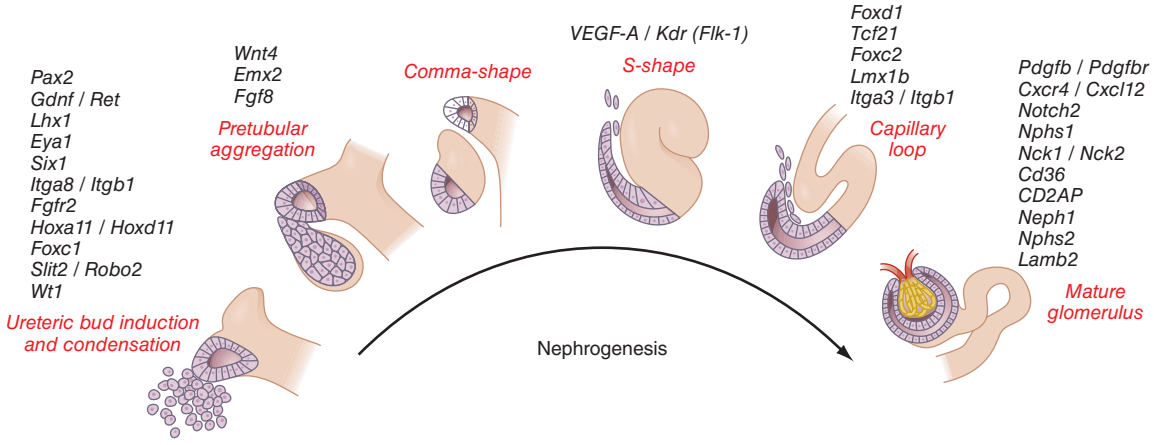


FIGURE 303-1 Genes controlling renal nephrogenesis. A growing number of genes have been identified at various stages of glomerulotubular development in the mammalian kidney. The genes listed have been tested in various genetically modified mice, and their location corresponds to the classical stages of kidney development postulated by Saxen in 1987.

longer loops of Henle, create an osmotic gradient for concentrating urine. How developmental instructions specify the differentiation of all these unique epithelia among various tubular segments is still unknown.

DETERMINANTS AND REGULATION OF GLOMERULAR FILTRATION

Renal blood flow normally drains ~20% of the cardiac output, or 1000 mL/min. Blood reaches each nephron through the afferent arteriole leading into a glomerular capillary where large amounts of fluid and solutes are filtered to form the tubular fluid. The distal ends of the glomerular capillaries coalesce to form an efferent arteriole leading to the first segment of a second capillary network (cortical peritubular capillaries or medullary vasa recta) surrounding the tubules **(Fig. 303-2*A*)**. Thus, nephrons have two capillary beds arranged in a series separated by the efferent arteriole that regulates the hydrostatic pressure in both capillary beds. The distal capillaries empty into small venous branches that coalesce into larger veins to eventually form the renal vein.

The hydrostatic pressure gradient across the glomerular capillary wall is the primary driving force for glomerular filtration. Oncotic pressure within the capillary lumen, determined by the concentration of unfiltered plasma proteins, partially offsets the hydrostatic pressure gradient and opposes filtration. As the oncotic pressure rises along the length of the glomerular capillary, the driving force for filtration falls to zero en route to the efferent arteriole. Approximately 20% of the renal plasma flow is filtered into Bowman space, and the ratio of glomerular filtration rate (GFR) to renal plasma flow determines the filtration fraction. Several factors, mostly hemodynamic, contribute to the regulation of filtration under physiologic conditions.

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

TGF changes the rate of filtration and tubular flow by reflex vasoconstriction or dilatation of the afferent arteriole. TGF is mediated by specialized cells in the thick ascending limb of the loop of Henle called the *macula densa* that act as sensors of solute concentration and tubular fluid flow rate. With high tubular flow rates, a proxy for an inappropriately high filtration rate, there is increased solute delivery to the macula densa **(Fig. 303-2*B*)** that evokes vasoconstriction of the afferent arteriole causing GFR to return toward normal. One component of the soluble signal from the macula densa is adenosine triphosphate (ATP) released by the cells during increased NaCl reabsorption. ATP is metabolized in the extracellular space to generate adenosine, a potent vasoconstrictor of the afferent arteriole. During conditions associated with a fall in filtration rate, reduced solute delivery to the macula densa attenuates TGF, allowing afferent arteriolar dilatation and restoring GFR to normal levels. Angiotensin II and reactive oxygen species enhance, while nitric oxide (NO) blunts TGF.

The third component underlying autoregulation of GFR involves angiotensin II. During states of reduced renal blood flow, renin is released from granular cells within the wall of the afferent arteriole near the macula densa in a region called the juxtaglomerular apparatus (Fig. 303-2*B*). Renin, a proteolytic enzyme, catalyzes the conversion of angiotensinogen to angiotensin I, which is subsequently converted to angiotensin II by angiotensin-converting enzyme (ACE) **(Fig. 303-2*C*)**. Angiotensin II evokes vasoconstriction of the efferent arteriole, and the resulting increased glomerular hydrostatic pressure elevates GFR to normal levels.

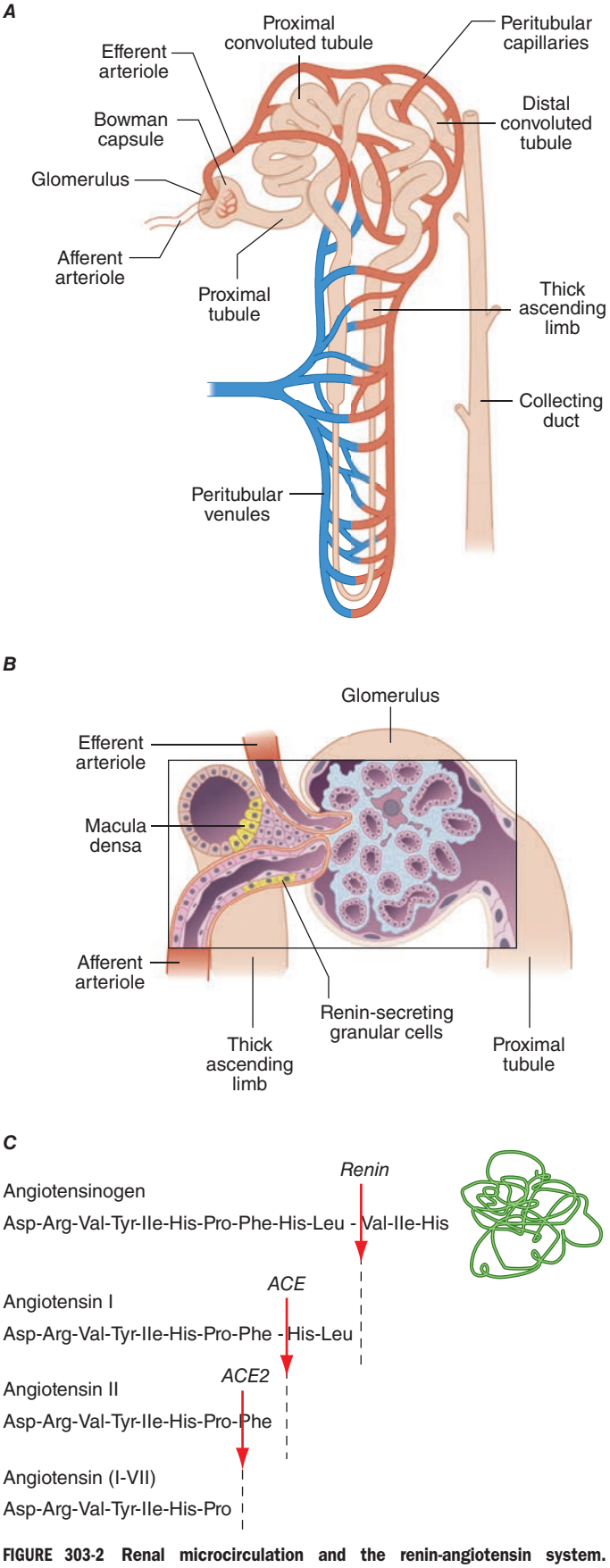


FIGURE 303-2 Renal microcirculation and the renin-angiotensin system. ***A.*** Diagram illustrating relationships of the nephron with glomerular and peritubular capillaries. ***B.*** Expanded view of the glomerulus with its juxtaglomerular apparatus including the macula densa and adjacent afferent arteriole. ***C.*** Proteolytic processing steps in the generation of angiotensins.

MECHANISMS OF RENAL TUBULAR TRANSPORT

The renal tubules are composed of highly differentiated epithelia that vary dramatically in morphology and function along the nephron (Fig. 303-3). The cells lining the various tubular segments form monolayers connected to one another by a specialized region of the adjacent lateral membranes called the *tight junction*. Tight junctions form an occlusive barrier that separates the lumen of the tubule from the interstitial spaces surrounding the tubule and also apportions the cell membrane into discrete domains: the apical membrane facing the tubular lumen and the basolateral membrane facing the interstitium. This regionalization allows cells to allocate membrane proteins and lipids asymmetrically. Owing to this feature, renal epithelial cells are said to be *polarized*. The asymmetric assignment of membrane proteins, especially proteins mediating transport processes, provides the machinery for directional movement of fluid and solutes by the nephron.

EPITHELIAL SOLUTE TRANSPORT

There are two types of epithelial transport. Movement of fluid and solutes sequentially across the apical and basolateral cell membranes (or vice versa) mediated by transporters, channels, or pumps is called *cellular transport*. By contrast, movement of fluid and solutes through the narrow passageway between adjacent cells is called *paracellular transport*. Paracellular transport occurs through tight junctions, indicating that they are not completely "tight" or occlusive. Indeed, some epithelial cell layers allow rather robust paracellular transport to occur (*leaky epithelia*), whereas other epithelia have more restrictive tight junctions (*tight epithelia*). In addition, because the ability of ions to flow through the paracellular pathway determines the electrical resistance across the epithelial monolayer, leaky and tight epithelia are also referred to as low- or high-resistance epithelia, respectively. The proximal tubule contains leaky epithelia, whereas distal nephron segments, such as the collecting duct, contain tight epithelia. Leaky epithelia are

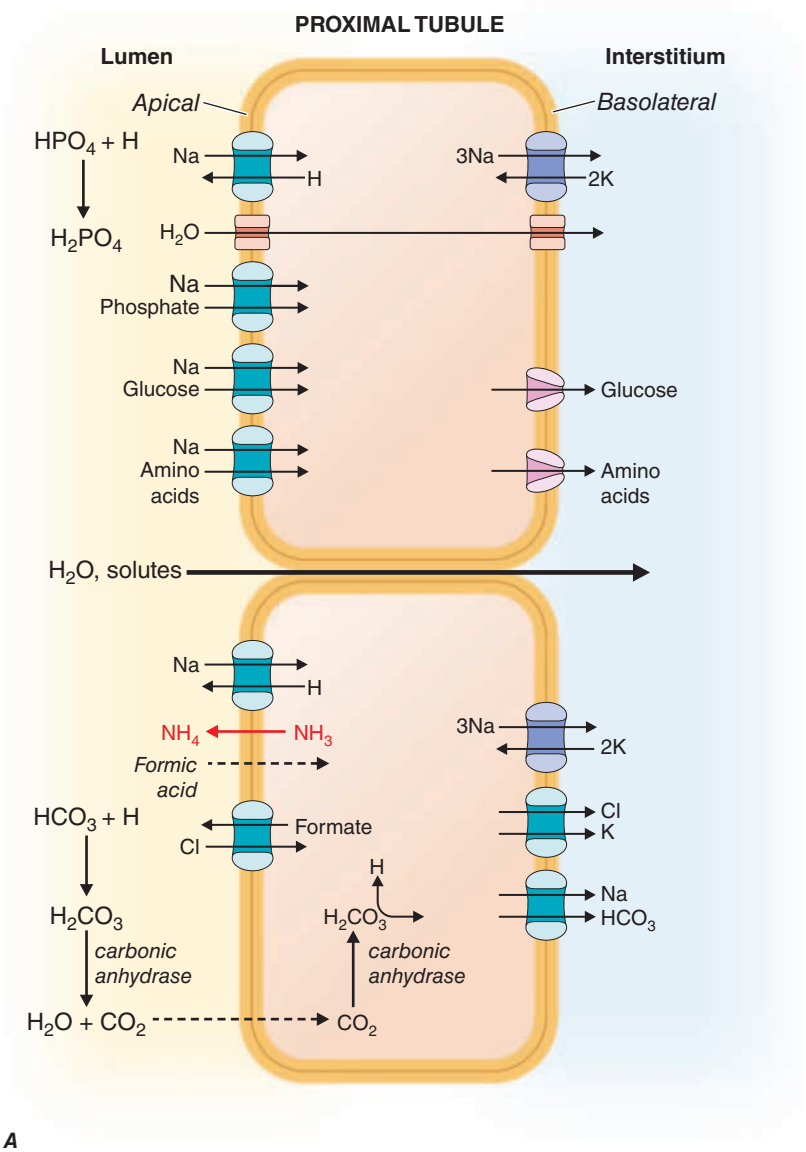
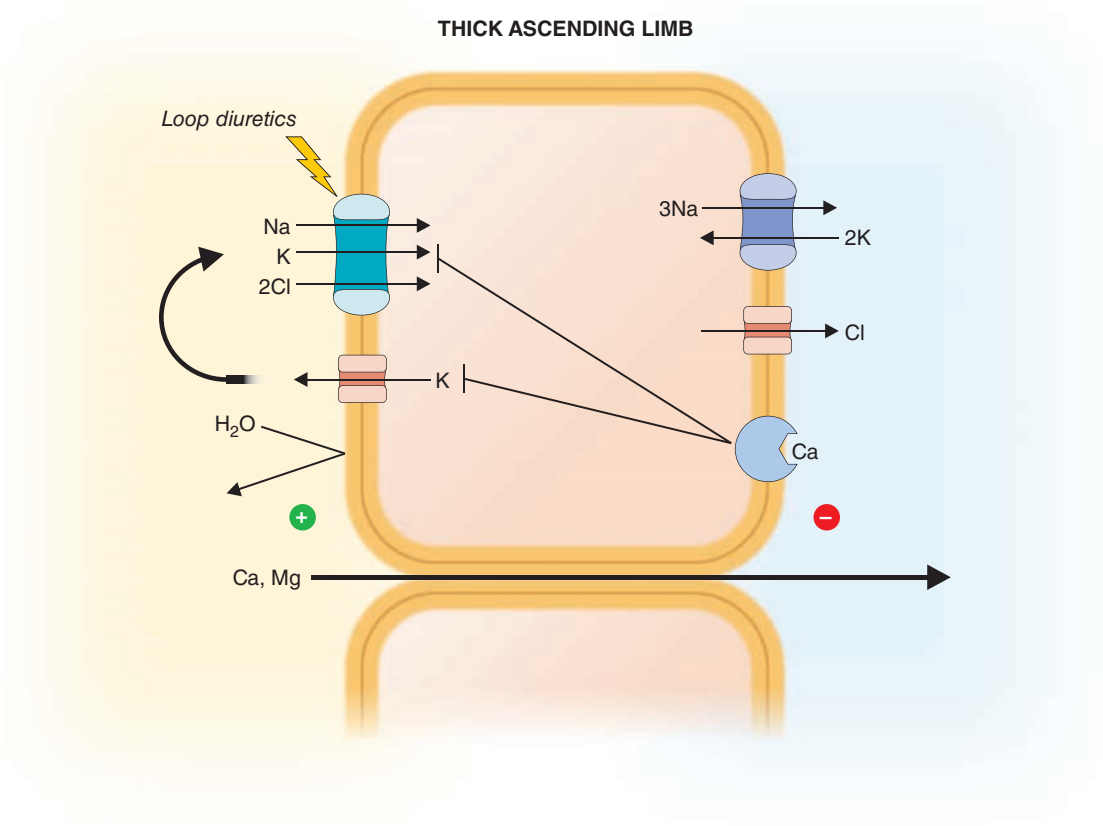


FIGURE 303-3 Transport activities of the major nephron segments. Representative cells from five major tubular segments are illustrated with the lumen side (apical membrane) facing left and interstitial side (basolateral membrane) facing right. ***A.*** Proximal tubular cells. ***B.*** Typical cell in the thick ascending limb of the loop of Henle. ***C.*** Distal convoluted tubular cell. ***D.*** Overview of entire nephron. ***E.*** Cortical collecting duct cells. ***F.*** Typical cell in the inner medullary collecting duct. The major membrane transporters, channels, and pumps are drawn with *arrows* indicating the direction of solute or water movement. For some events, the stoichiometry of transport is indicated by numerals preceding the solute. Targets for major diuretic agents are labeled. The actions of hormones are illustrated by *arrows with plus signs* for stimulatory effects and *lines with perpendicular ends* for inhibitory events. The *dashed line* indicates water impermeability of cell membranes in the thick ascending limb and distal convoluted tubule.



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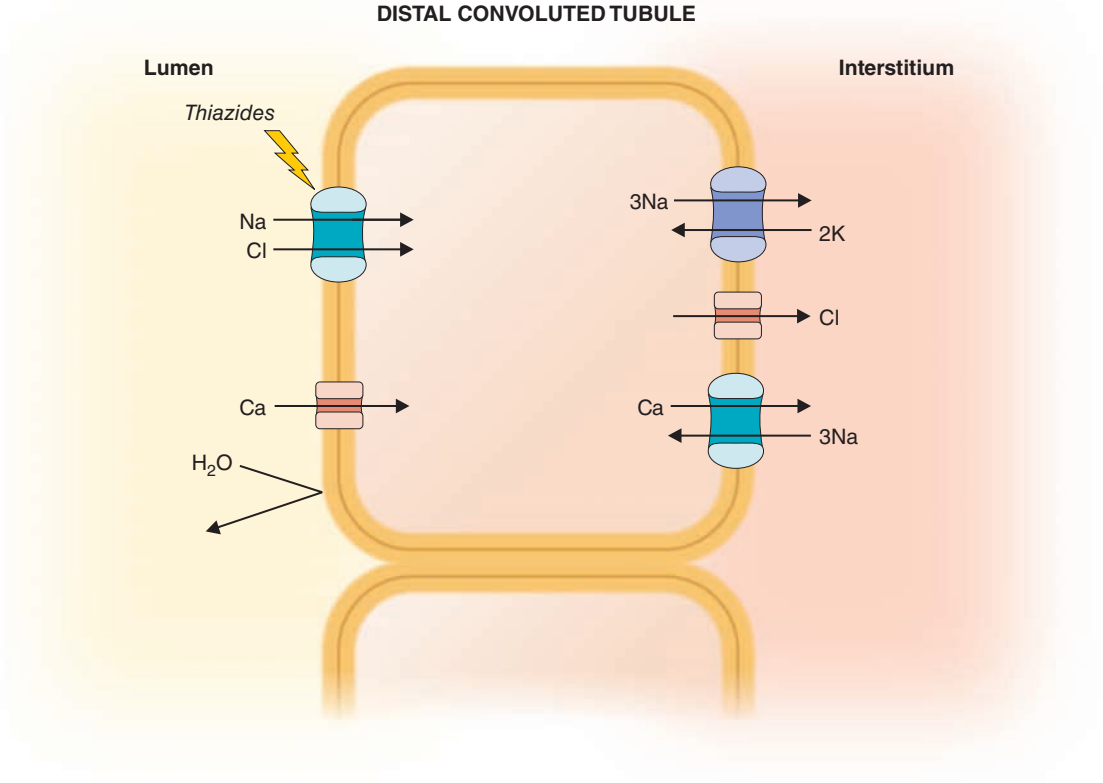

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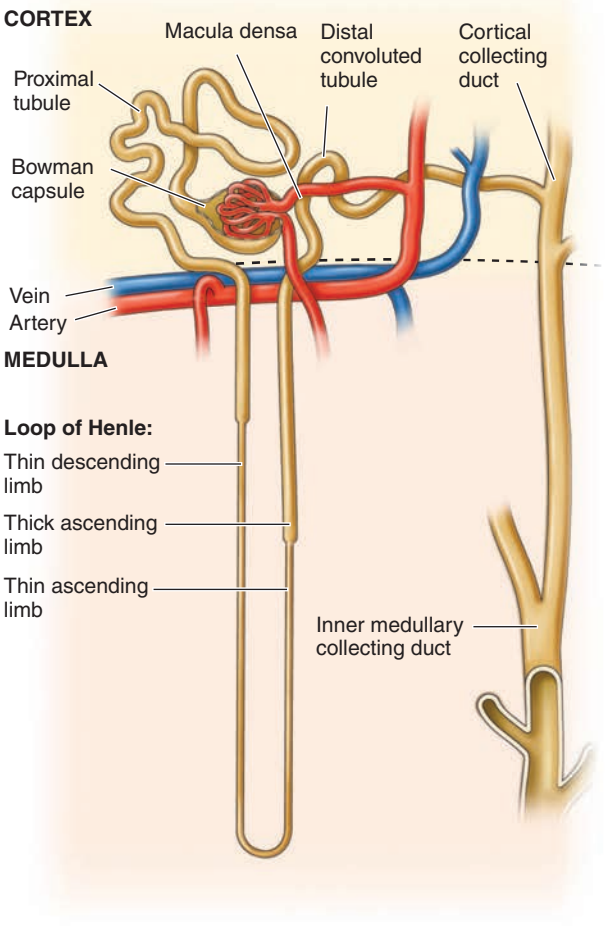
FIGURE 303-3 (*Continued*)



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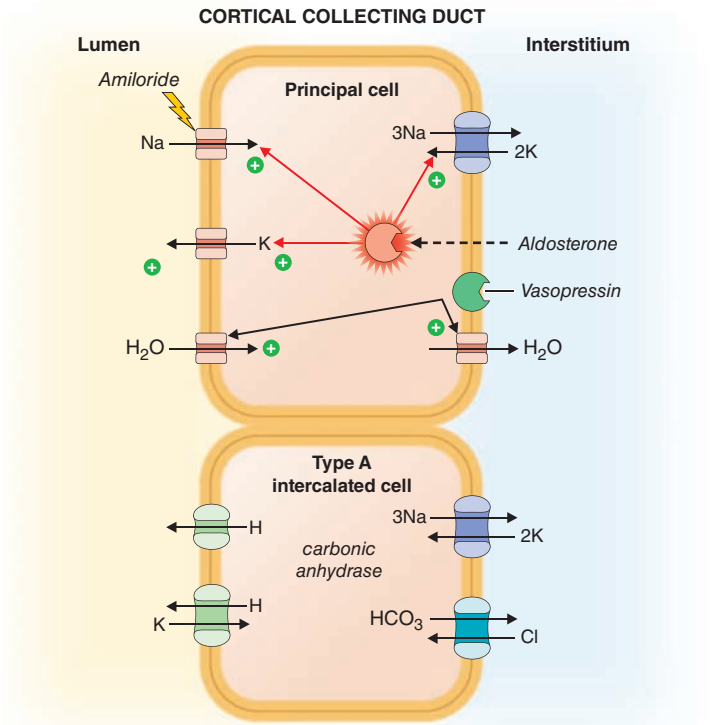

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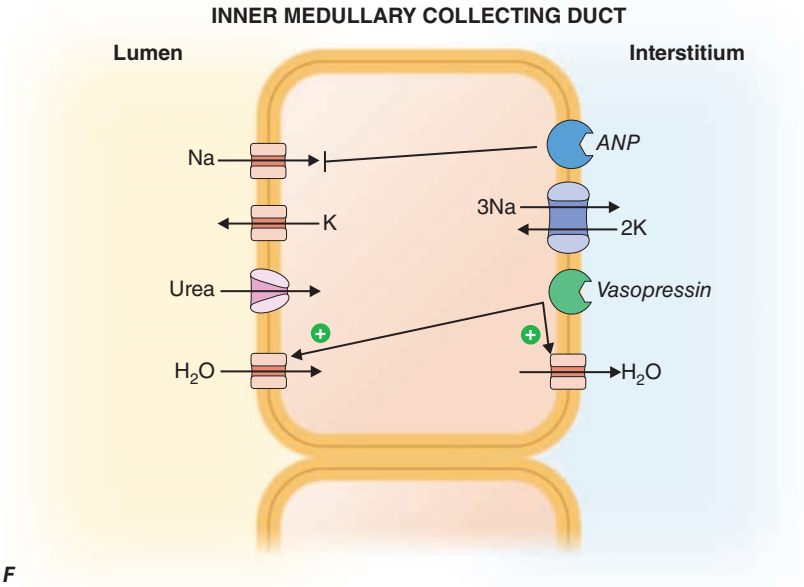

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FIGURE 303-3 (*Continued*)

most well suited for bulk fluid reabsorption, whereas tight epithelia allow for more refined control and regulation of transport.

MEMBRANE TRANSPORT

Cell membranes are composed of hydrophobic lipids that repel water and aqueous solutes. The movement of solutes and water across cell membranes is made possible by discrete classes of integral membrane proteins, including channels, pumps, and transporters. These different mechanisms mediate specific types of transport activities, including *active transport* (pumps), *passive transport* (channels), *facilitated diffusion* (transporters), and *secondary active transport* (cotransporters). Active transport requires metabolic energy generated by the hydrolysis of ATP. Active transport pumps are ion-translocating ATPases, including the ubiquitous Na^+/K^+-ATPase, the H^+-ATPases, and Ca^{2+}-ATPases.

TABLE 303-1 Inherited Disorders Affecting Renal Tubular Ion and Solute Transport

DISEASE OR SYNDROME	GENE	OMIM[a]
Disorders Involving the Proximal Tubule		
Proximal renal tubular acidosis	Sodium bicarbonate cotransporter (*SLC4A4*, 4q21)	604278
Fanconi-Bickel syndrome	Glucose transporter, GLUT2 (*SLC2A2*, 3q26.2)	227810
Isolated renal glycosuria	Sodium glucose cotransporter (*SLC5A2*, 16p11.2)	233100
Cystinuria		
Type I	Cystine, dibasic and neutral amino acid transporter (*SLC3A1*, 2p16.3)	220100
Non-type I	Amino acid transporter, light subunit (*SLC7A9*, 19q13.1)	600918
Lysinuric protein intolerance	Amino acid transporter (*SLC7A7*, 4q11.2)	222700
Hartnup disorder	Neutral amino acid transporter (*SLC6A19*, 5p15.33)	34500
Hereditary hypophosphatemic rickets with hypercalcemia	Sodium phosphate cotransporter (*SLC34A3*, 9q34)	241530
Renal hypouricemia		
Type 1	Urate-anion exchanger (*SLC22A12*, 11q13)	220150
Type 2	Urate transporter, GLUT9 (*SLC2A9*, 4p16.1)	612076
Dent disease	Chloride channel, ClC-5 (*CLCN5*, Xp11.22)	300009
X-linked recessive nephrolithiasis with renal failure	Chloride channel, ClC-5 (*CLCN5*, Xp11.22)	310468
X-linked recessive hypophosphatemic rickets	Chloride channel, ClC-5 (*CLCN5*, Xp11.22)	307800
Disorders Involving the Loop of Henle		
Bartter's syndrome		
Type 1	Sodium, potassium chloride cotransporter (*SLC12A1*, 15q21.1)	241200
Type 2	Potassium channel, ROMK (*KCNJ1*, 11q24)	601678
Type 3	Chloride channel, ClC-Kb (*CLCNKB*, 1p36)	602023
with sensorineural deafness	Chloride channel accessory subunit, Barttin (*BSND*, 1p31)	602522
Autosomal dominant hypocalcemia with Bartter-like syndrome	Calcium-sensing receptor (*CASR*, 3q13.33)	601199
Familial hypocalciuric hypercalcemia	Calcium-sensing receptor (*CASR*, 3q13.33)	145980
Primary hypomagnesemia	Claudin-16 or paracellin-1 (*CLDN16* or *PCLN1*, 3q27)	248250
Isolated renal magnesium loss	Sodium potassium ATPase, γ_1-subunit (*ATP1G1*, 11q23)	154020
Disorders Involving the Distal Tubule and Collecting Duct		
Gitelman syndrome	Sodium chloride cotransporter (*SLC12A3*, 16q13)	263800
Primary hypomagnesemia with secondary hypocalcemia	Melastatin-related transient receptor potential cation channel 6 (*TRPM6*, 9q22)	602014
Pseudoaldosteronism (Liddle's syndrome)	Epithelial sodium channel β and γ subunits (*SCNN1B*, *SCNN1G*, 16p12.1)	177200
Recessive pseudohypoaldosteronism type 1	Epithelial sodium channel, α, β, and γ subunits (*SCNN1A*, 12p13; *SCNN1B*, *SCNN1G*, 16pp12.1)	264350
Pseudohypoaldosteronism type 2 (Gordon's hyperkalemia-hypertension syndrome)	Kinases WNK-1, WNK-4 (*WNK1*, 12p13; *WNK4*, 17q21.31)	145260
X-linked nephrogenic diabetes insipidus	Vasopressin V2 receptor (AVPR2, Xq28)	304800
Nephrogenic diabetes insipidus (autosomal)	Water channel, aquaporin-2 (*AQP2*, 12q13)	125800
Distal renal tubular acidosis		
autosomal dominant	Anion exchanger-1 (*SLC4A1*, 17q21.31)	179800
autosomal recessive	Anion exchanger-1 (*SLC4A1*, 17q21.31)	602722
with neural deafness	Proton ATPase, β1 subunit (*ATP6V1B1*, 2p13.3)	192132
with normal hearing	Proton ATPase, 116-kD subunit (*ATP6V0A4*, 7q34)	602722

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

Active transport creates asymmetric ion concentrations across a cell membrane and can move ions against a chemical gradient. The potential energy stored in a concentration gradient of an ion such as Na^+ can be used to drive transport through other mechanisms (secondary active transport). Pumps are often *electrogenic*, meaning they can create an asymmetric distribution of electrostatic charges across the membrane and establish a voltage or membrane potential. The movement of solutes through a membrane protein by simple diffusion is called passive transport. This activity is mediated by channels created by selectively permeable membrane proteins, and it allows solute or water to move across a membrane driven by favorable *concentration gradients* or *electrochemical potential*. Facilitated diffusion is a specialized type of passive transport mediated by simple transporters called *carriers* or *uniporters*. For example, hexose transporters such as GLUT2 mediate glucose transport by tubular cells. These transporters are driven by the concentration gradient for glucose that is highest in extracellular fluids and lowest in the cytoplasm due to rapid metabolism. Many other transporters operate by translocating two or more ions/solutes in concert either in the same direction (*symporters* or *cotransporters*) or in opposite directions (*antiporters* or *exchangers*) across the cell membrane. The movement of two or more ions/solutes may produce no net change in the balance of electrostatic charges across the membrane (*electroneutral*), or a transport event may alter the balance of charges (*electrogenic*). Several inherited disorders of renal tubular solute and water transport occur as a consequence of mutations in genes encoding a variety of channels, transporter proteins, and their regulators **(Table 303-1)**.

SEGMENTAL NEPHRON FUNCTIONS

Each anatomic segment of the nephron has unique characteristics and specialized functions enabling selective transport of solutes and water (Fig. 303-3). Through sequential events of reabsorption and secretion along the nephron, tubular fluid is progressively conditioned into urine. Knowledge of the major tubular mechanisms responsible for solute and water transport is critical for understanding hormonal regulation of kidney function and the pharmacologic manipulation of renal excretion.

PROXIMAL TUBULE

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

Solute and water pass through these tight junctions to enter the lateral intercellular space where absorption by the peritubular capillaries occurs. Bulk fluid reabsorption by the proximal tubule is driven by high oncotic pressure and low hydrostatic pressure within the peritubular capillaries. Cellular transport of most solutes by the proximal tubule is coupled to the Na^+ concentration gradient established by the activity of a basolateral Na^+/K^+-ATPase (Fig. 303-3*A*). This active transport mechanism maintains a steep Na^+ gradient by keeping intracellular Na^+ concentrations low. Solute reabsorption from the tubular lumen is coupled to the Na^+ gradient by Na^+-dependent transporters such as Na^+-glucose and Na^+-phosphate cotransporters present in apical membranes. In addition to the paracellular route, water reabsorption also occurs through the cellular pathway enabled by constitutively active water channels (aquaporin-1) present on both apical and basolateral membranes.

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

The proximal tubule contributes to acid secretion by two mechanisms involving the titration of the urinary buffers ammonia (NH_3) and phosphate. Renal NH_3 is produced by glutamine metabolism in the proximal tubule. Subsequent diffusion of NH_3 out of the proximal tubular cell enables trapping of H^+, which is secreted by Na^+/H^+ exchange, in the lumen as ammonium ion (NH_4^+). Cellular K^+ levels inversely modulate proximal tubular ammoniagenesis, and in the setting of high serum K^+ from hypoaldosteronism, reduced ammoniagenesis promotes type IV renal tubular acidosis. Filtered hydrogen phosphate ion (HPO_4^{2-}) is also titrated in the proximal tubule by secreted H^+ to form $H_2PO_4^-$, and this reaction constitutes a major component of the urinary buffer referred to as titratable acid. Most filtered phosphate ion is reabsorbed by the proximal tubule through a sodium-coupled cotransport process that is regulated by parathyroid hormone (PTH).

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

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

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

Calcium and phosphorus homeostasis depends upon normal functioning of the proximal tubule. Approximately 60–70% of filtered calcium and ~85% of filtered phosphorus (in the form of inorganic phosphate) are reabsorbed by the proximal tubule. Whereas calcium reabsorption is mostly by passive diffusion through the paracellular route, phosphate reabsorption is mediated by sodium-coupled cotransport. In addition to direct reabsorption, the proximal tubule contributes to systemic mineral balance by participating in specific endocrine pathways. Circulating 25-hydroxy vitamin D (calcidiol) is bioactivated by proximal tubular 1α-hydroxylase to produce 1,25-di-hydroxy vitamin D (calcitriol), the most active form of the hormone, that acts on the small intestine to promote calcium absorption. Phosphate balance is affected by circulating fibroblast growth hormone 23 (FGF23), a bone-derived hormone that interacts with its receptor (FGFR1) and co-receptor (Klotho) on proximal tubular cells to suppress sodium-phosphate cotransport and promote renal phosphate excretion. PTH stimulates proximal tubular 1α-hydroxylation of vitamin D while it suppresses sodium-phosphate cotransport. Derangements in PTH and FGF23 account for abnormal calcium and phosphate balance in chronic kidney disease.

The proximal tubule, through distinct classes of Na^+-dependent and Na^+-independent transport systems, reabsorbs amino acids efficiently. These transporters are specific for different groups of amino acids. For example, cystine, lysine, arginine, and ornithine are transported by a system comprising two proteins encoded by the *SLC3A1* and *SLC7A9* genes. Mutations in either *SLC3A1* or *SLC7A9* impair reabsorption of these amino acids and cause the disease cystinuria. Peptide hormones, such as insulin and growth hormone, β_2-microglobulin, albumin, and other small proteins, are taken up by the proximal tubule through a process of absorptive endocytosis and are degraded in acidified endocytic lysosomes. Acidification of these vesicles depends on a vacuolar H^+-ATPase and Cl^- channel. Impaired acidification of endocytic vesicles because of mutations in a Cl^- channel gene (*CLCN5*) causes low-molecular-weight proteinuria in Dent disease.

LOOP OF HENLE

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

The descending thin limb is highly water permeable owing to dense expression of constitutively active aquaporin-1 water channels. By contrast, water permeability is negligible in the ascending limb. In the thick ascending limb, there is a high level of secondary active NaCl

transport enabled by the $Na^+/K^+/2Cl^-$ cotransporter on the apical membrane in series with basolateral Cl^- channels and Na^+/K^+-ATPase (Fig. 303-3*B*). The $Na^+/K^+/2Cl^-$ cotransporter is the primary target for loop diuretics. Tubular fluid K^+ is the limiting substrate for this cotransporter (tubular concentration of K^+ is similar to plasma, about 4 meq/L), but transporter activity is maintained by K^+ recycling through an apical potassium channel. The cotransporter also enables reabsorption of NH_4^+ in lieu of K^+, and this leads to accumulation of both NH_4^+ and NH_3 in the medullary interstitium. An inherited disorder of the thick ascending limb, Bartter's syndrome, also results in a salt-wasting renal disease associated with hypokalemia and metabolic alkalosis. Loss-of-function mutations in one of five distinct genes encoding components of the $Na^+/K^+/2Cl^-$ cotransporter (*NKCC2*), apical K^+ channel (*KCNJ1*), basolateral Cl^- channel (*CLCNKB*, *BSND*), or calcium-sensing receptor (*CASR*) can cause Bartter's syndrome.

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

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

DISTAL CONVOLUTED TUBULE

The distal convoluted tubule reabsorbs ~5% of the filtered NaCl. This segment is composed of a tight epithelium with little water permeability. The major NaCl-transporting pathway uses an apical membrane, electroneutral thiazide-sensitive Na^+/Cl^- cotransporter in tandem with basolateral Na^+/K^+-ATPase and Cl^- channels (Fig. 303-3C). Apical Ca^{2+}-selective channels (TRPV5) and basolateral Na^+/Ca^{2+} exchange mediate calcium reabsorption in the distal convoluted tubule. Ca^{2+} reabsorption is inversely related to Na^+ reabsorption and is stimulated by PTH. Blocking apical Na^+/Cl^- cotransport will reduce intracellular Na^+, favoring increased basolateral Na^+/Ca^{2+} exchange and passive apical Ca^{2+} entry. Loss-of-function mutations of *SLC12A3* encoding the apical Na^+/Cl^- cotransporter cause Gitelman syndrome, a salt-wasting disorder associated with hypokalemic alkalosis and hypocalciuria. Mutations in genes encoding WNK kinases, WNK-1 and WNK-4, cause pseudohypoaldosteronism type II (Gordon syndrome) characterized by familial hypertension with hyperkalemia. WNK kinases influence the activity of several tubular ion transporters. Mutations in this disorder lead to overactivity of the apical Na^+/Cl^- cotransporter in the distal convoluted tubule as the primary stimulus for increased salt reabsorption, extracellular volume expansion, and hypertension. Hyperkalemia may be caused by diminished activity of apical K^+ channels in the collecting duct, a primary route for K^+ secretion. Mutations in *TRPM6* encoding Mg^{2+} permeable ion channels also cause familial hypomagnesemia with hypocalcemia. A molecular complex of TRPM6 and TRPM7 proteins is critical for Mg^{2+} reabsorption in the distal convoluted tubule.

COLLECTING DUCT

The collecting duct modulates the final composition of urine. The two major divisions, the cortical collecting duct and inner medullary collecting duct, contribute to reabsorbing ~4–5% of filtered Na^+ and are important for hormonal regulation of salt and water balance. Cells in both segments of the collecting duct express vasopressin-regulated water channels (aquaporin-2 on the apical membrane, aquaporin-3 and -4 on the basolateral membrane). The antidiuretic hormone vasopressin binds to the V2 receptor on the basolateral membrane and triggers an intracellular signaling cascade through G-protein-mediated activation of adenylyl cyclase, resulting in an increase in the cellular levels of cyclic AMP. This signaling cascade stimulates the insertion of water channels into the apical membrane of collecting duct cells to promote increased water permeability. This increase in permeability enables water reabsorption and production of concentrated urine. In the absence of vasopressin, collecting duct cells are water impermeable, and urine remains dilute.

The cortical collecting duct contains *high-resistance epithelia* with two cell types. Principal cells are the main water, Na^+-reabsorbing, and K^+-secreting cells, and the site of action of aldosterone, K^+-sparing diuretics, and mineralocorticoid receptor antagonists such as spironolactone and eplerenone. The other cells are type A and B intercalated cells. Type A intercalated cells mediate acid secretion and bicarbonate reabsorption also under the influence of aldosterone. Type B intercalated cells mediate bicarbonate secretion and acid reabsorption.

Virtually all transport is mediated through the cellular pathway for both principal cells and intercalated cells. In principal cells, passive apical Na^+ entry occurs through an amiloride-sensitive, epithelial Na^+ channel (ENaC) with basolateral exit mediated by the Na^+/K^+-ATPase (Fig. 303-3*D*). This Na^+ reabsorptive process is tightly regulated by aldosterone and is physiologically activated by a variety of proteolytic enzymes that cleave extracellular domains of ENaC; plasmin in the tubular fluid of nephrotic patients, for example, activates ENaC, leading to sodium retention. Aldosterone enters the cell across the basolateral membrane, binds to a cytoplasmic mineralocorticoid receptor, and then translocates into the nucleus, where it modulates gene transcription, resulting in increased Na^+ reabsorption and K^+ secretion. Activating mutations in ENaC increase Na^+ reclamation and produce hypokalemia, hypertension, and metabolic alkalosis (Liddle's syndrome). The potassium-sparing diuretics amiloride and triamterene block ENaC, causing reduced Na^+ reabsorption.

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

Intercalated cells do not participate in Na^+ reabsorption but, instead, mediate acid-base secretion. These cells perform two types of transport: active H^+ transport mediated by H^+-ATPase (proton pump), and Cl^-/HCO_3^- exchange. Intercalated cells arrange the two transport mechanisms on opposite membranes to enable either acid or base secretion. Type A intercalated cells have an apical proton pump that mediates acid secretion and a basolateral Cl^-/HCO_3^- anion exchanger for bicarbonate reabsorption (Fig. 303-3*E*). Aldosterone increases the number of H^+-ATPase pumps, sometimes contributing to the development of metabolic alkalosis. Secreted H^+ is buffered by NH_3 that has diffused into the collecting duct lumen from the surrounding interstitium. By contrast, type B intercalated cells have the Cl^-/HCO_3^- exchanger on the apical membrane to mediate bicarbonate secretion while the proton pump resides on the basolateral membrane to enable acid reabsorption. Under conditions of acidemia, the kidney preferentially uses type A intercalated cells to secrete the excess H^+ and generate more HCO_3^-. The opposite is true in states of bicarbonate excess with alkalemia where the type B intercalated cells predominate. An extracellular protein called *hensin* mediates this adaptation.

Inner medullary collecting duct cells share many similarities with principal cells of the cortical collecting duct. They have apical Na^+ and K^+ channels that mediate Na^+ reabsorption and K^+ secretion, respectively (Fig. 303-3*F*). Sodium reabsorption by inner medullary collecting duct cells is also inhibited by the natriuretic peptides called *atrial natriuretic peptide* or *renal natriuretic peptide* (urodilatin); the same gene encodes both peptides but uses different posttranslational processing of a common preprohormone to generate different proteins. Atrial natriuretic peptides are secreted by atrial myocytes in response to volume expansion, whereas urodilatin is secreted by renal tubular epithelia. Natriuretic peptides interact with either apical (urodilatin) or basolateral (atrial natriuretic peptides) receptors on inner medullary collecting duct cells to stimulate guanylyl cyclase and increase levels of cytoplasmic cGMP. This effect in turn reduces the activity of the apical Na^+ channel in these cells and attenuates net Na^+ reabsorption, producing natriuresis.

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

HORMONAL REGULATION OF SODIUM AND WATER BALANCE

The balance of solute and water in the body is determined by the amounts ingested, distributed to various fluid compartments, and excreted by skin, bowel, and kidneys. *Tonicity*, the osmolar state determining the volume behavior of cells in a solution, is regulated by water balance **(Fig. 303-4*A*)**, and *extracellular blood volume* is regulated by Na^+ balance **(Fig. 303-4*B*)**. The kidney is a critical modulator of both physiologic processes.

WATER BALANCE

Tonicity depends on the variable concentration of *effective osmoles* inside and outside the cell causing water to move in either direction across its membrane. Classic effective osmoles, like Na^+, K^+, and their anions, are solutes trapped on either side of a cell membrane, where they collectively partition and obligate water to move and find equilibrium in proportion to retained solute; Na^+/K^+-ATPase keeps most K^+ inside cells and most Na^+ outside. Normal tonicity (~280 mosmol/L) is rigorously defended by osmoregulatory mechanisms that control water balance to protect tissues from inadvertent *dehydration* (cell shrinkage) or *water intoxication* (cell swelling), both of which are deleterious to cell function (Fig. 303-4*A*).

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

The kidneys play a vital role in maintaining water balance through the regulation of renal water excretion. The ability to concentrate urine to an osmolality exceeding that of plasma enables water conservation, whereas the ability to produce urine more dilute than plasma promotes excretion of excess water. For water to enter or exit a cell, the cell membrane must express aquaporins. In the kidney, aquaporin-1 is constitutively active in all water-permeable segments (e.g., proximal tubule, descending thin limb of the loop of Henle), whereas aquaporin-2, -3, and -4 in the collecting duct promote vasopressin-regulated water permeability. Net water reabsorption is ultimately driven by the osmotic gradient between dilute tubular fluid and a hypertonic medullary interstitium.

SODIUM BALANCE

The perception of *extracellular blood volume* is determined, in part, by the integration of arterial tone, cardiac stroke volume, heart rate, and the water and solute content of extracellular fluid. Na^+ and accompanying anions are the most abundant extracellular effective osmoles and together support a blood volume around which pressure is generated. Under normal conditions, this volume is regulated by sodium balance (Fig. 303-4*B*), and the balance between daily Na^+ intake and excretion is under the influence of *baroreceptors* in regional blood vessels and vascular hormone sensors modulated by atrial natriuretic peptides, the renin-angiotensin-aldosterone system, Ca^{2+} signaling, adenosine, vasopressin, and the neural adrenergic axis. If Na^+ intake exceeds Na^+ excretion (positive Na^+ balance), then an increase in blood volume will trigger a proportional increase in urinary Na^+ excretion. Conversely, when Na^+ intake is less than urinary excretion (negative Na^+ balance), blood volume will decrease and trigger enhanced renal Na^+ reabsorption, leading to decreased urinary Na^+ excretion.

The renin-angiotensin-aldosterone system is the best-understood hormonal system modulating renal Na^+ excretion. Renin is synthesized and secreted by granular cells in the wall of the afferent arteriole. Its secretion is controlled by several factors, including β_1-adrenergic stimulation to the afferent arteriole, input from the macula densa, and prostaglandins. Renin and ACE activity eventually produce angiotensin II that directly and indirectly promotes renal Na^+ and water reabsorption. Stimulation of proximal tubular Na^+/H^+ exchange by angiotensin II directly increases Na^+ reabsorption. Angiotensin II also promotes Na^+ reabsorption along the collecting duct by stimulating aldosterone secretion by the adrenal cortex. Constriction of the efferent glomerular arteriole by angiotensin II indirectly increases the filtration fraction and raises peritubular capillary oncotic pressure to promote tubular Na^+ reabsorption. Finally, angiotensin II inhibits renin secretion through a negative feedback loop. Alternative metabolism of angiotensin by ACE2 generates the vasodilatory peptide angiotensin 1-7 that acts through Mas receptors to counterbalance several actions of angiotensin II on blood pressure and renal function (Fig. 303-2*C*).

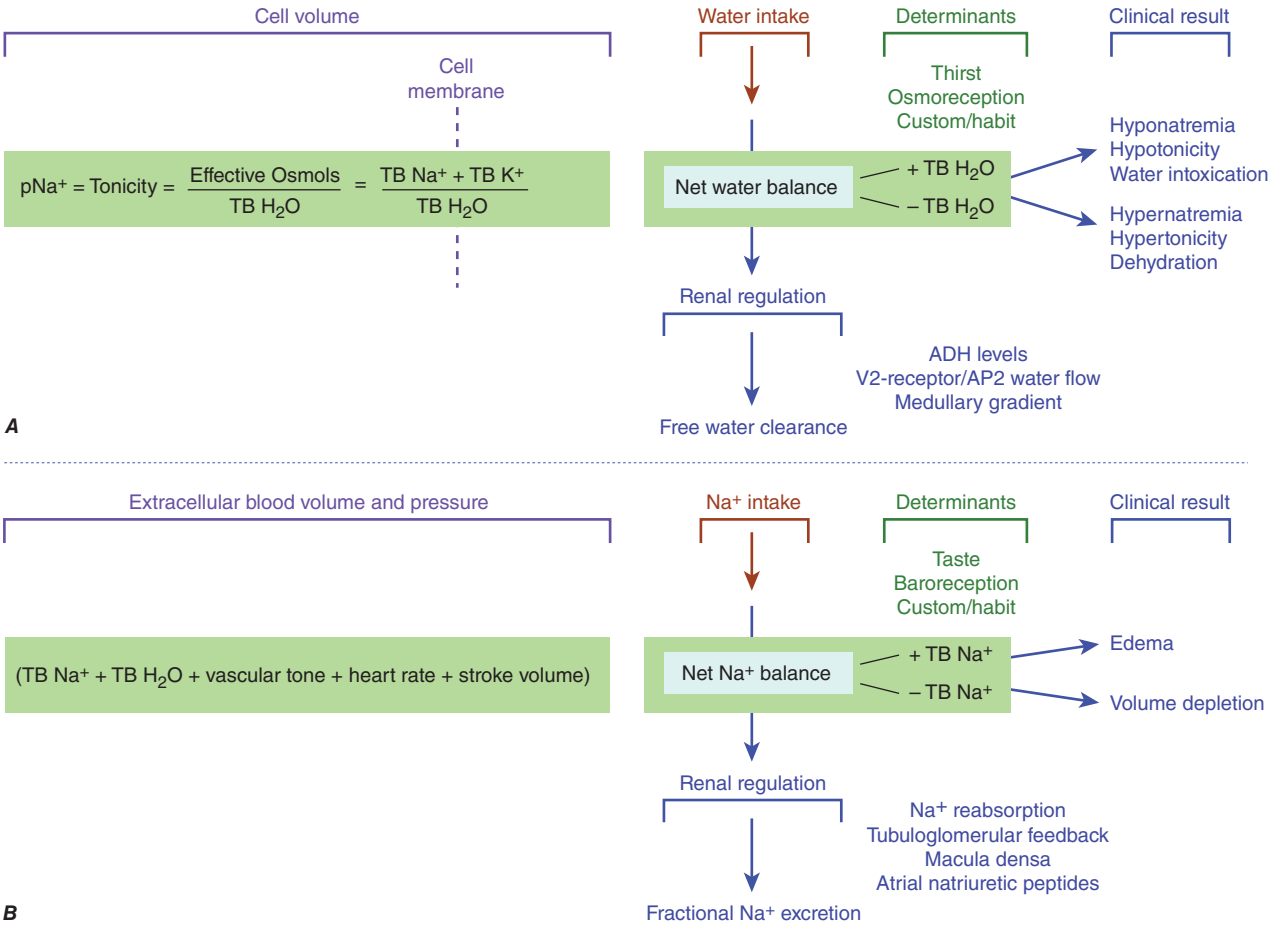

FIGURE 303-4 Determinants of sodium and water balance. ***A.*** Plasma Na^+ concentration is a surrogate marker for plasma tonicity, the volume behavior of cells in a solution. Tonicity is determined by the number of effective osmoles in the body divided by the total body H_2O (TB H_2O), which translates simply into the total body Na (TB Na^+) and anions outside the cell separated from the total body K (TB K^+) inside the cell by the cell membrane. Net water balance is determined by the integrated functions of thirst, osmoreception, Na reabsorption, vasopressin release, and the strength of the medullary gradient in the kidney, keeping tonicity within a narrow range of osmolality around 280 mosmol/L. When water metabolism is disturbed and total body water increases, hyponatremia, hypotonicity, and water intoxication occur; when total body water decreases, hypernatremia, hypertonicity, and dehydration occur. ***B.*** Extracellular blood volume and pressure are an integrated function of total body Na^+ (TB Na^+), total body H_2O (TB H_2O), vascular tone, heart rate, and stroke volume that modulates volume and pressure in the vascular tree of the body. This extracellular blood volume is determined by net Na balance under the control of taste, baroreception, habit, Na^+ reabsorption, macula densa/tubuloglomerular feedback, and natriuretic peptides. When Na^+ metabolism is disturbed and total body Na^+ increases, edema occurs; when total body Na^+ is decreased, volume depletion occurs. ADH, antidiuretic hormone; AQP2, aquaporin-2.

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

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

FURTHER READING

Bhave G, Neilson EG: Body fluid dynamics: Back to the future. J Am Soc Nephrol 22:2166, 2011.

Carlstrom M et al: Renal autoregulation in health and disease. Physiol Rev 95:405, 2015.

Combes AN et al: Cell-cell interactions driving kidney morphogenesis. Curr Top Dev Biol 112:467, 2015.

Curthoys NP, Moe OW: Proximal tubule function and response to acidosis. Clin J Am Soc Nephrol 9:1627, 2014.

Hadchouel J et al: Regulation of renal electrolyte transport by WNK and SPAK-OSR1 kinases. Annu Rev Physiol 78:367, 2016.

Jung HJ, Kwon TH: Molecular mechanisms regulating aquaporin-2 in kidney collecting duct. Am J Physiol Renal Physiol 331:F1318, 2016.

Mount DB: Thick ascending limb of the loop of Henle. Clin J Am Soc Nephrol 9:1974, 2014.

Nigam SK et al: Handling of drugs, metabolites, and uremic toxins by kidney proximal tubule drug transporters. Clin J Am Soc Nephrol 10:2039, 2015.

Palmer LG, Schnermann J: Integrated control of Na transport along the nephron. Clin J Am Soc Nephrol 10:676, 2015.

Pearce D et al: Collecting duct principal cell transport processes and their regulation. Clin J Am Soc Nephrol 10:135, 2015.

Terker AS, Ellison DH: Renal mineralocorticoid receptor and electrolyte homeostasis. Am J Physiol Regul Integr Comp Physiol 309:R1068, 2015.

304 Acute Kidney Injury

Sushrut S. Waikar, Joseph V. Bonventre

Acute kidney injury (AKI) is defined by the impairment of kidney filtration and excretory function over days to weeks, resulting in the retention of nitrogenous and other waste products normally cleared by the kidneys. AKI is not a single disease but, rather, a designation for a heterogeneous group of conditions that share common diagnostic features: specifically, an increase in serum creatinine (SCr) concentration often associated with a reduction in urine volume. It is important to recognize that AKI is a clinical diagnosis and not a structural one. A patient may have AKI with or without injury to the kidney parenchyma. AKI can range in severity from asymptomatic and transient changes in laboratory parameters of glomerular filtration rate (GFR), to overwhelming and rapidly fatal derangements in effective circulating volume regulation and electrolyte and acid-base composition of the plasma.

EPIDEMIOLOGY

AKI complicates 5–7% of acute care hospital admissions and up to 30% of admissions to the intensive care unit. The incidence of AKI has grown by more than fourfold in the United States since 1988 and is estimated to have a yearly incidence of 500 per 100,000 population, higher than the yearly incidence of stroke. AKI is associated with a markedly increased risk of death in hospitalized individuals, particularly in those admitted to the ICU where in-hospital mortality rates may exceed 50%. AKI increases the risk for the development or worsening of chronic kidney disease (CKD). Patients who survive and recover from an episode of severe AKI requiring dialysis are at increased risk for the later development of dialysis-requiring end-stage kidney disease. AKI may be community-acquired or hospital-acquired. Common causes of community-acquired AKI include volume depletion, heart failure, adverse effects of medications, obstruction of the urinary tract, or malignancy. The most common clinical settings for hospital-acquired AKI are sepsis, major surgical procedures, critical illness involving heart or liver failure, and nephrotoxic medication administration.

AKI IN THE DEVELOPING WORLD

AKI is also a major medical complication in the developing world, where the epidemiology differs from that in developed countries due to differences in demographics, economics, environmental factors, and comorbid disease burden. While certain features of AKI are common in the developed and developing countries—particularly since urban centers of some developing countries increasingly resemble those in the developed world—many etiologies for AKI are region-specific such as envenomations from snakes, spiders, caterpillars, and bees; infectious causes such as malaria and leptospirosis; and crush injuries and resultant rhabdomyolysis from earthquakes.

ETIOLOGY AND PATHOPHYSIOLOGY

The causes of AKI have traditionally been divided into three broad categories: prerenal azotemia, intrinsic renal parenchymal disease, and postrenal obstruction **(Fig. 304-1)**.

PRERENAL AZOTEMIA

Prerenal azotemia (from "azo," meaning nitrogen, and "-emia," meaning in the blood) is the most common form of AKI. It is the designation for a rise in SCr or BUN concentration due to inadequate renal plasma flow and intraglomerular hydrostatic pressure to support normal glomerular filtration. The most common clinical conditions associated with prerenal azotemia are hypovolemia, decreased cardiac output, and medications that interfere with renal autoregulatory responses such as nonsteroidal anti-inflammatory drugs (NSAIDs) and inhibitors of angiotensin II **(Fig. 304-2)**. Prerenal azotemia may coexist with other forms of intrinsic AKI associated with processes acting directly on the renal parenchyma. Prolonged periods of prerenal azotemia may lead to ischemic injury, often termed acute tubular necrosis (ATN). By definition, prerenal azotemia involves no parenchymal damage to the kidney and is rapidly reversible once parenchymal blood flow and intraglomerular hemodynamics are restored.

Normal GFR is maintained in part by renal blood flow and the relative resistances of the afferent and efferent renal arterioles, which determine the glomerular plasma flow rate and the transcapillary hydraulic pressure gradient that drive glomerular ultrafiltration. Mild degrees of hypovolemia and reductions in cardiac output elicit compensatory

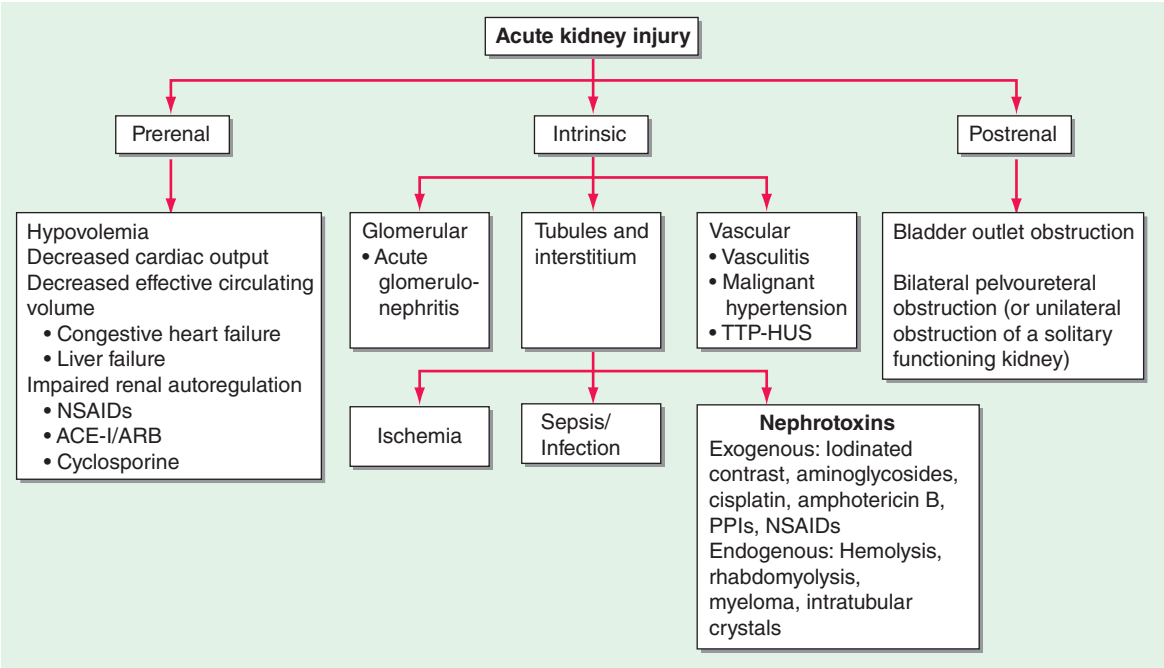

FIGURE 304-1 Classification of the major causes of acute kidney injury. ACE-I, angiotensin-converting enzyme inhibitor-I; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitors; TTP-HUS, thrombotic thrombocytopenic purpura–hemolytic-uremic syndrome.

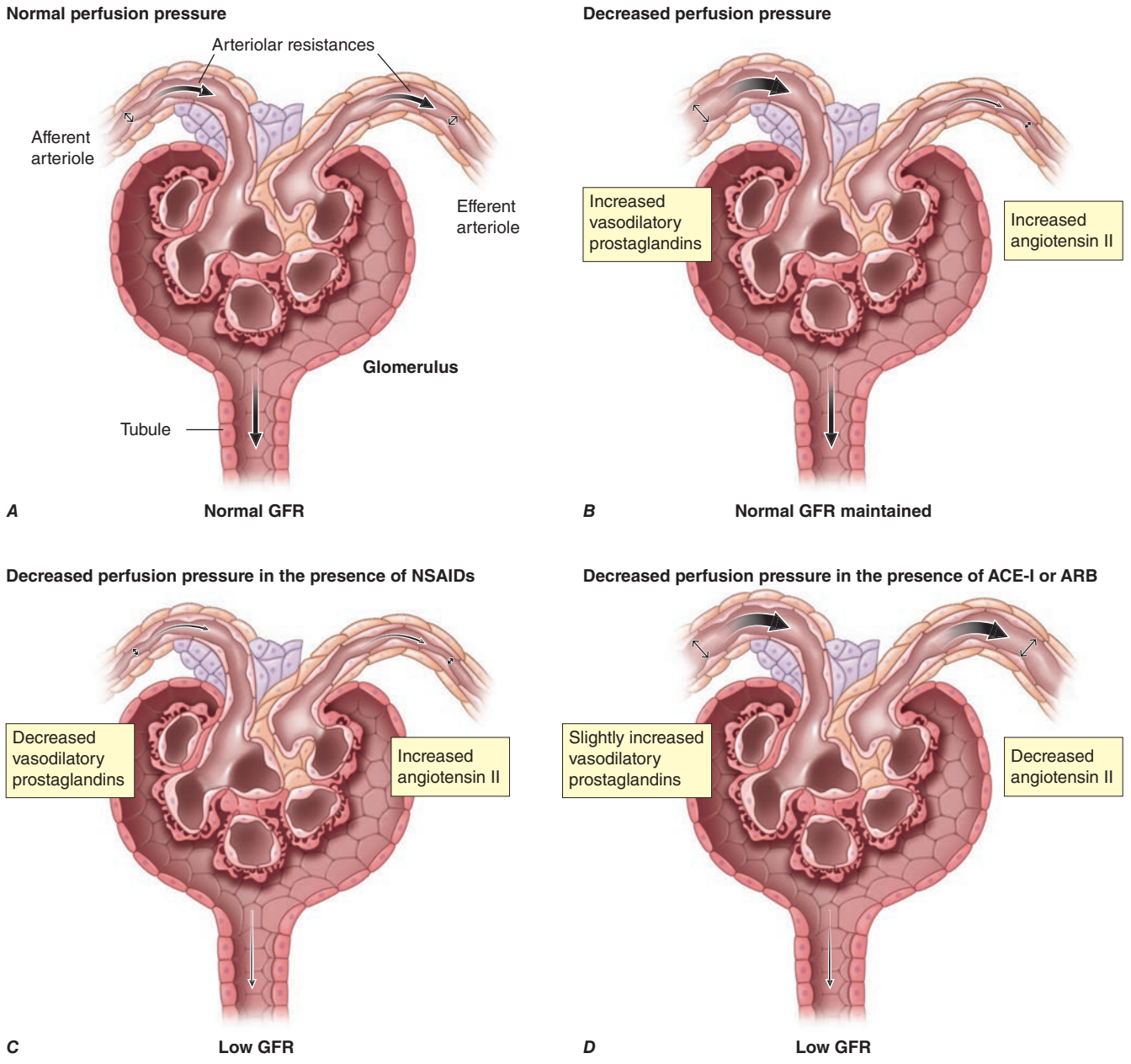

FIGURE 304-2 Intrarenal mechanisms for autoregulation of the glomerular filtration rate (GFR) under decreased perfusion pressure and reduction of the GFR by drugs. ***A.*** Normal conditions and a normal GFR. ***B.*** Reduced perfusion pressure within the autoregulatory range. Normal glomerular capillary pressure is maintained by afferent vasodilatation and efferent vasoconstriction. ***C.*** Reduced perfusion pressure with a nonsteroidal anti-inflammatory drug (NSAID). Loss of vasodilatory prostaglandins increases afferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease. ***D.*** Reduced perfusion pressure with an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB). Loss of angiotensin II action reduces efferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease. *(From JG Abuelo: N Engl J Med 357:797-805, 2007; with permission.)*

renal physiologic changes. Because renal blood flow accounts for 20% of the cardiac output, renal vasoconstriction and salt and water reabsorption occur as homeostatic responses to decreased effective circulating volume or cardiac output in order to maintain blood pressure and increase intravascular volume to sustain perfusion to the cerebral and coronary vessels. Mediators of this response include angiotensin II, norepinephrine, and vasopressin (also termed antidiuretic hormone). Glomerular filtration can be maintained despite reduced renal blood flow by angiotensin II–mediated renal efferent vasoconstriction, which maintains glomerular capillary hydrostatic pressure closer to normal and thereby prevents marked reductions in GFR if renal blood flow reduction is not excessive.

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

A number of factors determine the robustness of the autoregulatory response and the risk of prerenal azotemia. Atherosclerosis, long-standing hypertension, and older age can lead to hyalinosis and myointimal hyperplasia, causing structural narrowing of the intrarenal arterioles and impaired capacity for renal afferent vasodilation. In CKD, renal afferent vasodilation may be operating at maximal capacity in order to maximize GFR in response to reduced functional

renal mass. Drugs can affect the compensatory changes evoked to maintain GFR. Nonsteroidal anti-inflammatory agents (NSAIDs) inhibit renal prostaglandin production, limiting renal afferent vasodilation. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) limit renal efferent vasoconstriction; this effect is particularly pronounced in patients with bilateral renal artery stenosis or unilateral renal artery stenosis (in the case of a solitary functioning kidney) because, as indicated above, efferent arteriolar vasoconstriction is needed to maintain GFR due to low renal perfusion. The combined use of NSAIDs with ACE inhibitors or ARBs poses a particularly high risk for developing prerenal azotemia.

Many individuals with advanced liver disease exhibit a hemodynamic profile that resembles prerenal azotemia in the setting of total-body volume overload. Systemic vascular resistance is markedly reduced due to primary arterial vasodilation in the splanchnic circulation, resulting ultimately in activation of vasoconstrictor responses similar to those seen in hypovolemia. AKI is a common complication in this setting, and it can be triggered by volume depletion and spontaneous bacterial peritonitis. A particularly poor prognosis is seen in the case of type 1 hepatorenal syndrome, in which AKI, defined as >two-fold increase in SCr to >2.5 mg/dL, within 2 weeks without an alternate cause (e.g., shock and nephrotoxic drugs), persists despite volume administration and withholding of diuretics. Type 2 hepatorenal syndrome is a less severe form characterized mainly by refractory ascites. The hepatorenal syndrome, defined as it is above, is difficult to distinguish from prerenal azotemia. An older way of characterizing hepatorenal was prerenal azotemia that would not improve, often leading to intrinsic renal AKI, unless a definitive procedure to improve hemodynamics, such as porto-systemic shunt placement or liver transplant, was performed. We still find this latter construct of use.

INTRINSIC AKI

The most common causes of intrinsic AKI are sepsis, ischemia, and nephrotoxins, both endogenous and exogenous **(Fig. 304-3)**. In many cases, prerenal azotemia advances to tubular injury. Although classically termed "acute tubular necrosis," human biopsy confirmation of tubular necrosis is, in general, often lacking in cases of sepsis and ischemia; indeed, processes such as inflammation, apoptosis, and altered regional perfusion may be important contributors pathophysiologically. ATN is also often diagnosed clinically without biopsy confirmation in settings such as sepsis with multiple alternate potential diagnoses, including drug-induced interstitial nephritis and immune complex glomerulonephritis. These and other causes of intrinsic AKI are considered to be less common and can be conceptualized anatomically according to the major site of renal parenchymal damage: glomeruli, tubulointerstitium, and vessels.

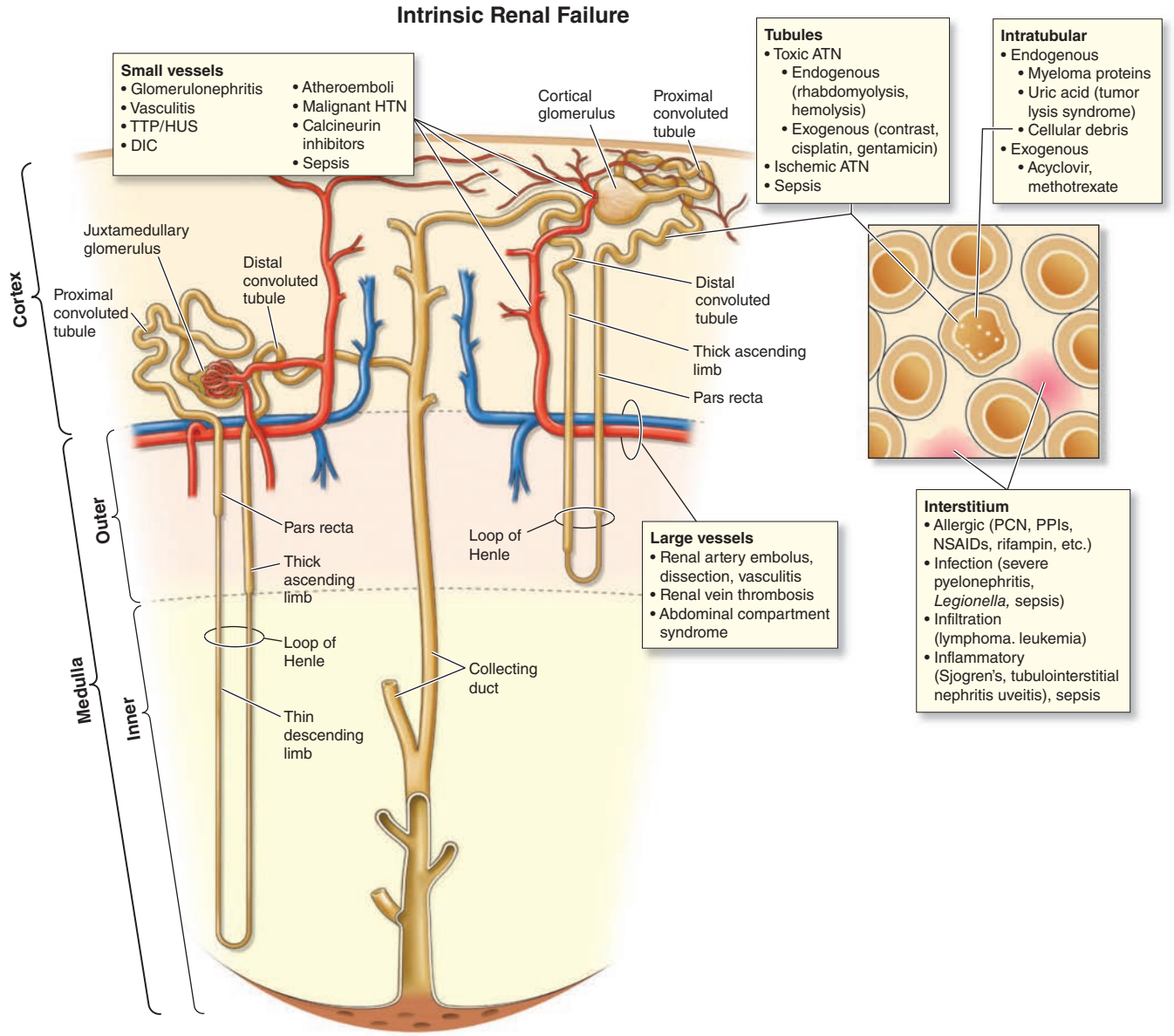

FIGURE 304-3 Major causes of intrinsic acute kidney injury. ATN, acute tubular necrosis; DIC, disseminated intravascular coagulation; HTN, hypertension; PCN, penicillin; PPI, proton pump inhibitors; TTP/HUS, thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome; TINU, tubulointerstitial nephritis-uveitis.

SEPSIS-ASSOCIATED AKI

In the United States, more than one million cases of sepsis occur each year. AKI complicates more than 50% of cases of severe sepsis and greatly increases the risk of death. Sepsis is also a very important cause of AKI in the developing world. Decreases in GFR with sepsis can occur even in the absence of overt hypotension, although most cases of severe AKI typically occur in the setting of hemodynamic collapse requiring vasopressor support. While there is clearly tubular injury associated with AKI in sepsis as manifest by the presence of tubular debris and casts in the urine, postmortem examinations of kidneys from individuals with severe sepsis suggest that other factors, perhaps related to inflammation, mitochondrial dysfunction, and interstitial edema, must also be considered in the pathophysiology of sepsis-induced AKI.

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

ISCHEMIA-ASSOCIATED AKI

Healthy kidneys receive 20% of the cardiac output and account for 10% of resting oxygen consumption, despite constituting only 0.5% of the human body mass. The kidneys are also the site of one of the most hypoxic regions in the body, the renal medulla. The outer medulla is particularly vulnerable to ischemic damage because of the architecture of the blood vessels that supply oxygen and nutrients to the tubules. In the outer medulla enhanced leukocyte-endothelial interactions in the small vessels lead to inflammation and reduced local blood flow to the metabolically very active S3 segment of the proximal tubule, which depends on oxidative metabolism for survival. Mitochondrial dysfunction due to ischemia and mitochondrial release of reactive oxygen species also play a role in renal tubular injury. Ischemia alone in a normal kidney is usually not sufficient to cause severe AKI, as evidenced by the relatively low risk of severe AKI even after total interruption of renal blood flow during suprarenal aortic clamping or cardiac arrest. Clinically, AKI more commonly develops when ischemia occurs in the context of limited renal reserve (e.g., CKD or older age) or coexisting insults such as sepsis, vasoactive or nephrotoxic drugs, rhabdomyolysis, or the systemic inflammatory states associated with burns and pancreatitis. Prerenal azotemia and ischemia-associated AKI represent a continuum of the manifestations of renal hypoperfusion. Persistent preglomerular vasoconstriction may be a common underlying cause of the reduction in GFR seen in AKI; implicated factors for vasoconstriction include activation of tubuloglomerular feedback from enhanced delivery of solute to the macula densa following proximal tubule injury, increased basal vascular tone and reactivity to vasoconstrictive agents, and decreased vasodilator responsiveness. Other contributors to low GFR include backleak of filtrate across damaged and denuded tubular epithelium and mechanical obstruction of tubules from necrotic debris (Fig. 304-4).

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

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

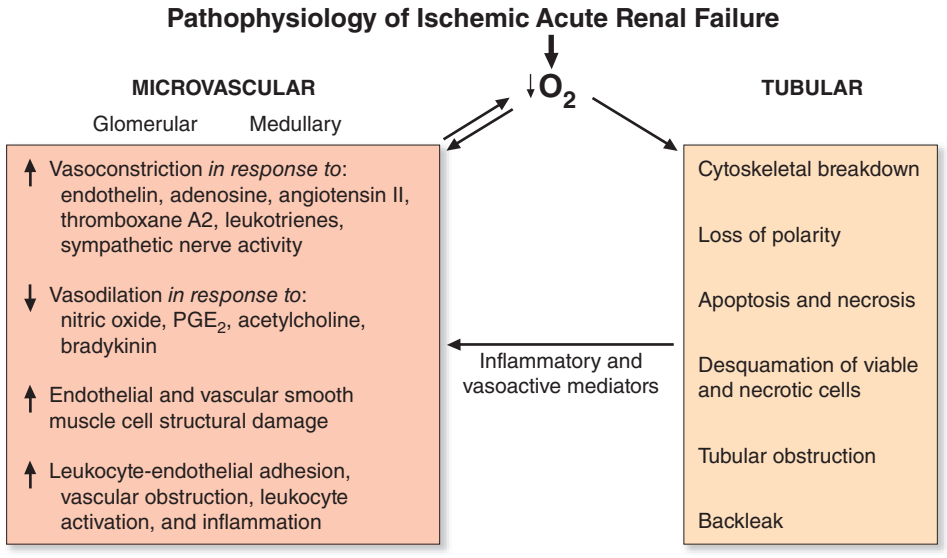

FIGURE 304-4 Interacting microvascular and tubular events contributing to the pathophysiology of ischemic acute kidney injury. PGE_2, prostaglandin E_2. *(From JV Bonventre, JM Weinberg: J Am Soc Nephrol 14:2199, 2003.)*

Diseases of the Microvasculature Leading to Ischemia Microvascular causes of AKI include the thrombotic microangiopathies (due to cocaine, certain chemotherapeutic agents, antiphospholipid antibody syndrome, radiation nephritis, malignant hypertensive nephrosclerosis, and thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome [TTP-HUS]), scleroderma, and atheroembolic disease. Large-vessel diseases associated with AKI include renal artery dissection, thromboembolism, or thrombosis, and renal vein compression or thrombosis.

NEPHROTOXIN-ASSOCIATED AKI

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

Contrast Agents Iodinated contrast agents used for cardiovascular and computed tomography (CT) imaging are a cause of AKI. The risk of AKI, or "contrast nephropathy," is negligible in those with normal renal function but increases in the setting of CKD, particularly diabetic nephropathy. The most common clinical course of contrast nephropathy is characterized by a rise in SCr beginning 24–48 h following exposure, peaking within 3–5 days, and resolving within 1 week. More severe, dialysis-requiring AKI is uncommon except in the setting of significant preexisting CKD, often in association with congestive heart failure or other coexisting causes for ischemia-associated AKI. Patients with multiple myeloma and renal disease are particularly susceptible. Low fractional excretion of sodium (FeNa) and relatively benign urinary sediment without features of tubular necrosis (see below) are common findings. Contrast nephropathy is thought to occur from a combination of factors, including (1) hypoxia in the renal outer medulla due to perturbations in renal microcirculation and occlusion of small vessels; (2) cytotoxic damage to the tubules directly or via the generation of oxygen-free radicals, especially because the concentration of the agent within the tubule is markedly increased; and (3) transient tubule obstruction with precipitated contrast material. Other diagnostic agents implicated as a cause of AKI are high-dose gadolinium used for magnetic resonance imaging (MRI) and oral sodium phosphate solutions used as bowel purgatives.

Antibiotics Several antimicrobial agents are commonly associated with AKI. *Vancomycin* may be associated with AKI, particularly when trough levels are high and when used in combination with other nephrotoxic antibiotics. *Aminoglycosides and amphotericin B* both cause tubular necrosis. Nonoliguric AKI (i.e., with a urine volume >400 mL/day) accompanies 10–30% of courses of aminoglycoside antibiotics, even when plasma levels are in the therapeutic range. Aminoglycosides are freely filtered across the glomerulus and then accumulate within the renal cortex, where concentrations can greatly exceed those of the plasma. AKI typically manifests after 5–7 days of therapy and can present even after the drug has been discontinued. Hypomagnesemia is a common finding.

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

Acyclovir can precipitate in tubules and cause AKI by tubular obstruction, particularly when given as an intravenous bolus at high doses (500 mg/m^2) or in the setting of hypovolemia. *Foscarnet, pentamidine, tenofovir*, and *cidofovir* are also frequently associated with AKI due to tubular toxicity. AKI secondary to acute interstitial nephritis can occur as a consequence of exposure to many antibiotics, including *penicillins, cephalosporins, quinolones, sulfonamides*, and *rifampin*.

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

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

Endogenous Toxins AKI may be caused by a number of endogenous compounds, including myoglobin, hemoglobin, uric acid, and myeloma light chains. Myoglobin can be released by injured muscle cells, and hemoglobin can be released during massive hemolysis leading to pigment nephropathy. Rhabdomyolysis may result from traumatic crush injuries, muscle ischemia during vascular or orthopedic surgery, compression during coma or immobilization, prolonged seizure activity, excessive exercise, heat stroke or malignant hyperthermia, infections, metabolic disorders (e.g., hypophosphatemia, severe hypothyroidism), and myopathies (drug-induced, metabolic, or inflammatory). Pathogenic factors for AKI due to endogenous toxins include intrarenal vasoconstriction, direct proximal tubular toxicity, and mechanical obstruction of the distal nephron lumen when myoglobin or hemoglobin precipitates with Tamm-Horsfall protein (uromodulin, the most common protein in urine and produced in the thick ascending limb of the loop of Henle), a process favored by acidic urine. Tumor lysis syndrome may follow initiation of cytotoxic therapy in patients with high-grade lymphomas and acute lymphoblastic leukemia; massive release of uric acid (with serum levels often exceeding 15 mg/dL) leads to precipitation of uric acid in the renal tubules and AKI (Chap. 71). Other features of tumor lysis syndrome include hyperkalemia and hyperphosphatemia. The tumor lysis syndrome can also occasionally occur spontaneously or with treatment for solid tumors or multiple myeloma. Myeloma light chains can also cause AKI by direct tubular toxicity and by binding to Tamm-Horsfall protein to form obstructing intratubular casts. Hypercalcemia, which can also be seen in multiple myeloma, may cause AKI by intense renal vasoconstriction and volume depletion.

Other Causes of Acute Tubulointerstitial Disease Leading to AKI While many of the ischemic and toxic causes of AKI previously described result in tubulointerstitial disease, many drugs are also associated with the development of an allergic response characterized by an inflammatory infiltrate and often peripheral and urinary eosinophilia. Proton pump inhibitors and NSAIDS are commonly used drugs that have been associated with acute tubulointerstitial nephritis. AKI

may be also caused by severe infections and infiltrative malignant or nonmalignant (e.g., sarcoidosis) diseases.

Glomerulonephritis Diseases involving the glomerular podocytes, mesangial and endothelial cells can lead to AKI by compromising the filtration barrier and blood flow within the renal circulation. Although glomerulonephritis is a less common (~5%) cause of AKI, early recognition is particularly important because the diseases can respond to timely treatment with immunosuppressive agents or therapeutic plasma exchange, and the treatment may reverse the AKI.

POSTRENAL AKI

(See also Chap. 313) Postrenal AKI occurs when the normally unidirectional flow of urine is acutely blocked either partially or totally, leading to increased retrograde hydrostatic pressure and interference with glomerular filtration. Obstruction to urinary flow may be caused by functional or structural derangements anywhere from the renal pelvis to the tip of the urethra (Fig. 304-5). Normal urinary flow rate does not rule out the presence of partial obstruction, because the GFR is normally two orders of magnitude higher than the urinary flow rate and hence a preservation of urine output may be misleading in hiding the postrenal partial obstruction. For AKI to occur in individuals with two healthy functional kidneys, obstruction must affect both kidneys in order to observe large increases in SCr. Unilateral obstruction may cause AKI in the setting of significant underlying CKD or, in rare cases, from reflex vasospasm of the contralateral kidney. Bladder neck obstruction is a common cause of postrenal AKI which impacts both kidneys. This can be due to prostate disease (benign prostatic hypertrophy or prostate cancer), neurogenic bladder, or therapy with anticholinergic drugs. Obstructed Foley catheters can cause postrenal AKI if not recognized and relieved. Other causes of lower tract obstruction are blood clots, calculi, and urethral strictures. Ureteric obstruction can occur from intraluminal obstruction (e.g., calculi, blood clots, sloughed renal papillae), infiltration of the ureteric wall (e.g., neoplasia), or external compression (e.g., retroperitoneal fibrosis, neoplasia, abscess, or inadvertent surgical damage). The pathophysiology of postrenal AKI involves hemodynamic alterations triggered by an abrupt increase in intratubular pressures. An initial period of hyperemia from afferent arteriolar dilation is followed by intrarenal vasoconstriction from the generation of angiotensin II, thromboxane A2, and vasopressin, and a reduction in NO production. Secondary reductions in glomerular function are due to underperfusion of glomeruli and, possibly, changes in the glomerular ultrafiltration coefficient.

DIAGNOSTIC EVALUATION (TABLE 304-1)

By current definitions the presence of AKI is defined by an elevation in the SCr concentration or reduction in urine output. AKI is currently defined by a rise from baseline of at least 0.3 mg/dL within 48 h or at least 50% higher than baseline within 1 week, or a reduction in urine output to <0.5 mL/kg per h for longer than 6 h. As indicated above, it is important to recognize that given this definition, some patients with AKI will not have tubular or glomerular damage (e.g., prerenal azotemia). The distinction between AKI and CKD is important for proper diagnosis and treatment. The distinction is straightforward when a recent baseline SCr concentration is available, but more difficult in the many instances in which the baseline is unknown. In such cases, clues suggestive of CKD can come from radiologic studies (e.g., small, shrunken kidneys with cortical thinning on renal ultrasound, or evidence of renal osteodystrophy) or laboratory tests such as normocytic anemia in the absence of blood loss or secondary hyperparathyroidism with hyperphosphatemia and hypocalcemia, consistent with CKD. No set of tests, however, can rule out AKI superimposed on CKD because AKI is a frequent complication in patients with CKD, further complicating the distinction. Serial blood tests showing a continued substantial rise of SCr represents clear evidence of AKI. Once the diagnosis of AKI is established, its cause needs to be determined since the elevation of SCr or reduction in urine output can be due to a large number of physiological and pathophysiological processes.

HISTORY AND PHYSICAL EXAMINATION

The clinical context, careful history taking, and physical examination often narrow the differential diagnosis for the cause of AKI. Prerenal azotemia should be suspected in the setting of vomiting, diarrhea, glycosuria causing polyuria, and several medications including diuretics, NSAIDs, ACE inhibitors, and ARBs. Physical signs of orthostatic hypotension, tachycardia, reduced jugular venous pressure, decreased skin turgor, and dry mucous membranes are often present in prerenal azotemia. Congestive heart failure, liver disease, and nephrotic syndrome can be associated with reductions in renal blood flow and/or alterations in intrarenal hemodynamics leading to reduced GFR. Extensive vascular disease raises the possibility of renal artery disease, especially if kidneys are known to be asymmetric in size. Atheroembolic disease can be associated with livedo reticularis and other signs of emboli to the legs. The presence of sepsis is an important clue to causation although, as described above, the detailed pathophysiology may be multifactorial.

A history of prostatic disease, nephrolithiasis, or pelvic or paraaortic malignancy would suggest the possibility of postrenal AKI. Whether or not symptoms are present early during obstruction of the urinary tract depends on the location of obstruction. Colicky flank pain radiating to the groin suggests acute ureteric obstruction. Nocturia and urinary frequency or hesitancy can be seen in prostatic disease. Abdominal fullness and suprapubic pain can accompany bladder enlargement. Definitive diagnosis of obstruction requires radiologic investigations.

A careful review of all medications is imperative in the evaluation of an

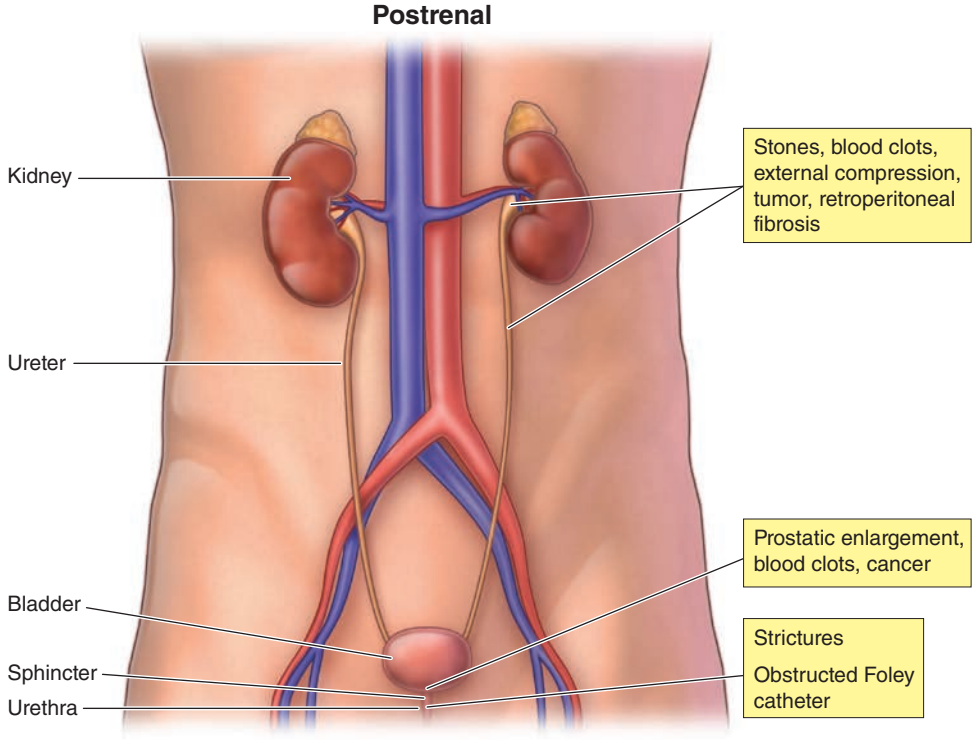

FIGURE 304-5 Anatomic sites and causes of obstruction leading to postrenal acute kidney injury.

TABLE 304-1 Major Causes, Clinical Features, and Diagnostic Studies for Prerenal and Intrinsic Acute Kidney Injury

ETIOLOGY	CLINICAL FEATURES	LABORATORY FEATURES	COMMENTS
Prerenal azotemia	History of poor fluid intake or fluid loss (hemorrhage, diarrhea, vomiting, sequestration into extravascular space); NSAID/ACE-I/ARB; heart failure; evidence of volume depletion (tachycardia, absolute or postural hypotension, low jugular venous pressure, dry mucous membranes), decreased effective circulatory volume (cirrhosis, heart failure)	BUN/creatinine ratio above 20, FeNa <1%, hyaline casts in urine sediment, urine specific gravity >1.018, urine osmolality >500 mOsm/kg	Low FeNa, high specific gravity and osmolality may not be seen in the setting of CKD, diuretic use; BUN elevation out of proportion to creatinine may alternatively indicate upper GI bleed or increased catabolism. Response to restoration of hemodynamics is most diagnostic.
Sepsis-associated AKI	Sepsis, sepsis syndrome, or septic shock. Overt hypotension not always seen in mild to moderate AKI	Positive culture from normally sterile body fluid; urine sediment often contains granular casts, renal tubular epithelial cell casts	FeNa may be low (<1%), particularly early in the course, but is usually >1% with osmolality <500 mOsm/kg
Ischemia-associated AKI	Systemic hypotension, often superimposed upon sepsis and/or reasons for limited renal reserve such as older age, CKD	Urine sediment often contains granular casts, renal tubular epithelial cell casts. FeNa typically >1%.	
Nephrotoxin-Associated AKI: Endogenous			
Rhabdomyolysis	Traumatic crush injuries, seizures, immobilization	Elevated myoglobin, creatine kinase; urine heme positive with few red blood cells	FeNa may be low (<1%)
Hemolysis	Recent blood transfusion with transfusion reaction	Anemia, elevated LDH, low haptoglobin	FeNa may be low (<1%); evaluation for transfusion reaction
Tumor lysis	Recent chemotherapy	Hyperphosphatemia, hypocalcemia, hyperuricemia	
Multiple myeloma	Age >60 years, constitutional symptoms, bone pain	Monoclonal spike in urine or serum electrophoresis; low anion gap; anemia	Bone marrow or renal biopsy can be diagnostic
Nephrotoxin-Associated AKI: Exogenous			
Contrast nephropathy	Exposure to iodinated contrast	Characteristic course is rise in SCr within 1–2 d, peak within 3–5 d, recovery within 7 d	FeNa may be low (<1%)
Tubular injury	Aminoglycoside antibiotics, cisplatin, tenofovir, vancoycin, zoledronate, ethylene glycol, aristolochic acid, protein pump inhibitors, tacrolimus and melamine (to name a few)	Urine sediment often contains granular casts, renal tubular epithelial cell casts. FeNa typically >1%.	Can be oliguric or nonoliguric
Interstitial nephritis	Recent medication exposure (e.g., proton pump inhibitors, NSAIDs, antibiotics), can have fever, rash, arthralgias	Eosinophilia, sterile pyuria; often nonoliguric	Urine eosinophils have limited diagnostic accuracy; systemic signs of drug reaction often absent; kidney biopsy may be helpful
Other Causes of Intrinsic AKI			
Glomerulonephritis/vasculitis	Variable **(Chap. 308)** features include skin rash, arthralgias, sinusitis (AGBM disease), lung hemorrhage (AGBM, ANCA, lupus), recent skin infection or pharyngitis (poststreptococcal)	ANA, ANCA, AGBM antibody, hepatitis serologies, cryoglobulins, blood culture, decreased complement levels, ASO titer (abnormalities of these tests depending on etiology)	Kidney biopsy may be necessary
Interstitial nephritis	Nondrug-related causes include tubulointerstitial nephritis-uveitis (TINU) syndrome, *Legionella* infection	Eosinophilia, sterile pyuria; often nonoliguric	Urine eosinophils have limited diagnostic accuracy; kidney biopsy may be necessary
TTP/HUS	Neurologic abnormalities and/or AKI; recent diarrheal illness; use of calcineurin inhibitors; pregnancy or postpartum; spontaneous	Schistocytes on peripheral blood smear, elevated LDH, anemia, thrombocytopenia	"Typical HUS" refers to AKI with a diarrheal prodrome, often due to Shiga toxin released from *Escherichia coli* or other bacteria; "atypical HUS" is due to inherited or acquired complement dysregulation. "TTP-HUS" refers to sporadic cases in adults. Diagnosis may involve screening for ADAMTS13 activity, Shiga toxin–producing *E. coli*, genetic evaluation of complement regulatory proteins, and kidney biopsy.
Atheroembolic disease	Recent manipulation of the aorta or other large vessels; may occur spontaneously or after anticoagulation; retinal plaques, palpable purpura, livedo reticularis, GI bleed	Hypocomplementemia, eosinophiluria (variable), variable amounts of proteinuria	Skin or kidney biopsy can be diagnostic
Postrenal AKI	History of kidney stones, prostate disease, obstructed bladder catheter, retroperitoneal or pelvic neoplasm	No specific findings other than AKI; may have pyuria or hematuria	Imaging with computed tomography or ultrasound

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

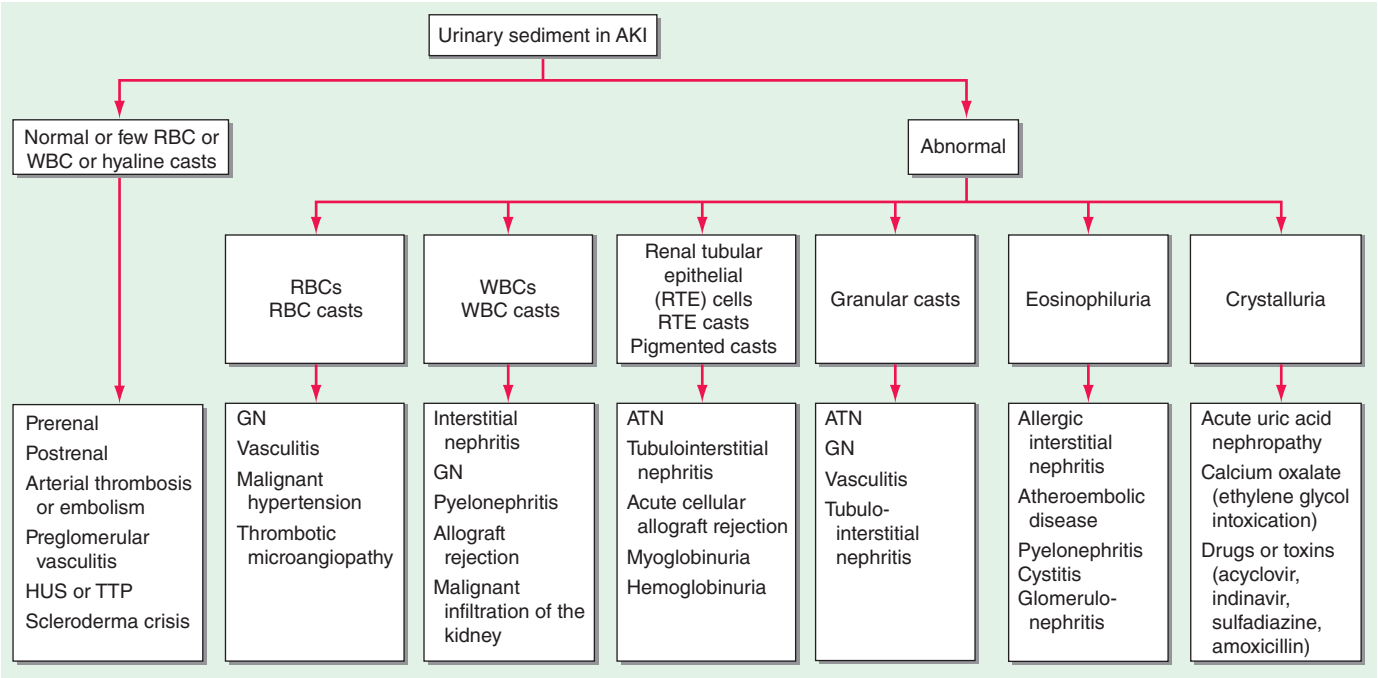

FIGURE 304-6 Interpretation of urinary sediment findings in acute kidney injury (AKI). ATN, acute tubular necrosis; GN, glomerulonephritis; HUS, hemolytic-uremic syndrome; RBCs, red blood cells; RTE, renal tubular epithelial; TTP, thrombotic thrombocytopenic purpura; WBCs, white blood cells. *(Adapted from L Yang, JV Bonventre: Diagnosis and clinical evaluation of acute kidney injury. In Comprehensive Nephrology, 4th ed. J Floege et al [eds]. Philadelphia, Elsevier, 2010.)*

individual with AKI. Not only are medications frequently a nephrotoxic cause of AKI, but doses of administered medications must be adjusted for reductions in kidney function. In this regard, it is important to recognize that reductions in true GFR are not reflected by equations which estimate GFR since those equations are dependent on SCr and the patient being in a steady state. With AKI, SCr will lag behind changes in filtration rate. Idiosyncratic reactions to a wide variety of medications can lead to allergic interstitial nephritis, which may be accompanied by fever, arthralgias, and a pruritic erythematous rash. The absence of systemic features of hypersensitivity, however, does not exclude the diagnosis of interstitial nephritis, and a kidney biopsy should be considered for definitive diagnosis.

AKI accompanied by palpable purpura, pulmonary hemorrhage, or sinusitis raises the possibility of systemic vasculitis with glomerulonephritis. A history of autoimmune disease, such as systemic lupus erythematosus, should lead to consideration of the possibility that the AKI is related to worsening of this underlying disease. Pregnancy should lead to the consideration of preeclampsia as a pathophysiological contributor to the AKI. A tense abdomen should prompt consideration of acute abdominal compartment syndrome, which requires measurement of bladder pressure. Signs of limb ischemia may be clues to the diagnosis of rhabdomyolysis.

URINE FINDINGS

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

The urinalysis and urine sediment examination are invaluable tools, but they require clinical correlation because of generally limited sensitivity and specificity **(Fig. 304-6)** **(Chap. A3)**. In the absence of preexisting proteinuria from CKD, AKI from ischemia or nephrotoxins leads to mild proteinuria (<1 g/d). Greater proteinuria in AKI suggests damage to the glomerular ultrafiltration barrier or excretion of myeloma light chains; the latter are not detected with conventional urine dipsticks (which detect albumin) and require the sulfosalicylic acid test or immunoelectrophoresis. Atheroemboli can cause a variable degree of proteinuria. Extremely heavy proteinuria ("nephrotic range," >3.5 g/d) can occasionally be seen in glomerulonephritis, vasculitis, or toxins/medications that can affect the glomerulus as well as the tubulointerstitium (e.g., NSAIDs). AKI can also complicate cases of minimal change disease, a cause of the nephrotic syndrome **(Chap. 303)**. If the dipstick is positive for hemoglobin but few red blood cells are evident in the urine sediment, then rhabdomyolysis or hemolysis should be suspected.

Prerenal azotemia may present with hyaline casts or an unremarkable urine sediment examination. Postrenal AKI may also lead to an unremarkable sediment, but hematuria and pyuria may be seen depending on the cause of obstruction. AKI from ATN due to ischemic injury, sepsis, or certain nephrotoxins has characteristic urine sediment findings: pigmented "muddy brown" granular casts and tubular epithelial cell casts. These findings may be absent in more than 20% of cases, however. Glomerulonephritis may lead to dysmorphic red blood cells or red blood cell casts. Interstitial nephritis may lead to white blood cell casts. The urine sediment findings overlap somewhat in glomerulonephritis and interstitial nephritis, and a diagnosis is not always possible on the basis of the urine sediment alone. Urine eosinophils have a limited role in differential diagnosis; they can be seen in interstitial nephritis, pyelonephritis, cystitis, atheroembolic disease, or glomerulonephritis. Crystalluria may be important diagnostically. The finding of oxalate crystals in AKI should prompt an evaluation for ethylene glycol toxicity. Abundant uric acid crystals may be seen in the tumor lysis syndrome.

BLOOD LABORATORY FINDINGS

Certain forms of AKI are associated with characteristic patterns in the rise and fall of SCr. Prerenal azotemia typically leads to modest rises in SCr that return to baseline with improvement in hemodynamic status. Contrast nephropathy leads to a rise in SCr within 24–48 h, peak within 3–5 days, and resolution within 5–7 days. In comparison, atheroembolic disease usually manifests with more subacute rises in

SCr, although severe AKI with rapid increases in SCr can occur in this setting. With many of the epithelial cell toxins such as aminoglycoside antibiotics and cisplatin, the rise in SCr is characteristically delayed for 3–5 days to 2 weeks after initial exposure.

A complete blood count may provide diagnostic clues. Anemia is common in AKI and is usually multifactorial in origin. It is not related to an effect of AKI solely on production of red blood cells because this effect in isolation takes longer to manifest. Peripheral eosinophilia can accompany interstitial nephritis, atheroembolic disease, polyarteritis nodosa, and Churg-Strauss vasculitis. Severe anemia in the absence of bleeding may reflect hemolysis, multiple myeloma, or thrombotic microangiopathy (e.g., hemolytic uremic syndrome [HUS] or TTP). Other laboratory findings of thrombotic microangiopathy include thrombocytopenia, schistocytes on peripheral blood smear, elevated lactate dehydrogenase level, and low haptoglobin content. Evaluation of patients suspected of having TTP or HUS includes measurement of levels of the von Willebrand factor cleaving protease (ADAMTS13) and testing for Shiga toxin–producing *Escherichia coli*. "Atypical HUS" constitutes the majority of adult cases of HUS; genetic testing is important because it is estimated that 60–70% of atypical HUS patients have mutations in genes encoding proteins that regulate the alternative complement pathway.

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

RENAL FAILURE INDICES

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

The FeNa is the fraction of the filtered sodium load that is reabsorbed by the tubules, and is a measure of both the kidney's ability to reabsorb sodium as well as endogenously and exogenously administered factors that affect tubular reabsorption. As such, it depends on sodium intake, effective intravascular volume, GFR, diuretic intake, and intact tubular reabsorptive mechanisms. With prerenal azotemia, the FeNa may be <1%, suggesting avid tubular sodium reabsorption. In patients with CKD, a FeNa significantly >1% can be present despite a superimposed prerenal state. The FeNa may also be >1% despite hypovolemia due to treatment with diuretics. Low FeNa is often seen early in glomerulonephritis and other disorders and, hence, should not be taken as prima facie evidence of prerenal azotemia. Low FeNa is therefore suggestive, but not synonymous, with effective intravascular volume depletion, and should not be used as the sole guide for volume management. The response of urine output to crystalloid or colloid fluid administration may be both diagnostic and therapeutic in prerenal azotemia. In ischemic AKI, the FeNa is frequently >1% because of tubular injury and resultant inability to reabsorb sodium. Several causes of ischemia-associated and nephrotoxin-associated AKI can present with FeNa <1%, however, including sepsis (often early in the course), rhabdomyolysis, and contrast nephropathy.

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

RADIOLOGIC EVALUATION

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

KIDNEY BIOPSY

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

NOVEL BIOMARKERS

BUN and creatinine are functional biomarkers of glomerular filtration rather than tissue injury biomarkers and, therefore, may be suboptimal for the diagnosis of actual parenchymal kidney damage. BUN and creatinine are also relatively slow to rise after kidney injury. Several novel biomarkers have been investigated and show promise for earlier and accurate diagnosis of AKI and for predicting AKI prognosis. In cases of oliguric AKI, the urinary flow rate in response to bolus intravenous furosemide 1.0–1.5 mg/kg can be used a prognostic test: urine output of less than 200 mL over 2 h after intravenous furosemide may identify patients at higher risk of progression to more severe AKI, and the need for renal replacement therapy. The severity or risk of progressive AKI may also be reflected in findings on urine microscopy. In one study involving review of fresh urine sediments by board-certified nephrologists, a greater number of renal tubular epithelial cells and/or granular casts in the urine sediment was associated with both the severity and worsening of AKI. Novel protein biomarkers of kidney injury have also

been identified in animal models of AKI and further tested in humans. *Kidney injury molecule-1* (KIM-1) is a type 1 transmembrane protein that is abundantly expressed in proximal tubular cells injured by ischemia or nephrotoxins such as cisplatin. KIM-1 is not expressed in appreciable quantities in the absence of tubular injury or in extrarenal tissues. KIM-1's functional role may be to confer phagocytic properties to tubular cells, enabling them to clear debris from the tubular lumen after kidney injury and also may reduce the inflammatory response to acute injury. KIM-1 can be detected shortly after ischemic or nephrotoxic injury in the urine and, therefore, may be an easily tested biomarker in the clinical setting. *Neutrophil gelatinase associated lipocalin* (NGAL, also known as lipocalin-2 or siderocalin) is another novel biomarker of AKI. NGAL was first discovered as a protein in granules of human neutrophils. NGAL can bind to iron siderophore complexes and may have tissue-protective effects in the proximal tubule. NGAL is highly upregulated after inflammation and kidney injury and can be detected in the plasma and urine within 2 h of cardiopulmonary bypass–associated AKI. In 2014, the U.S. Food and Drug Administration approved the marketing of a test based on the combination of the urinary concentrations of two cell-cycle arrest biomarkers, insulin-like growth factor binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinase-2 (TIMP-2) as predictive biomarkers for higher risk of the development of moderate to severe AKI in critically ill patients. A number of other biomarkers are under investigation for early and accurate identification of AKI and for risk stratification to identify individuals at increased risk. The optimal use of novel AKI biomarkers in clinical settings is an area of ongoing investigation.

COMPLICATIONS OF AKI

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

UREMIA

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

HYPERVOLEMIA AND HYPOVOLEMIA

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

HYPONATREMIA

Abnormalities in plasma electrolyte composition can be mild or life threatening. The dysfunctional kidney has limited ability to regulate electrolyte balance. Administration of excessive hypotonic crystalloid or isotonic dextrose solutions can result in hypoosmolality and hyponatremia, which, if severe, can cause neurologic abnormalities, including seizures.

HYPERKALEMIA

An important complication of AKI is hyperkalemia. Marked hyperkalemia is particularly common in rhabdomyolysis, hemolysis, and tumor lysis syndrome due to release of intracellular potassium from damaged cells. Muscle weakness may be a symptom of hyperkalemia. Potassium affects the cellular membrane potential of cardiac and neuromuscular tissues. The more serious complication of hyperkalemia is due to effects on cardiac conduction, leading to potentially fatal arrhythmias.

ACIDOSIS

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

HYPERPHOSPHATEMIA AND HYPOCALCEMIA

AKI can lead to hyperphosphatemia, particularly in highly catabolic patients or those with AKI from rhabdomyolysis, hemolysis, and tumor lysis syndrome. Metastatic deposition of calcium phosphate can lead to hypocalcemia. AKI-associated hypocalcemia may also arise from derangements in the vitamin D–parathyroid hormone–fibroblast growth factor-23 axis. Hypocalcemia is often asymptomatic but can lead to perioral paresthesias, muscle cramps, seizures, carpopedal spasms, and prolongation of the QT interval on electrocardiography. Calcium levels should be corrected for the degree of hypoalbuminemia, if present, or ionized calcium levels should be followed. Mild, asymptomatic hypocalcemia does not require treatment.

BLEEDING

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

INFECTIONS

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

CARDIAC COMPLICATIONS

The major cardiac complications of AKI are arrhythmias, pericarditis, and pericardial effusion. In addition, volume overload and uremia may lead to cardiac injury and impaired cardiac function. In animal studies cellular apoptosis and capillary vascular congestion as well as mitochondrial dysfunction have been described in the heart after renal ischemia reperfusion.

MALNUTRITION

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

PREVENTION AND TREATMENT OF AKI

The management of individuals with and at risk for AKI varies according to the underlying cause **(Table 304-2)**. Common to all are several principles. Optimization of hemodynamics, correction of fluid and electrolyte imbalances, discontinuation of nephrotoxic medications, and dose adjustment of administered medications are all critical. Common causes of AKI such as sepsis and ischemic ATN do not yet have specific therapies once injury is established, but meticulous clinical attention is needed to support the patient until (if) AKI resolves. The kidney possesses remarkable capacity to repair itself after even severe, dialysis-requiring AKI, when baseline renal function was intact. However, many patients with AKI, particularly when superimposed on preexisting CKD, do not recover fully and may remain dialysis dependent. It has become increasingly apparent that AKI predisposes to accelerated progression of CKD, and CKD is an important risk factor for AKI.

Prerenal Azotemia Prevention and treatment of prerenal azotemia require optimization of renal perfusion. The composition of replacement fluids should be targeted to the type of fluid lost.

TABLE 304-2 Management of Acute Kidney Injury

General Issues

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

Specific Issues

1. Nephrotoxin-specific
   a. Rhabdomyolysis: aggressive intravenous fluids; consider forced alkaline diuresis
   b. Tumor lysis syndrome: aggressive intravenous fluids and allopurinol or rasburicase
2. Volume overload
   a. Salt and water restriction
   b. Diuretics
   c. Ultrafiltration
3. Hyponatremia
   a. Restriction of enteral free water intake, minimization of hypotonic intravenous solutions including those containing dextrose
   b. Hypertonic saline is rarely necessary in AKI. Vasopressin antagonists are generally not needed.
4. Hyperkalemia
   a. Restriction of dietary potassium intake
   b. Discontinuation of potassium-sparing diuretics, ACE inhibitors, ARBs, NSAIDs
   c. Loop diuretics to promote urinary potassium loss
   d. Potassium binding ion-exchange resin (sodium polystyrene sulfonate)
   e. Insulin (10 units regular) and glucose (50 mL of 50% dextrose) to promote entry of potassium intracellularly
   f. Inhaled beta-agonist therapy to promote entry of potassium intracellularly
   g. Calcium gluconate or calcium chloride (1 g) to stabilize the myocardium
5. Metabolic acidosis
   a. Sodium bicarbonate (if pH <7.2 to keep serum bicarbonate >15 mmol/L)
   b. Administration of other bases, e.g., THAM
   c. Renal replacement therapy
6. Hyperphosphatemia
   a. Restriction of dietary phosphate intake
   b. Phosphate binding agents (calcium acetate, sevelamer hydrochloride, aluminum hydroxide—taken with meals)
7. Hypocalcemia
   a. Calcium carbonate or calcium gluconate if symptomatic
8. Hypermagnesemia
   a. Discontinue Mg^{2+} containing antacids
9. Hyperuricemia
   a. Acute treatment is usually not required except in the setting of tumor lysis syndrome (see above)
10. Nutrition
    a. Sufficient protein and calorie intake (20–30 kcal/kg per day) to avoid negative nitrogen balance. Nutrition should be provided via the enteral route if possible.
11. Drug dosing
    a. Careful attention to dosages and frequency of administration of drugs, adjustment for degree of renal failure
    b. Note that serum creatinine concentration may overestimate renal function in the non–steady state characteristic of patients with AKI

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drug; THAM, tris (hydroxymethyl) aminomethane.

Severe acute blood loss should be treated with packed red blood cells. Isotonic crystalloid and/or colloid should be used for less severe acute hemorrhage or plasma loss in the case of burns and pancreatitis. Crystalloid solutions are less expensive and probably equally efficacious as colloid solutions. Hydroxyethyl starch solutions increase the risk of severe AKI and are contraindicated. Crystalloid has been reported to be preferable to albumin in the setting of traumatic brain injury. Isotonic crystalloid (e.g., 0.9% saline) or colloid should be used for volume resuscitation in severe hypovolemia, whereas hypotonic crystalloids (e.g., 0.45% saline) suffice for less severe hypovolemia and can also be used in the setting of hypernatremia. Excessive chloride administration from 0.9% saline may lead to hyperchloremic metabolic acidosis and may impair GFR. Bicarbonate-containing solutions (e.g., dextrose water with 150 mEq sodium bicarbonate) can be used if metabolic acidosis is a concern. Whether buffered crystalloid solutions containing bicarbonate or lactate offer advantages over normal saline for volume repletion in most critically ill patients is not yet established.

Optimization of cardiac function in AKI may require use of inotropic agents, preload- and afterload-reducing agents, antiarrhythmic drugs, and mechanical aids such as ventricular assist devices. Invasive hemodynamic monitoring to guide therapy may be necessary.

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

Intrinsic AKI Several agents have been tested and have failed to show benefit in the treatment of acute tubular injury. These include atrial natriuretic peptide, low-dose dopamine, endothelin antagonists, erythropoietin, loop diuretics, calcium channel blockers, α-adrenergic receptor blockers, prostaglandin analogs, antioxidants, antibodies against leukocyte adhesion molecules, and insulin-like growth factor, among many others. Most studies have enrolled patients with severe and well-established AKI, and treatment may have been initiated too late. Novel kidney injury biomarkers may provide an opportunity to test agents earlier in the course of AKI.

AKI due to acute glomerulonephritis or vasculitis may respond to immunosuppressive agents and/or plasmapheresis (Chap. 303). Allergic interstitial nephritis due to medications requires discontinuation of the offending agent. Glucocorticoids have been used, but not tested in randomized trials, in cases where AKI persists or worsens despite discontinuation of the suspected medication. AKI due to scleroderma (scleroderma renal crisis) should be treated with ACE inhibitors. Idiopathic TTP-HUS is a medical emergency and should be treated promptly with plasma exchange. Pharmacologic blockade of complement activation may be effective in atypical HUS.

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

Postrenal AKI Prompt recognition and relief of urinary tract obstruction can forestall the development of permanent structural damage induced by urinary stasis. The site of obstruction defines

the treatment approach. Transurethral or suprapubic bladder catheterization may be all that is needed initially for urethral strictures or functional bladder impairment. Ureteric obstruction may be treated by percutaneous nephrostomy tube placement or ureteral stent placement. Relief of obstruction is usually followed by an appropriate diuresis for several days. In rare cases, severe polyuria persists due to tubular dysfunction and may require continued administration of intravenous fluids and electrolytes for a period of time.

SUPPORTIVE MEASURES FOR AKI

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

Electrolyte and Acid-Base Abnormalities The treatment of dysnatremias and hyperkalemia is described in Chap. 49. Metabolic acidosis is generally not treated unless severe (pH <7.20 and serum bicarbonate <15 mmol/L). Acidosis can be treated with oral or intravenous sodium bicarbonate (Chap. 51), but overcorrection should be avoided because of the possibility of metabolic alkalosis, hypocalcemia, hypokalemia, and volume overload. Hyperphosphatemia is common in AKI and can usually be treated by limiting intestinal absorption of phosphate using phosphate binders (calcium carbonate, calcium acetate, lanthanum, sevelamer, or aluminum hydroxide). Hypocalcemia does not usually require therapy unless symptoms are present. Ionized calcium should be monitored rather than total calcium when hypoalbuminemia is present.

Malnutrition Protein energy wasting is common in AKI, particularly in the setting of multisystem organ failure. Inadequate nutrition may lead to starvation ketoacidosis and protein catabolism. Excessive nutrition may increase the generation of nitrogenous waste and lead to worsening azotemia. Total parenteral nutrition requires large volumes of fluid administration and may complicate efforts at volume control. According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, patients with AKI should achieve a total energy intake of 20–30 kcal/kg per day. Protein intake should vary depending on the severity of AKI: 0.8–1.0 g/kg per day in noncatabolic AKI without the need for dialysis; 1.0–1.5 g/kg per day in patients on dialysis; and up to a maximum of 1.7 g/kg per day if hypercatabolic and receiving continuous renal replacement therapy. Trace elements and water-soluble vitamins should also be supplemented in AKI patients treated with dialysis and continuous renal replacement therapy.

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

Dialysis Indications and Modalities (See also Chap. 306) Dialysis is indicated when medical management fails to control volume overload, hyperkalemia, or acidosis; in some toxic ingestions; and when there are severe complications of uremia (asterixis, pericardial rub or effusion, encephalopathy, uremic bleeding). The timing of dialysis is still a matter of debate. Late initiation of dialysis carries the risk of avoidable volume, electrolyte, and metabolic complications of AKI. On the other hand, initiating dialysis too early may unnecessarily expose individuals to intravenous lines and invasive procedures, with the attendant risks of infection, bleeding, procedural complications, and hypotension. The initiation of dialysis should not await the development of a life-threatening complication of renal failure. Many nephrologists initiate dialysis for AKI empirically when the BUN exceeds a certain value (e.g., 100 mg/dL) in patients without clinical signs of recovery of kidney function. The available modes for renal replacement therapy in AKI require either access to the peritoneal cavity (for peritoneal dialysis) or the large blood vessels (for hemodialysis, hemofiltration, and other hybrid procedures). Small solutes are removed across a semipermeable membrane down their concentration gradient ("diffusive" clearance) and/or along with the movement of plasma water ("convective" clearance). The choice of modality is often dictated by the immediate availability of technology and the expertise of medical staff.

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

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

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

Peritoneal dialysis can be performed through a temporary intraperitoneal catheter, although it is rarely used in the United States for AKI in adults. Peritoneal dialysis has enjoyed widespread use internationally, particularly when hemodialysis technology is not as readily available. Dialysate solution is instilled into and removed from the peritoneal cavity at regular intervals in order to achieve diffusive and convective clearance of solutes across the peritoneal membrane; ultrafiltration of

water is achieved by the presence of an osmotic gradient across the peritoneal membrane achieved by high concentrations of dextrose in the dialysate solution. Because of its continuous nature, it is often better tolerated than intermittent procedures like hemodialysis in hypotensive patients. Peritoneal dialysis may not be sufficient for hypercatabolic patients due to inherent limitations in dialysis efficacy.

OUTCOME AND PROGNOSIS

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

FURTHER READING

Bonventre JV, Yang L: Cellular pathophysiology of ischemic acute kidney injury. J Clin Invest 121:4210, 2011.

Gaudry S et al: Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med 375:122, 2016.

Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guidelines for Acute Kidney Injury. Kidney Int. Supp 2:1, 2012.

Lameire NH et al: Acute kidney injury: An increasing global concern. Lancet 382:170, 2013.

Zeng X et al: Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. Clin J Am Soc Nephrol 9:12, 2014.

305 Chronic Kidney Disease

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Chronic kidney disease (CKD) encompasses a spectrum of pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR). The risk of CKD progression is closely linked to both the GFR and the amount of albuminuria. **Figure 305-1** provides a staging of CKD stratified by the estimates of both of these parameters.

The dispiriting term *end-stage renal disease* represents a stage of CKD where the accumulation of toxins, fluid, and electrolytes normally excreted by the kidneys leads to death unless the toxins are removed by renal replacement therapy, using dialysis or kidney transplantation. These interventions are discussed in **Chaps. 306 and 307**. *End-stage renal disease* will be supplanted in this chapter by the term *stage 5 CKD*.

PATHOPHYSIOLOGY OF CKD

The pathophysiology of CKD involves two broad sets of mechanisms of damage: (1) initiating mechanisms specific to the underlying etiology (e.g., abnormalities in kidney development or integrity, immune complex deposition and inflammation in certain types of glomerulonephritis, or toxin exposure in certain diseases of the renal tubules and interstitium) and (2) hyperfiltration and hypertrophy of the remaining viable nephrons, that are a common consequence following long-term reduction of renal mass, irrespective of underlying etiology and lead to further decline in kidney function (**Chap. 333e** from the 19th edition of *Harrison's*). The responses to reduction in nephron number are mediated by vasoactive hormones, cytokines, and growth factors. Eventually, these short-term adaptations of hyperfiltration and hypertrophy to maintain GFR become maladaptive as the increased pressure and flow within the nephron predisposes to distortion of glomerular architecture, abnormal podocyte function, and disruption of the filtration barrier leading to sclerosis and dropout of the remaining nephrons **(Fig. 305-2)**. Increased intrarenal activity of the renin-angiotensin system (RAS) appears to contribute both to the initial compensatory hyperfiltration and to the subsequent maladaptive hypertrophy and sclerosis. This process explains why a reduction in renal mass from an isolated insult may lead to a progressive decline in renal function over many years **(Fig. 305-3)**.

IDENTIFICATION OF RISK FACTORS AND STAGING OF CKD

It is important to identify factors that increase the risk for CKD, even in individuals with normal GFR. Risk factors include small for gestation birth weight, childhood obesity, hypertension, diabetes mellitus, autoimmune disease, advanced age, African ancestry, a family history of kidney disease, a previous episode of acute kidney injury, and the presence of proteinuria, abnormal urinary sediment, or structural abnormalities of the urinary tract. It has been increasingly recognized that one or more episodes of acute kidney injury are associated with an increased risk of developing CKD.

Many rare inherited forms of CKD follow a Mendelian inheritance pattern, often as part of a systemic syndrome, with the most common in this category being autosomal dominant polycystic kidney disease. In addition, recent research in the genetics of predisposition to common complex diseases **(Chap. 456)** has revealed DNA sequence variants at a number of genetic loci that are associated with common forms of CKD. A striking example is the finding of allelic versions of the *APOL1* gene, of West African population ancestry, which contributes to the several-fold higher frequency of certain common etiologies of nondiabetic CKD (e.g., focal segmental glomerulosclerosis) observed among African and Hispanic Americans, in major regions of continental Africa and the global African diaspora. The prevalence in West African populations seems to have arisen as an evolutionary adaptation conferring protection from tropical pathogens. As in other common diseases with a heritable component, environmental triggers (such as a viral pathogen) transform genetic risk into disease.

To stage CKD, it is necessary to estimate the GFR rather than relying on serum creatinine concentration **(Table 305-1)**. Many laboratories now report an estimated GFR, or eGFR, using one of these equations. These equations are valid only if the patient is in steady state, that is, the serum creatinine is neither rising nor falling over days.

The normal annual mean decline in GFR with age from the peak GFR (~120 mL/min per 1.73 m^2) attained during the third decade of life is ~1 mL/min per year per 1.73 m^2, reaching a mean value of 70 mL/min per 1.73 m^2 at age 70, with considerable inter-individual variability. Although reduced GFR is expected with aging, the lower GFR signifies a true loss of kidney function with attendant consequences in terms of risk of CKD complications, and requirement for dose adjustment of medications. The mean GFR is lower in women than in men. For example, a woman in her eighties with a laboratory report of serum creatinine in the normal range may have a GFR of <50 mL/min per 1.73 m^2. Relatedly, even a mild elevation in serum creatinine concentration often signifies a substantial reduction in GFR in older individuals.

Measurement of albuminuria is also helpful for monitoring nephron injury and the response to therapy in many forms of CKD, especially chronic glomerular diseases. The cumbersome 24-h urine collection has been replaced by measurement of urinary albumin to creatinine ratio (UACR) in one and preferably several spot first-morning urine samples as a measure pointing to glomerular injury. Even in patients with negative conventional dipstick tests for elevated total protein excretion, UACR above 17 mg albumin/g creatinine in men and 25 mg albumin/g creatinine in women serves as a marker not only for early detection of primary kidney disease, but for systemic microvas-cular disease as well. The presence of albuminuria in general serves as a well-studied screening marker for the presence of systemic microvas-cular disease and endothelial dysfunction.

A Kidney Failure Risk (KFR) equation has been devised to predict the risk of progression to stage 5 dialysis-dependent kidney disease. The equation is available on many sites online (for example,

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min/1.73 m²) description and range				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

FIGURE 305-1 Kidney Disease Improving Global Outcome (KDIGO) classification of chronic kidney disease (CKD). Gradation of color from green to red corresponds to increasing risk and progression of CKD. GFR, glomerular filtration rate. *(Reproduced with permission from Kidney Int Suppl 3:5–14, 2013.)*

www.kidneyfailurerisk.com) and uses age, sex, region (North American or non-North American), GFR and the urine albumin/creatinine. It has been validated in several cohorts around the world, although the risk for progression appears to be greater in North America, accounting for the regional adjustment in the equation.

Stages 1 and 2 CKD are usually asymptomatic, such that the recognition of CKD occurs more often as a result of laboratory testing in clinical settings other than suspicion of kidney disease. Moreover, in the absence of the risk factors noted above, population-wide screening is not recommended. With progression to CKD stages 3 and 4, clinical and laboratory complications become more prominent. Virtually all organ systems are affected, but the most evident complications include anemia and associated easy fatigability; decreased appetite with progressive malnutrition; abnormalities in calcium, phosphorus, and mineral-regulating hormones, such as $1,25(OH)_2D_3$ (calcitriol), parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF-23); and abnormalities in sodium, potassium, water, and acid-base homeostasis. Many patients, especially the elderly, will have eGFR values compatible with stage 2 or 3 CKD. However, the majority of these patients will show no further deterioration of renal function. The primary care physician is advised to recheck kidney function, and if it is stable and not associated with proteinuria, the patient can usually be

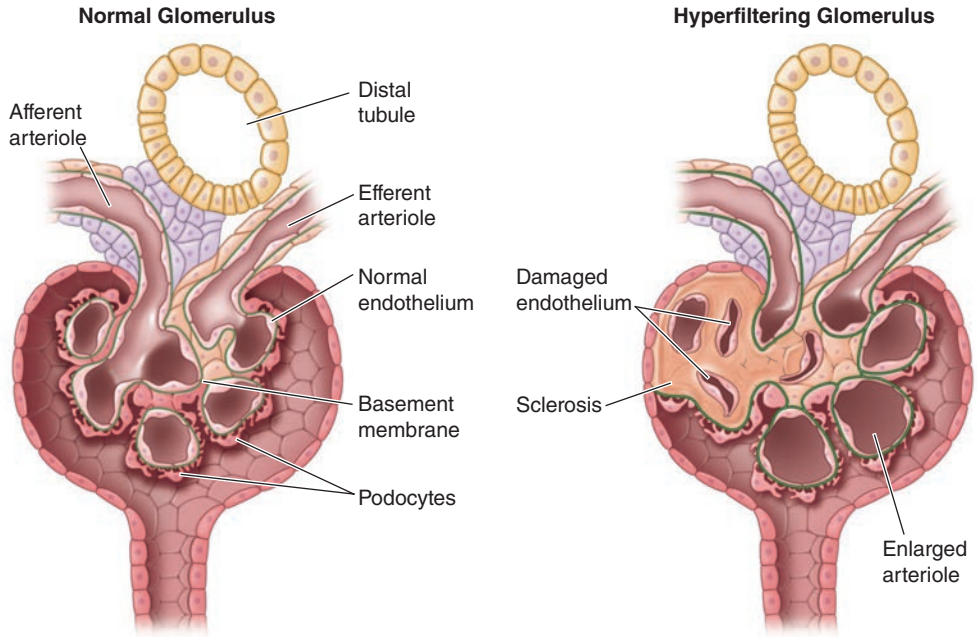

FIGURE 305-2 ***Left:*** Schema of the normal glomerular architecture. ***Right:*** Secondary glomerular changes associated with a reduction in nephron number, including enlargement of capillary lumens and focal adhesions, which are thought to occur consequent to compensatory hyperfiltration and hypertrophy in the remaining nephrons. *(Modified from JR Ingelfinger: N Engl J Med 348:99, 2003.)*

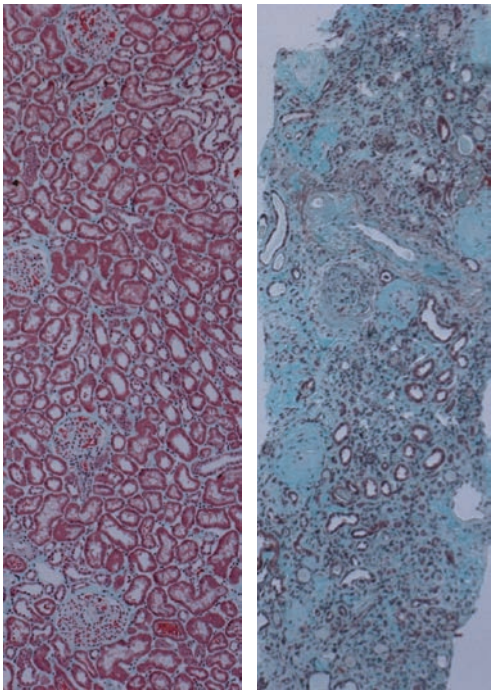

FIGURE 305-3 ***Left:*** Low-power photomicrograph of a normal kidney showing normal glomeruli and healthy tubulointerstitium without fibrosis. ***Right:*** Low-power photomicrograph of chronic kidney disease with sclerosis of many glomeruli and severe tubulointerstitial fibrosis (Masson trichrome, 40× magnification). *(Slides courtesy of the late Dr. Andrew Herzenberg.)*

followed with interval repeat testing without referral to nephrologist. However, caution should be exercised in terms of potential exposure to nephrotoxins or interventions that risk acute kidney injury (AKI) and also with respect to medication dose adjustment. If repeat testing shows declining GFR, albuminuria, or uncontrolled hypertension, referral to a nephrologist is appropriate. If the patient progresses to stage 5 CKD, toxins accumulate such that patients usually experience a marked disturbance in their activities of daily living, well-being, nutritional status, and water and electrolyte homeostasis, eventuating in the *uremic syndrome*.

ETIOLOGY AND EPIDEMIOLOGY

It has been estimated from population data that at least 6% of the adult population in the United States has CKD at stages 1 and 2. An additional 4.5% of the U.S. population is estimated to have stages 3 and 4 CKD. **Table 305-2** lists the five most frequent categories of causes of CKD, cumulatively accounting for >90% of the CKD disease burden worldwide. The relative contribution of each category varies among different geographic regions. The most frequent cause of CKD in North America and Europe is diabetic nephropathy, most often secondary to type 2 diabetes mellitus. Patients with newly diagnosed

TABLE 305-1 Recommended Equations for Estimation of Glomerular Filtration Rate (GFR) Using Serum Creatinine Concentration (S_{CR}), Age, Sex, Race, and Body Weight

1. Equation from the Modification of Diet in Renal Disease Study
Estimated GFR (mL/min per 1.73 m^2) = $1.86 \times (S_{Cr})^{-1.154} \times (age)^{-0.203}$
Multiply by 0.742 for women
Multiply by 1.21 for African ancestry
2. CKD-EPI Equation
$GFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age}$
Multiply by 1.018 for women
Multiply by 1.159 for African ancestry
where S_{Cr} is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of S_{Cr}/κ or 1, and max indicates the maximum of S_{Cr}/κ or 1.

Abbreviation: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

TABLE 305-2 Leading Categories of Etiologies of CKD[a]

- Diabetic nephropathy
- Glomerulonephritis
- Hypertension-associated CKD (includes vascular and ischemic kidney disease and primary glomerular disease with associated hypertension)
- Autosomal dominant polycystic kidney disease
- Other cystic and tubulointerstitial nephropathy

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

CKD often have hypertension. When no overt evidence for a primary glomerular or tubulointerstitial kidney disease process is present, CKD is frequently attributed to hypertension. However, it is now appreciated that such individuals can be considered in two categories. The first includes patients with a subclinical primary glomerulopathy, such as focal segmental or global glomerulosclerosis **(Chap. 308)**. The second includes patients in whom progressive nephrosclerosis and hypertension is the renal correlate of a systemic vascular disease, often also involving large- and small-vessel cardiac and cerebral pathology. This latter combination is especially common in the elderly, in whom chronic renal ischemia as a cause of CKD may be underdiagnosed. The increasing incidence of CKD in the elderly has been ascribed, in part, to decreased mortality rate from the cardiac and cerebral complications of atherosclerotic vascular disease, enabling a greater segment of the population to progress to more advanced stages of CKD. Nevertheless, it should be appreciated that the majority of patients with early stages of CKD succumb to cardiovascular and cerebrovascular complications before they progress to the more advanced stages of CKD. Indeed, even a minor decrement in GFR or the presence of albuminuria is now recognized as a major risk factor for cardiovascular disease.

PATHOPHYSIOLOGY AND BIOCHEMISTRY OF UREMIA

Although serum urea and creatinine concentrations are used to measure the excretory capacity of the kidneys, accumulation of these two molecules themselves does not account for the many symptoms and signs that characterize the uremic syndrome in advanced renal failure. Large numbers of toxins that accumulate when GFR declines have been implicated in the uremic syndrome. These include water-soluble, hydrophobic, protein-bound, charged, and uncharged nitrogen-containing non-volatile products of metabolism. It is thus evident that the serum concentrations of urea and creatinine should be viewed as being readily measured, but very incomplete surrogate markers for retained toxins, and monitoring the levels of urea and creatinine in the patient with impaired kidney function represents a vast oversimplification of the uremic state.

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

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

CLINICAL AND LABORATORY MANIFESTATIONS OF CKD AND UREMIA

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

FLUID, ELECTROLYTE, AND ACID-BASE DISORDERS

Sodium and Water Homeostasis With normal renal function, tubular excretion of filtered sodium and water matches intake. Many forms of kidney disease (e.g., glomerulonephritis) disrupt this balance such that dietary intake of sodium exceeds its urinary excretion, leading to sodium retention and attendant extracellular fluid volume (ECFV) expansion. This expansion may contribute to hypertension, which itself can accelerate nephron injury. As long as water intake does not exceed the capacity for renal water clearance, the ECFV expansion will be isotonic and the patient will have a normal plasma sodium concentration. Hyponatremia is not commonly seen in CKD patients but, when present, often responds to water restriction. The patient with ECFV expansion (peripheral edema, sometimes hypertension poorly responsive to therapy) should be counseled regarding salt restriction. Thiazide diuretics have limited utility in stages 3–5 CKD, such that administration of loop diuretics, including furosemide, bumetanide, or torsemide, may also be needed. Resistance to loop diuretics in CKD often mandates use of higher doses than those used in patients with higher GFR. The combination of loop diuretics with metolazone may be helpful. Diuretic resistance with intractable edema and hypertension in advanced CKD may serve as an indication to initiate dialysis.

In addition to problems with salt and water excretion, some patients with CKD may instead have impaired renal conservation of sodium and water. When an extrarenal cause for fluid loss, such as gastrointestinal (GI) loss, is present, these patients may be prone to ECFV depletion because of the inability of the failing kidney to reclaim filtered sodium adequately. Furthermore, depletion of ECFV, whether due to GI losses or overzealous diuretic therapy, can further compromise kidney function through underperfusion, or a "prerenal" state, leading to acute-on-chronic kidney failure. In this setting, holding or adjusting the diuretic dose or even cautious volume repletion with normal saline may return the ECFV to normal and restore renal function to baseline.

Potassium Homeostasis In CKD, the decline in GFR is not necessarily accompanied by a parallel decline in urinary potassium excretion, which is predominantly mediated by aldosterone-dependent secretion in the distal nephron. Another defense against potassium retention in these patients is augmented potassium excretion in the GI tract. Notwithstanding these two homeostatic responses, hyperkalemia may be precipitated in certain settings. These include increased dietary potassium intake, hemolysis, hemorrhage, transfusion of stored red blood cells, and metabolic acidosis. Importantly, a host of medications can inhibit renal potassium excretion and lead to hyperkalemia. The most important medications in this respect include the RAS inhibitors and spironolactone and other potassium-sparing diuretics such as amiloride, eplerenone, and triamterene. The benefits of the RAS inhibitors in ameliorating the progression of CKD and its complications often favor their cautious and judicious use with very close monitoring of plasma potassium concentration.

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

Hypokalemia is not common in CKD and usually reflects markedly reduced dietary potassium intake, especially in association with excessive diuretic therapy or concurrent GI losses. The use of potassium supplements and potassium-sparing diuretics may be risky in patients with impaired renal function, and needs to be monitored closely.

Metabolic Acidosis Metabolic acidosis is a common disturbance in advanced CKD. The majority of patients can still acidify the urine, but they produce less ammonia and, therefore cannot excrete the normal quantity of protons. Hyperkalemia, if present, further depresses ammonia production. The combination of hyperkalemia and hyperchloremic metabolic acidosis is often present, even at earlier stages of CKD (stages 1–3), in patients with diabetic nephropathy or in those with predominant tubulointerstitial disease or obstructive uropathy.

With worsening renal function, the total urinary net daily acid excretion is usually limited to 30–40 mmol, and the anions of retained organic acids can then lead to an anion-gap metabolic acidosis. Thus, the non-anion-gap metabolic acidosis seen in earlier stages of CKD may be complicated by the addition of an anion-gap metabolic acidosis as CKD progresses. In most patients, the metabolic acidosis is mild; the pH is rarely <7.32 and can usually be corrected with oral sodium bicarbonate supplementation. Animal and human studies have suggested that even modest degrees of metabolic acidosis may be associated with the development of protein catabolism. Alkali supplementation may, in addition, attenuate the catabolic state and possibly slow CKD progression and is recommended when the serum bicarbonate concentration falls below 20–23 mmol/L. The concomitant sodium load mandates careful attention to volume status and the need for diuretic agents.

TREATMENT

Fluid, Electrolyte, and Acid-Base Disorders

Dietary salt restriction and the use of loop diuretics, occasionally in combination with metolazone, may be needed to maintain euvolemia. Water restriction is indicated only if there is a problem with hyponatremia.

Hyperkalemia often responds to dietary restriction of potassium, the use of kaliuretic diuretics, and avoidance of both potassium supplements (including occult sources, such as dietary salt substitutes) and dose reduction or avoidance of potassium-retaining medications (especially angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]). Kaliuretic diuretics promote urinary potassium excretion, whereas potassium-binding resins, such as calcium resonium, sodium polystyrene or patiromer can promote potassium loss through the GI tract and may reduce the incidence of hyperkalemia. Intractable hyperkalemia is an indication (although uncommon) to consider institution of dialysis in a CKD patient. The renal tubular acidosis and subsequent anion-gap metabolic acidosis in progressive CKD will respond to alkali supplementation, typically with sodium bicarbonate. Recent studies suggest that this replacement should be considered when the serum bicarbonate concentration falls below 20–23 mmol/L to avoid the protein catabolic state seen with even mild degrees of metabolic acidosis and to slow the progression of CKD.

DISORDERS OF CALCIUM AND PHOSPHATE METABOLISM

The principal complications of abnormalities of calcium and phosphate metabolism in CKD occur in the skeleton and the vascular bed, with occasional severe involvement of soft tissues. It is likely that disorders of bone turnover and disorders of vascular and soft tissue calcification are related to each other (Fig. 305-3).

Bone Manifestations of CKD The major disorders of bone disease can be classified into those associated with high bone turnover with increased PTH levels (including *osteitis fibrosa cystica*, the classic lesion of secondary hyperparathyroidism), osteomalacia due to reduced action of the active forms of vitamin D, and low bone turnover with low or normal PTH levels (adynamic bone disease) or most often combinations of the foregoing.

The pathophysiology of secondary hyperparathyroidism and the consequent high-turnover bone disease is related to abnormal mineral

metabolism through the following events: (1) declining GFR leads to reduced excretion of phosphate and, thus, phosphate retention; (2) the retained phosphate stimulates increased synthesis of both FGF-23 by osteocytes and PTH and stimulates growth of parathyroid gland mass; and (3) decreased levels of ionized calcium, resulting from suppression of calcitriol production by FGF-23 and by the failing kidney, as well as phosphate retention, also stimulate PTH production. Low calcitriol levels contribute to hyperparathyroidism, both by leading to hypocalcemia and also by a direct effect on PTH gene transcription. These changes start to occur when the GFR falls below 60 mL/min.

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

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

Adynamic bone disease is increasing in prevalence, especially among diabetics and the elderly. It is characterized by reduced bone volume and mineralization and may result from excessive suppression of PTH production, chronic inflammation, or both. Suppression of PTH can result from the use of vitamin D preparations or from excessive calcium exposure in the form of calcium-containing phosphate binders or high-calcium dialysis solutions. Complications of adynamic bone disease include an increased incidence of fracture and bone pain and an association with increased vascular and cardiac calcification. Occasionally the calcium will precipitate in the soft tissues into large concretions termed "tumoral calcinosis" **(Fig. 305-4)**. Patients with adynamic bone disease often experience the most severe symptoms of musculoskeletal pain, owing to the inability to repair the microfractures that occur properly as a part of healthy skeletal homeostasis with regular physical activity. Osteomalacia is a distinct process, consequent to reduced production and action of $1,25(OH)_2D_3$, leading to non-mineralized osteoid.

Tumoral Calcinosis in a Dialysis Patient

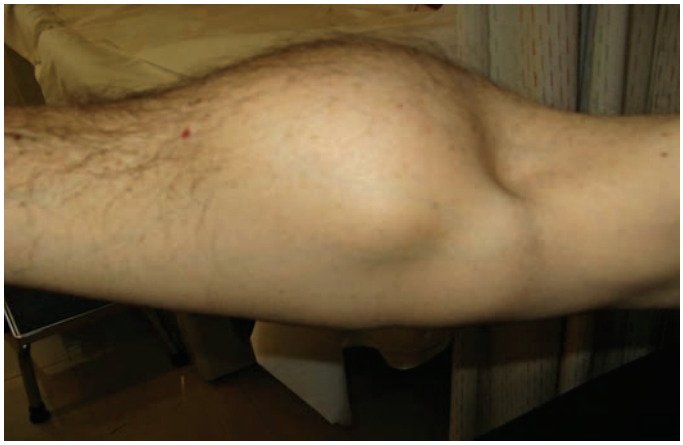

FIGURE 305-4 Tumoral calcinosis. This patient was on hemodialysis for many years and was nonadherent to dietary phosphorus restriction or the use of phosphate binders. He was chronically severely hyperphosphatemic. He developed an enlarging painful mass on his arm that was extensively calcified.

Calcium, Phosphorus, and the Cardiovascular System

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

Other Complications of Abnormal Mineral Metabolism

Calciphylaxis is a devastating condition seen almost exclusively in patients with advanced CKD. It is heralded by livedo reticularis and advances to patches of ischemic necrosis, especially on the legs, thighs, abdomen, and breasts **(Fig. 305-5)**. Pathologically, there is evidence of vascular occlusion in association with extensive vascular and soft tissue calcification. It appears that this condition is increasing in incidence. Originally it was ascribed to severe abnormalities in calcium and phosphorus control in dialysis patients, usually associated with advanced hyperparathyroidism. However, more recently, calciphylaxis has been seen with increasing frequency in the absence of severe hyperparathyroidism. Other etiologies have been suggested, including the increased use of oral calcium as a phosphate binder. Warfarin is commonly used in hemodialysis patients in whom most direct oral anticoagulants (DOACs) are contraindicated, and one of the effects of warfarin therapy is to decrease the vitamin K–dependent regeneration of matrix GLA protein. This latter protein is important in preventing vascular

Calciphylaxis

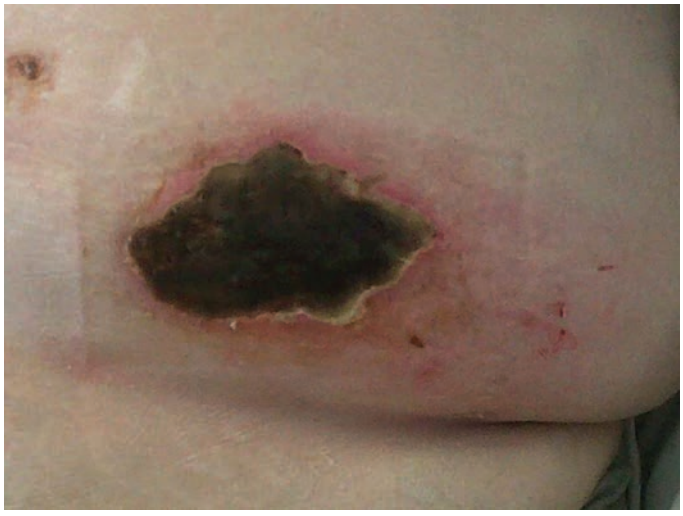

FIGURE 305-5 Calciphylaxis. This peritoneal dialysis patient was on chronic warfarin therapy for atrial fibrillation. She noticed a small painful nodule on the abdomen that was followed by progressive skin necrosis and ulceration of the anterior abdominal wall. She was treated with hyperbaric oxygen, intravenous thiosulfate, and discontinuation of warfarin, with slow resolution of the ulceration.

calcification. Thus, warfarin treatment is considered a risk factor for calciphylaxis, and if a patient develops this syndrome, this medication should be discontinued and replaced with another anticoagulant.

TREATMENT

Disorders of Calcium and Phosphate Metabolism

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

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

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

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

CARDIOVASCULAR ABNORMALITIES

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

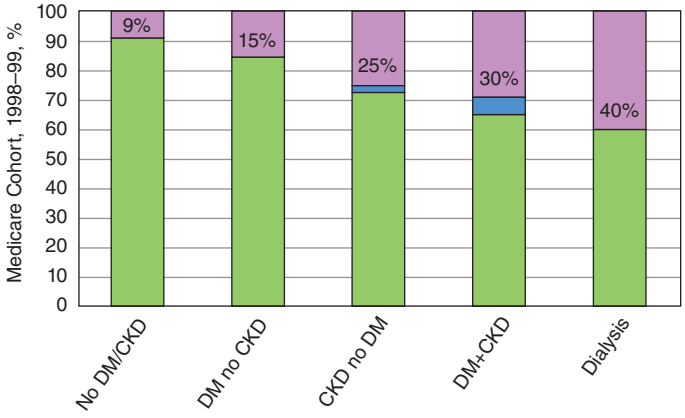

FIGURE 305-6 **U.S. Renal Data System** showing increased likelihood of dying rather than starting dialysis or reaching stage 5 chronic kidney disease (CKD). 1, Death; 2, ESRD; 3, event-free. DM; diabetes mellitus. *(Data from RN Foley et al: J Am Soc Nephrol 16:489–495, 2005.)*

Ischemic Vascular Disease The increased prevalence of vascular disease in CKD patients derives from both traditional ("classic") and nontraditional (CKD-related) risk factors. Traditional risk factors include hypertension, hypervolemia, dyslipidemia, sympathetic overactivity, and hyperhomocysteinemia. The CKD-related risk factors comprise anemia, hyperphosphatemia, hyperparathyroidism, increased FGF-23, sleep apnea, and generalized inflammation. The inflammatory state appears to accelerate vascular occlusive disease, and low levels of fetuin may permit more rapid vascular calcification, especially in the face of hyperphosphatemia. Other abnormalities seen in CKD may augment myocardial ischemia, including left ventricular hypertrophy and microvascular disease. In addition, hemodialysis, with its attendant episodes of hypotension and hypovolemia, may further aggravate coronary ischemia and repeatedly stun the myocardium. Interestingly, however, the largest increment in cardiovascular mortality rate in dialysis patients is not necessarily directly associated with documented acute myocardial infarction but, instead, is the result of congestive heart failure and sudden death.

Cardiac troponin levels are frequently elevated in CKD without evidence of acute ischemia. The elevation complicates the diagnosis of acute myocardial infarction in this population. Serial measurements may be needed. Therefore, the trend in levels over the hours after presentation may be more informative than a single, elevated level. Interestingly, consistently elevated levels are an independent prognostic factor for adverse cardiovascular events in this population.

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

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

The absence of hypertension may signify poor left ventricular function. Indeed, in epidemiologic studies of dialysis patients, low blood pressure actually carries a worse prognosis than does high blood pressure. This mechanism, in part, accounts for the "reverse causation" seen in dialysis patients, wherein the presence of traditional risk factors, such as hypertension, hyperlipidemia, and obesity, appear to portend a better prognosis. Importantly, these observations derive from cross-sectional studies of late-stage CKD patients and should not be interpreted to discourage appropriate management of these risk factors in CKD patients, especially at early stages. In contrast to the general population, it is possible that in late-stage CKD, low blood pressure, reduced body mass index, and hypolipidemia indicate the presence of an advanced malnutrition-inflammation state, with poor prognosis.

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

TREATMENT

Cardiovascular Abnormalities

MANAGEMENT OF HYPERTENSION

The overarching goal of hypertension therapy in CKD is to prevent the extrarenal complications of high blood pressure, such as cardiovascular disease and stroke. Although a clear-cut generalizable benefit in slowing progression of CKD remains as yet unproven, the benefit for cardiac and cerebrovascular health is compelling. In all patients with CKD, blood pressure should be controlled to levels recommended by national guideline panels. In CKD patients with diabetes or proteinuria >1 g per 24 h, blood pressure should be reduced to <130/80 mmHg, if achievable without prohibitive adverse effects. Salt restriction should be the first line of therapy. When volume management alone is not sufficient, the choice of antihypertensive agent is similar to that in the general population. ACE inhibitors and ARBs appear to slow the rate of decline of kidney function in a manner that extends beyond reduction of systemic arterial pressure and that involves correction of the intraglomerular hyperfiltration and hypertension. Occasionally, introduction of ACE inhibitors and ARBs can actually precipitate an episode of acute kidney injury, especially when used in combination in patients with ischemic renovascular disease. Slight reduction of GFR (<30% of baseline) may signify a salutary reduction in intra-glomerular hypertension and hyperfiltration, and, if stable over time, can be tolerated with continued monitoring. Progressive decline in GFR should prompt discontinuation of these agents. The use of ACE inhibitors and ARBs may also be complicated by the development of hyperkalemia. Often the concomitant use of a combination of kaliuretic diuretics (e.g., furosemide with metolazone), or a potassium-lowering GI tract binder, such as patrimer, can improve potassium excretion in addition to improving blood pressure control. Potassium-sparing diuretics should be used with caution or avoided altogether in most patients.

The recent movement to even lower blood pressure targets in the general population may not be applicable to patients with CKD, who often lack autoregulation to maintain GFR in the face of low perfusion pressure. If a patient experiences sudden decline in kidney function with intensification of antihypertensive therapy, consideration should be given to reducing therapy.

MANAGEMENT OF CARDIOVASCULAR DISEASE

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

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

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

TREATMENT

Pericardial Disease

Uremic pericarditis is an absolute indication for the urgent initiation of dialysis or for intensification of the dialysis prescription in those already receiving dialysis. Because of the propensity to hemorrhage in pericardial fluid, hemodialysis should be performed without heparin. A pericardial drainage procedure should be considered in patients with recurrent pericardial effusion, especially with echocardiographic signs of impending tamponade. Non-uremic causes of pericarditis and effusion include viral, malignant, tuberculous, and autoimmune etiologies. It may also be seen after myocardial infarction and as a complication of treatment with the antihypertensive drug minoxidil.

HEMATOLOGIC ABNORMALITIES

Anemia A normocytic, normochromic anemia is observed as early as stage 3 CKD and is almost universal by stage 4. The primary cause is insufficient production of EPO by the diseased kidneys. Additional factors are reviewed in **Table 305-3**.

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

TREATMENT

Anemia

The availability of recombinant human ESA has been one of the most significant advances in the care of renal patients since the introduction of dialysis and renal transplantation. Its routine use

TABLE 305-3 Causes of Anemia in CKD

Relative deficiency of erythropoietin
Diminished red blood cell survival
Bleeding diathesis
Iron deficiency due to poor dietary absorption and gastrointestinal blood loss
Hyperparathyroidism/bone marrow fibrosis
Chronic inflammation
Folate or vitamin B_{12} deficiency
Hemoglobinopathy
Comorbid conditions: hypo-/hyperthyroidism, pregnancy, HIV-associated disease, autoimmune disease, immunosuppressive drugs

has obviated the need for regular blood transfusions in severely anemic CKD patients, thus dramatically reducing the incidence of transfusion-associated infections and iron overload. Frequent blood transfusions in dialysis patients also lead to the development of alloantibodies that can sensitize the patient to donor kidney antigens and make renal transplantation more problematic.

Adequate bone marrow iron stores should be available before treatment with ESA is initiated. Iron supplementation is usually essential to ensure an optimal response to ESA in patients with CKD because the demand for iron by the marrow frequently exceeds the amount of iron that is immediately available for erythropoiesis (measured by percent transferrin saturation), as well as the amount in iron stores (measured by serum ferritin). For the CKD patient not yet on dialysis or the patient treated with peritoneal dialysis, oral iron supplementation should be attempted. If there is GI intolerance or poor GI absorption, the patient may have to undergo IV iron infusion. For patients on hemodialysis, IV iron can be administered during dialysis, keeping in mind that iron therapy can increase the susceptibility to bacterial infections, and that the adverse effects of free serum iron are still under investigation. In addition to iron, an adequate supply of other major substrates and cofactors for red cell production must be ensured, including vitamin B_{12} and folate. Anemia resistant to recommended doses of ESA in the face of adequate iron stores may be due to some combination of the following: acute or chronic inflammation, inadequate dialysis, severe hyperparathyroidism, chronic blood loss or hemolysis, chronic infection, or malignancy.

Randomized, controlled trials of ESA in CKD have failed to show an improvement in cardiovascular outcomes with this therapy. Indeed, there has been an indication that the use of ESA in CKD may be associated with an increased risk of stroke in those with type 2 diabetes, an increase in thromboembolic events, and perhaps a faster progression of renal decline. Therefore, any benefit in terms of improvement of anemic symptoms needs to be balanced against the potential cardiovascular risk. Although further studies are needed, it is quite clear that complete normalization of the hemoglobin concentration has not been demonstrated to be of incremental benefit to CKD patients. Current practice is to target a hemoglobin concentration of 100–115 g/L.

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

TREATMENT

Abnormal Hemostasis

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

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

Certain anticoagulants, such as fractionated low-molecular-weight heparin, may need to be avoided or dose-adjusted in these patients, with monitoring of factor Xa activity where available. It is often more prudent to use conventional unfractionated heparin, titrated to the measured partial thromboplastin time, in hospitalized patients requiring an alternative to warfarin anticoagulation. The new classes of oral anticoagulants are all, in part, renally eliminated and need to be avoided or dose adjusted in the face of decreased GFR **(Chap. 114)**.

NEUROMUSCULAR ABNORMALITIES

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

Peripheral neuropathy usually becomes clinically evident after the patient reaches stage 4 CKD, although electrophysiologic and histologic evidence occurs earlier. Initially, sensory nerves are involved more than motor, lower extremities more than upper, and distal parts of the extremities more than proximal. The "restless leg syndrome" is characterized by ill-defined sensations of sometimes debilitating discomfort in the legs and feet relieved by frequent leg movement. Evidence of peripheral neuropathy without another cause (e.g., diabetes mellitus) is an indication for starting renal replacement therapy. Many of the complications described above will resolve with dialysis, although subtle nonspecific abnormalities may persist.

GASTROINTESTINAL AND NUTRITIONAL ABNORMALITIES

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

Protein restriction may be useful to decrease nausea and vomiting; however, it may put the patient at risk for malnutrition and should be carried out, if possible, in consultation with a registered dietitian specializing in the management of CKD patients. Weight loss and protein-energy malnutrition, a consequence of low protein and caloric intake, is common in advanced CKD and is often an indication for initiation of renal replacement therapy. Metabolic acidosis and the activation of inflammatory cytokines can promote protein catabolism. A number of indices are useful in nutritional assessment and include dietary history, including food diary and subjective global assessment; edema-free body weight; and measurement of urinary protein nitrogen appearance. Dual-energy x-ray absorptiometry is now widely used to estimate lean body mass versus fluid weight. Nutritional guidelines for patients with CKD are summarized in the "Treatment" section.

ENDOCRINE-METABOLIC DISTURBANCES

Glucose metabolism is impaired in CKD. However, fasting blood glucose is usually normal or only slightly elevated, and mild glucose intolerance does not require specific therapy. Because the kidney contributes to insulin removal from the circulation, plasma levels of insulin are slightly to moderately elevated in most uremic patients, both in the fasting and postprandial states. Because of this diminished renal degradation of insulin, patients on insulin therapy may need progressive reduction in dose as their renal function worsens. Many anti-hyperglycemic agents, including the gliptins, require dose reduction in renal failure, and some, such as metformin and sulfonylureas

are contraindicated when the GFR is less than half of normal. A recent exception is the class of drugs that inhibit sodium-glucose transport in the proximal tubule, resulting in glucose lowering, accompanied by striking reductions in kidney function decline and in cardiovascular events. The stabilization of GFR in many patients with this therapeutic intervention represents a major, important added beneficial effect of these drugs. Their long-term stabilizing effect on GFR and urine albumin excretion appears to result from correction of hyperfiltration early in type 2 diabetes mellitus *via* re-activation of the tubuloglomerular feedback loop. This represents a fortunate convergence of pathophysiology of glomerular hyperfiltration in diabetes with drug discovery.

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

DERMATOLOGIC ABNORMALITIES

Abnormalities of the skin are prevalent in progressive CKD. Pruritus is quite common and one of the most vexing manifestations of the uremic state. In advanced CKD, even on dialysis, patients may become more pigmented, and this is felt to reflect the deposition of retained pigmented metabolites, or *urochromes*. Although many of the cutaneous abnormalities improve with dialysis, pruritus is often tenacious. The first lines of management are to rule out unrelated skin disorders, such as scabies, and to treat hyperphosphatemia, which can cause itch. Local moisturizers, mild topical glucocorticoids, oral antihistamines, and ultraviolet radiation have been reported to be helpful.

A skin condition unique to CKD patients called *nephrogenic fibrosing dermopathy* consists of progressive subcutaneous induration, especially on the arms and legs. The condition is seen very rarely in patients with CKD who have been exposed to the magnetic resonance contrast agent gadolinium. Current recommendations are that patients with CKD stage 3 (GFR 30–59 mL/min) should minimize exposure to gadolinium, and those with CKD stages 4–5 (GFR <30 mL/min) should avoid the use of gadolinium agents unless it is medically necessary. However, no patient should be denied an imaging investigation that is critical to management, and under such circumstances, rapid removal of gadolinium by hemodialysis (even in patient's not yet receiving renal replacement therapy) shortly after the procedure may mitigate this sometimes devastating complication.

EVALUATION AND MANAGEMENT OF PATIENTS WITH CKD

INITIAL APPROACH

History and Physical Examination Symptoms and overt signs of kidney disease are often subtle or absent until renal failure supervenes. Thus, the diagnosis of kidney disease often surprises patients and may be a cause of skepticism and denial. Particular aspects of the history that are germane to renal disease include a history of hypertension (which can cause CKD or more commonly be a consequence of CKD), diabetes mellitus, abnormal urinalyses, and problems with pregnancy such as preeclampsia or early pregnancy loss. A careful drug history should be elicited. Drugs to consider include nonsteroidal anti-inflammatory agents, cyclooxygenase-2 (COX-2) inhibitors, antimicrobials, chemotherapeutic agents, antiretroviral agents, proton pump inhibitors, phosphate-containing bowel cathartics, and lithium. In evaluating the uremic syndrome, questions about appetite, weight loss, nausea, hiccups, peripheral edema, muscle cramps, pruritus, and restless legs are especially helpful. A family history of kidney disease, together with assessment of manifestations in other organ systems such as auditory, visual, and integumentary, may lead to the diagnosis of a heritable form of CKD (e.g., Alport or Fabry disease, cystinosis) or shared environmental exposure to nephrotoxic agents (e.g., heavy metals, aristolochic acid). It should be noted that clustering of CKD, sometimes of different etiologies, is often observed within families.

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

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

Imaging Studies The most useful imaging study is a renal ultrasound, which can verify the presence of two kidneys, determine if they are symmetric, provide an estimate of kidney size, and rule out renal masses and evidence of obstruction. Because it takes time for kidneys to shrink as a result of chronic disease, the finding of bilaterally small kidneys supports the diagnosis of CKD of long-standing duration. If the kidney size is normal, it is possible that the renal disease is acute or subacute. The exceptions are diabetic nephropathy (where kidney size is increased at the onset of diabetic nephropathy before CKD supervenes), amyloidosis, and HIV nephropathy, where kidney size may be normal in the face of CKD. Polycystic kidney disease that has reached some degree of renal failure will almost always present with enlarged kidneys with multiple cysts (Chap. 309). A discrepancy >1 cm in kidney length suggests either a unilateral developmental abnormality or disease process or renovascular disease with arterial insufficiency affecting one kidney more than the other. The diagnosis of renovascular disease can be undertaken with different techniques, including Doppler sonography, nuclear medicine studies, or CT or magnetic resonance imaging (MRI) studies. If there is a suspicion of reflux nephropathy (recurrent childhood urinary tract infection, asymmetric renal size with scars on the renal poles), a voiding cystogram may be indicated. However, in most cases, by the time the patient has CKD, the reflux has resolved, and even if still present, repair does not improve renal function. Radiographic contrast imaging studies are not particularly helpful in the investigation of CKD. Intravenous or intraarterial dye should be avoided where possible in the CKD patient, especially with diabetic nephropathy, because of the risk of radiographic contrast dye–induced renal failure. When unavoidable, appropriate precautionary measures include avoidance of hypovolemia at the time of contrast exposure, minimization of the dye load, and choice of radiographic contrast preparations with the least nephrotoxic potential. Additional measures thought to attenuate contrast-induced worsening of renal function include judicious administration of sodium bicarbonate–containing solutions and *N* acetylcysteine.

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

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

ESTABLISHING THE DIAGNOSIS AND ETIOLOGY OF CKD

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

Although kidney biopsy can usually be performed in early CKD (stages 1–3), it is not always indicated. For example, in a patient with a history of type 1 diabetes mellitus for 15–20 years with retinopathy, nephrotic-range proteinuria, and absence of hematuria, the diagnosis of diabetic nephropathy is very likely and biopsy is usually not necessary. However, if there were some other finding not typical of diabetic nephropathy, such as hematuria or white blood cell casts, or absence of diabetic retinopathy, some other disease may be present and a biopsy may be indicated.

In the absence of a clinical diagnosis, kidney biopsy may be the only recourse to establish an etiology in early-stage CKD. However, as noted above, once the CKD is advanced and the kidneys are small and scarred, there is little utility and significant risk in attempting to arrive at a specific diagnosis. Genetic testing is increasingly entering the repertoire of diagnostic tests, since the patterns of injury and kidney morphologic abnormalities often reflect overlapping causal mechanisms, whose origins can sometimes be attributed to a genetic predisposition or cause.

TREATMENT

Chronic Kidney Disease

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

SLOWING THE PROGRESSION OF CKD

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

Reducing Intraglomerular Hypertension and Proteinuria Increased intraglomerular filtration pressures and glomerular hypertrophy develop as a response to loss of nephron number. This response is maladaptive, as it promotes the ongoing decline of kidney function even if the inciting process has been treated or spontaneously resolved. Control of glomerular hypertension is important in slowing the progression of CKD. Moreover, elevated blood pressure increases proteinuria by increasing its flux across the glomerular capillaries. Conversely, the renoprotective effect of antihypertensive medications is gauged through the consequent reduction of proteinuria. Thus, the more effective a given treatment is in lowering protein excretion, the greater the subsequent impact on protection from decline in GFR. This observation is the basis for the treatment guideline establishing 130/80 mmHg as a target blood pressure in proteinuric CKD patients.

Several controlled studies have shown that ACE inhibitors and ARBs are effective in slowing the progression of renal failure in patients with advanced stages of both diabetic and nondiabetic CKD, in large part through effects on efferent vasodilatation and the subsequent decline in glomerular hypertension. In the absence of an anti-proteinuric response with either agent alone, combined treatment with both ACE inhibitors and ARBs has been considered. The combination is associated with a greater reduction in proteinuria compared to either agent alone. Insofar as reduction in proteinuria is a surrogate for improved renal outcome, the combination would appear to be advantageous. However, there is a greater incidence of acute kidney injury and adverse cardiac events from such combination therapy. On balance, therefore, ACE inhibitor plus ARB therapy should be avoided. A progressive increase in serum creatinine concentration with these agents may suggest the presence of renovascular disease within the large or small arteries. Development of side effects may mandate the use of second-line antihypertensive agents instead of ACE inhibitors or ARBs. Among the calcium channel blockers, diltiazem and verapamil may exhibit superior antiproteinuric and renoprotective effects compared to the dihydropyridines. At least two different categories of response can be considered: one in which progression is strongly associated with systemic and intraglomerular hypertension and proteinuria (e.g., diabetic nephropathy, glomerular diseases) and in which ACE inhibitors and ARBs are likely to be the first choice; and another in which proteinuria is mild or absent initially (e.g., adult polycystic kidney disease and other tubulointerstitial diseases), where the contribution of intraglomerular hypertension is less prominent and other antihypertensive agents can be useful for control of systemic hypertension.

SLOWING THE PROGRESSION OF DIABETIC NEPHROPATHY

See Chap. 397

MANAGING OTHER COMPLICATIONS OF CKD

Medication Dose Adjustment Although the loading dose of most drugs is not affected by CKD because renal elimination is not used in the calculation, the maintenance doses of many drugs will need to be adjusted. For those agents in which >70% excretion is by a nonrenal route, such as hepatic elimination, dose adjustment may not be needed. Some drugs that should be avoided include metformin, meperidine, and oral anti-hyperglycemics that are eliminated by the kidney. NSAIDs should be avoided because of the risk of further worsening of kidney function. Many antibiotics, antihypertensives, and antiarrhythmics may require a reduction in dosage or change in the dose interval. Several online Web-based databases for dose adjustment of medications according to stage of

CKD or estimated GFR are available (e.g., *http://www.globalrph.com/index_renal.htm*). Nephrotoxic radiocontrast agents and gadolinium should be avoided or used according to strict guidelines when medically necessary as discussed above.

PREPARATION FOR RENAL REPLACEMENT THERAPY

(See also Chap. 307) Temporary relief of symptoms and signs of impending uremia, such as anorexia, nausea, vomiting, lassitude, and pruritus, may sometimes be achieved with dietary protein restriction. However, this carries a risk of malnutrition, and thus plans for more long-term management should be in place.

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

Recommendations for the Optimal Time for Initiation of Renal Replacement Therapy Because of the individual variability in the severity of uremic symptoms and renal function, it is ill-advised to assign an arbitrary urea nitrogen or creatinine level to the need to start dialysis. Moreover, patients may become accustomed to chronic uremia and deny symptoms, only to find that they feel better with dialysis and realize in retrospect how poorly they were feeling before its initiation.

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

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

Exploration of social support is also important. Early education of family members for selection and preparation of a home dialysis helper or a biologically or emotionally related potential living kidney donor should occur long before the onset of symptomatic renal failure.

Kidney transplantation **(Chap. 307)** offers the best potential for complete rehabilitation, because dialysis replaces only a small fraction of the kidneys' filtration function and none of the other renal functions, including endocrine and anti-inflammatory effects. Generally, kidney transplantation follows a period of dialysis treatment, although preemptive kidney transplantation (usually from a living donor) can be carried out if it is certain that the renal failure is irreversible.

IMPLICATIONS FOR GLOBAL HEALTH

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

There is also increasing recognition of endemic nephropathies in developing countries that particularly target young males working in agriculture. The extent of morbidity and mortality associated with these nephropathies is only starting to be appreciated. It is unclear what the cause is, but a combination of population genetic risk with endemic nephrotoxins, exposure to pesticides, NSAID use, and chronic volume depletion have all been suggested to contribute.

FURTHER READING

Coca SG et al: Chronic kidney disease after acute kidney injury: A systematic review and meta-analysis. Kidney Int 81:442, 2012.

Coresh J et al: Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA 311:2518, 2014.

Correa-Rotter R et al: CKD of unknown origin in Central America: The case for a Mesoamerican nephropathy. Am J Kidney Dis 63:506, 2014.

Tangri N et al: Multinational assessment of accuracy of equations for predicting risk of kidney failure: A meta-analysis. JAMA 315:164, 2016.

Wanner C et al: Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 375:323, 2016.

306 Dialysis in the Treatment of Renal Failure

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Dialysis may be required for the treatment of either acute or chronic kidney disease (CKD). The use of continuous renal replacement therapies (CRRT) and prolonged intermittent renal replacement therapy (PIRRT)/slow low-efficiency dialysis (SLED) is specific to the management of acute renal failure and is discussed in **Chap. 304**. These modalities are performed continuously (CRRT) or over 6–12 h per session (PIRRT/SLED), in contrast to the 3–4 h of an intermittent hemodialysis session. **Advantages and disadvantages of CRRT and PIRRT/SLED are discussed in Chap. 304.**

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

With the widespread availability of dialysis, the lives of hundreds of thousands of patients with ESRD have been prolonged. In the

United States alone, there are now ~675,000 patients with treated ESRD (kidney failure requiring dialysis or transplantation), the vast majority of whom require dialysis. Since 2000, the prevalence of treated ESRD has increased 74%, which reflects both a small increase in the incidence rate and marginally enhanced survival of patients receiving dialysis. The incidence rate for treated ESRD in the United States is 370 cases per million population per year; ESRD is disproportionately higher in African Americans (875 per million population per year) as compared with white Americans (285 per million population per year). In the United States, the leading cause of ESRD is diabetes mellitus, currently accounting for almost 45% of newly diagnosed cases of ESRD. Approximately 30% of patients have ESRD that has been attributed to hypertension, although it is unclear whether in these cases hypertension is the cause or a consequence of vascular disease or other unknown causes of kidney failure. Other prevalent causes of ESRD include glomerulonephritis, polycystic kidney disease, and obstructive uropathy. A fraction of the excess incidence of ESRD in African Americans is likely related to transmission of high-risk alleles for the *APOL1* gene.

Globally, mortality rates for patients with ESRD are lowest in Europe and Japan but very high in the developing world because of the limited availability of dialysis. In the United States, the mortality rate of patients on dialysis has decreased slightly but remains extremely high, with a 5-year survival rate of ~40% for patients receiving dialysis. Deaths are due mainly to cardiovascular diseases and infections (~40 and 10% of deaths, respectively). Older age, male sex, nonblack race, diabetes mellitus, malnutrition, and underlying heart disease are important predictors of death.

TREATMENT OPTIONS FOR PATIENTS WITH ESRD

Commonly accepted criteria for initiating patients on maintenance dialysis include the presence of uremic symptoms, the presence of hyperkalemia unresponsive to conservative measures, persistent extracellular volume expansion despite diuretic therapy, acidosis refractory to medical therapy, a bleeding diathesis, and a creatinine clearance or estimated glomerular filtration rate (GFR) <10 mL/min per 1.73 m^2 (see Chap. 305 for estimating equations). Timely referral to a nephrologist for advanced planning and creation of a dialysis access, education about ESRD treatment options, and management of the complications of advanced CKD, including hypertension, anemia, acidosis, and secondary hyperparathyroidism, is advisable. Recent data have suggested that a sizable fraction of ESRD cases result following episodes of acute renal failure, particularly among persons with underlying CKD. Furthermore, there is no benefit to initiating dialysis preemptively at a GFR of 10–14 mL/min per 1.73 m^2 compared to initiating dialysis for symptoms of uremia.

In ESRD, treatment options include hemodialysis (in center or at home); peritoneal dialysis, as either continuous ambulatory peritoneal dialysis (CAPD) or continuous cyclic peritoneal dialysis (CCPD); or transplantation (Chap. 307). Although there are significant geographic variations and differences in practice patterns, in-center hemodialysis remains the most common therapeutic modality for ESRD (>90% of patients) in the United States. In contrast to hemodialysis, peritoneal dialysis is continuous, but much less efficient, in terms of solute clearance. While no large-scale clinical trials have been completed comparing outcomes among patients randomized to either hemodialysis or peritoneal dialysis, outcomes associated with both therapies are similar in most reports, and the decision of which modality to select is often based on personal preferences and quality-of-life considerations.

HEMODIALYSIS

Hemodialysis relies on the principles of solute diffusion across a semipermeable membrane. Movement of metabolic waste products takes place down a concentration gradient from the circulation into the dialysate. The rate of diffusive transport increases in response to several factors, including the magnitude of the concentration gradient, the membrane surface area, and the mass transfer coefficient of the membrane. The latter is a function of the porosity and thickness of the membrane, the size of the solute molecule, and the conditions of flow on the two sides of the membrane. According to laws of diffusion, the larger the molecule, the slower its rate of transfer across the membrane. A small molecule, such as urea (60 Da), undergoes substantial clearance, whereas a larger molecule, such as creatinine (113 Da), is cleared less efficiently. In addition to diffusive clearance, movement of waste products from the circulation into the dialysate may occur as a result of ultrafiltration. Convective clearance occurs because of solvent drag, with solutes being swept along with water across the semipermeable dialysis membrane.

THE DIALYZER

There are three essential components to hemodialysis: the dialyzer, the composition and delivery of the dialysate, and the blood delivery system (Fig. 306-1). The dialyzer is a plastic chamber with the ability to perfuse blood and dialysate compartments simultaneously at very high flow rates. The hollow-fiber dialyzer is the most common in use in the United States. These dialyzers are composed of bundles of capillary tubes through which blood circulates while dialysate travels on the outside of the fiber bundle. Virtually all dialyzers now manufactured in the United States are "biocompatible" synthetic membranes derived from polysulfone or related compounds (versus older cellulose "bioincompatible" membranes that activated the complement cascade). The frequency of reprocessing and reuse of hemodialyzers and blood lines varies across the world. In general as the cost of disposable supplies has decreased, their use has increased. In the United States, reprocessing of dialyzers is now extremely rare. Formaldehyde, peracetic acid–hydrogen peroxide, glutaraldehyde, and bleach have all been used as reprocessing agents.

DIALYSATE

The potassium concentration of dialysate may be varied from 0 to 4 mmol/L depending on the predialysis serum potassium concentration. The use of 0 or 1 mmol/L potassium dialysate is becoming less common owing to data suggesting that patients who undergo treatments with very low potassium dialysate have an increased risk of sudden death, perhaps due to arrhythmias in the setting of potassium shifts. The usual dialysate calcium concentration is 1.25 mmol/L (2.5 mEq/L), although modification may be required in selected settings (e.g., higher dialysate calcium concentrations may be used in patients with hypocalcemia associated with secondary hyperparathyroidism or with "hungry bone syndrome" following parathyroidectomy). The usual dialysate sodium concentration is 136–140 mmol/L. In patients who frequently develop hypotension during their dialysis run, "sodium modeling" to counterbalance urea-related osmolar gradients may be employed. With sodium modeling, the dialysate sodium concentration is gradually lowered from the range of 145–155 mmol/L to isotonic concentrations (136–140 mmol/L) near the end of the dialysis treatment, typically declining either in steps or in a linear or exponential fashion. However, higher dialysate sodium concentrations and sodium modeling may predispose patients to positive sodium balance and increased thirst; thus, these strategies to ameliorate intradialytic hypotension may be undesirable in patients with hypertension or in patients with large interdialytic weight gains. Because patients are exposed to ~120 L of water during each dialysis treatment, water used for the dialysate is subjected to filtration, softening, deionization, and, ultimately, reverse osmosis to remove microbiologic contaminants and dissolved ions.

BLOOD DELIVERY SYSTEM

The blood delivery system is composed of the extracorporeal circuit and the dialysis access. The dialysis machine consists of a blood pump, dialysis solution delivery system, and various safety monitors. The blood pump moves blood from the access site, through the dialyzer, and back to the patient. The blood flow rate typically ranges from 250 to 450 mL/min, depending on the type and integrity of the vascular access. Negative hydrostatic pressure on the dialysate side can be manipulated to achieve desirable fluid removal or *ultrafiltration*. Dialysis membranes have different ultrafiltration coefficients (i.e., mL removed/min per mmHg) so that along with hydrostatic changes,

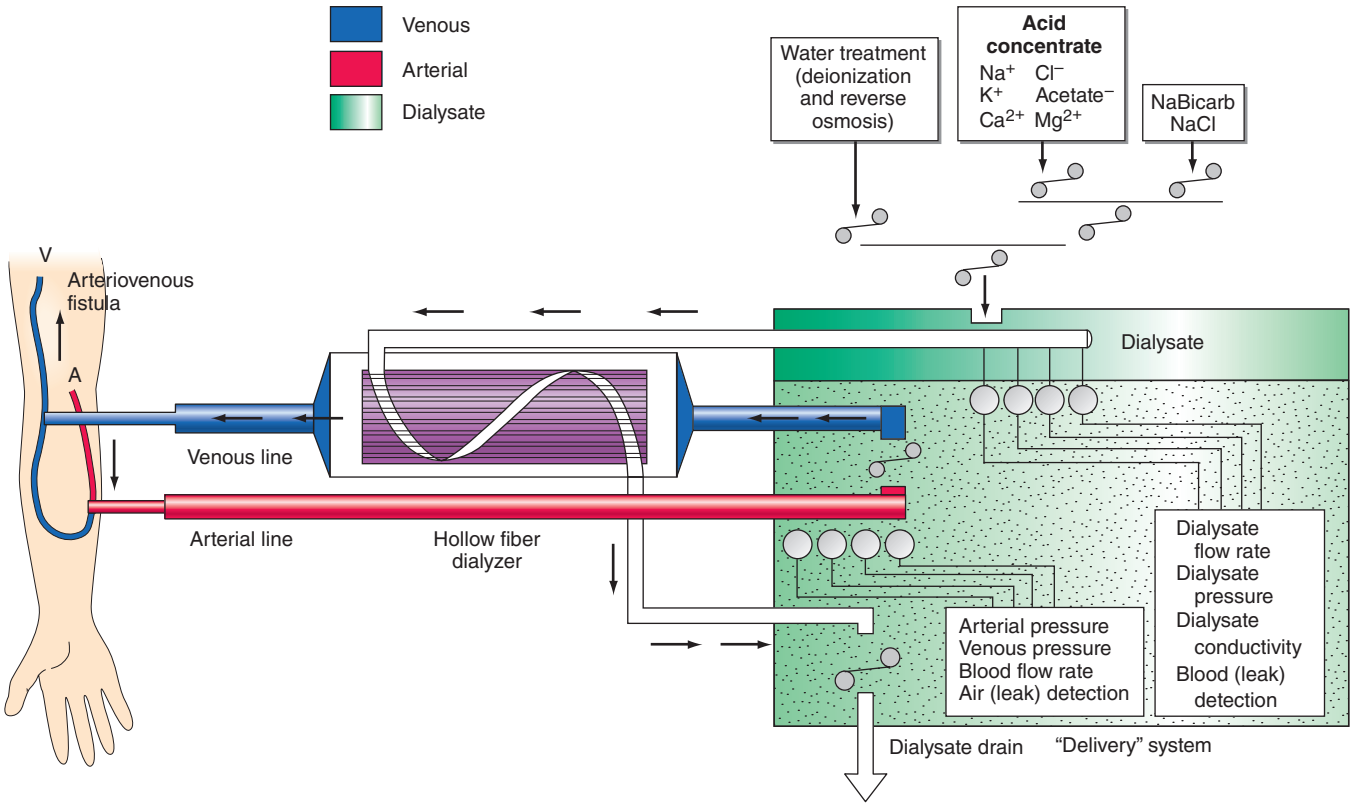

FIGURE 306-1 Schema for hemodialysis.

fluid removal can be varied. The dialysis solution delivery system dilutes the concentrated dialysate with water and monitors the temperature, conductivity, and flow of dialysate.

DIALYSIS ACCESS

The fistula, graft, or catheter through which blood is obtained for hemodialysis is often referred to as a *hemodialysis (or vascular) access*. A native fistula created by the anastomosis of an artery to a vein (e.g., the Brescia-Cimino fistula, in which the cephalic vein is anastomosed end-to-side to the radial artery) results in arterialization of the vein. This facilitates its subsequent use in the placement of large needles (typically 15 gauge) to access the circulation. Fistulas have the highest long-term patency rate of all hemodialysis access options. For patients in whom fistulas fail to mature, or in patients whose vasculature does not allow creation of a successful fistula (i.e., poor arterial inflow or recipient veins of inadequate caliber), patients undergo placement of an arteriovenous graft (i.e., the interposition of prosthetic material, usually polytetrafluoroethylene, between an artery and a vein) or a tunneled hemodialysis catheter. In recent years, nephrologists, vascular surgeons, and health care policy makers in the United States have encouraged creation of arteriovenous fistulas in a larger fraction of patients (the "fistula first" initiative). Unfortunately, even when created, arteriovenous fistulas may not mature sufficiently to provide reliable access to the circulation, or they may thrombose early in their development.

The most important complication of arteriovenous grafts is thrombosis of the graft and graft failure, due principally to intimal hyperplasia at the anastomosis between the graft and recipient vein. When grafts (or fistulas) fail, catheter-guided angioplasty can be used to dilate stenoses; monitoring of venous pressures on dialysis and of access flow, although not routinely performed, may assist in the early recognition of impending vascular access failure. In addition to increased rates of access failure, grafts and (in particular) catheters are associated with much higher rates of infection than fistulas.

Intravenous large-bore catheters are often used in patients with acute renal failure and CKD. For persons on maintenance hemodialysis, tunneled catheters (either two separate catheters or a single catheter with two lumens) are often used when arteriovenous fistulas and grafts have failed or are not feasible due to anatomic considerations. These catheters are tunneled under the skin; the tunnel reduces bacterial translocation from the skin, resulting in a lower infection rate than with nontunneled temporary catheters. Most tunneled catheters are placed in the internal jugular veins; the external jugular, femoral, and subclavian veins may also be used.

Nephrologists, interventional radiologists, and vascular surgeons generally prefer to avoid placement of catheters into the subclavian veins; while flow rates are usually excellent, subclavian stenosis is a frequent complication and, if present, will likely prohibit permanent vascular access (i.e., a fistula or graft) in the ipsilateral extremity. Infection rates may be higher with femoral catheters. For patients with multiple vascular access complications and no other options for permanent vascular access, tunneled catheters may be the last "lifeline" for hemodialysis. Translumbar or transhepatic approaches into the inferior vena cava may be required if the superior vena cava or other central veins draining the upper extremities are stenosed or thrombosed.

GOALS OF DIALYSIS

The hemodialysis procedure consists of pumping heparinized blood through the dialyzer at a flow rate of 250–450 mL/min, while dialysate flows in an opposite *counter-current* direction at 500–800 mL/min. The efficiency of dialysis is determined by blood and dialysate flow through the dialyzer as well as dialyzer characteristics (i.e., its efficiency in removing solute). The *dose* of dialysis, which is currently defined as a derivation of the fractional urea clearance during a single treatment, is further governed by patient size, residual kidney function, dietary protein intake, the degree of anabolism or catabolism, and the presence of comorbid conditions.

Since the landmark studies of Sargent and Gotch relating the measurement of the dose of dialysis using urea concentrations with morbidity in the National Cooperative Dialysis Study, the *delivered* dose of dialysis has been measured and considered as a quality assurance and improvement tool. While the fractional removal of urea nitrogen and derivations thereof are considered to be the standard methods by which "adequacy of dialysis" is measured, a large multicenter randomized clinical trial (the HEMO Study) failed to show a difference in mortality associated with a large difference in per-session urea clearance.

Current targets include a urea reduction ratio (the fractional reduction in blood urea nitrogen per hemodialysis session) of >65–70% and a body water–indexed clearance × time product (Kt/V) >1.2 or 1.05, depending on whether urea concentrations are "equilibrated." For the majority of patients with ESRD, between 9 and 12 h of dialysis are required each week, usually divided into three equal sessions. Several studies have suggested that longer hemodialysis session lengths may be beneficial (independent of urea clearance), although these studies are confounded by a variety of patient characteristics, including body size and nutritional status. Hemodialysis "dose" should be individualized, and factors other than the urea nitrogen should be considered, including the adequacy of ultrafiltration or fluid removal and control of hyperkalemia, hyperphosphatemia, and metabolic acidosis. A randomized clinical trial comparing 6 versus 3 times per week hemodialysis (the "Frequent Hemodialysis Network Daily Trial") demonstrated improved control of hypertension and hyperphosphatemia, reduced left ventricular mass, and improved self-reported physical health with more frequent hemodialysis. Secondary analyses also demonstrated improvements in other metrics of health-related quality of life, including improved self-reported general health and a reduced "time to recovery" (time until usual activities can be resumed) among patients randomized to more frequent hemodialysis. A companion trial in which frequent nocturnal hemodialysis was compared to conventional hemodialysis at home showed no significant effect on left ventricular mass or self-reported physical health. Finally, an evaluation of the U.S. Renal Data System registry showed a significant increase in mortality and hospitalization for heart failure after the longer interdialytic interval that occurs over the dialysis "weekend."

COMPLICATIONS DURING HEMODIALYSIS

Hypotension is the most common acute complication of hemodialysis, particularly among patients with diabetes mellitus. Numerous factors appear to increase the risk of hypotension, including excessive ultrafiltration with inadequate compensatory vascular filling, impaired vasoactive or autonomic responses, osmolar shifts, overzealous use of antihypertensive agents, and reduced cardiac reserve. Patients with arteriovenous fistulas and grafts may develop high-output cardiac failure due to shunting of blood through the dialysis access; on rare occasions, this may necessitate ligation of the fistula or graft. The management of hypotension during dialysis consists of discontinuing ultrafiltration, the administration of 100–250 mL of isotonic saline, or administration of salt-poor albumin. Hypotension during dialysis can frequently be prevented by careful evaluation of the dry weight and by ultrafiltration modeling, such that more fluid is removed at the beginning rather than the end of the dialysis procedure. Excessively rapid fluid removal (>13 mL/kg per h) should be avoided, as rapid fluid removal has been associated with adverse outcomes, including cardiovascular deaths. Additional maneuvers to prevent intradialytic hypotension include the performance of sequential ultrafiltration followed by dialysis, cooling of the dialysate during dialysis treatment, and avoiding heavy meals during dialysis. Midodrine, an oral selective α1 adrenergic agent, has been advocated by some practitioners, although there is insufficient evidence of its safety and efficacy to support its routine use.

Muscle cramps during dialysis are also a common complication. The etiology of dialysis-associated cramps remains obscure. Changes in muscle perfusion because of excessively rapid volume removal or targeted removal below the patient's estimated dry weight often precipitate dialysis-associated cramps. Strategies that may be used to prevent cramps include reducing volume removal during dialysis, ultrafiltration profiling, and the use of sodium modeling (see above).

Anaphylactoid reactions to the dialyzer, particularly on its first use, have been reported most frequently with the bioincompatible cellulosic-containing membranes. Dialyzer reactions can be divided into two types, A and B. Type A reactions are attributed to an IgE-mediated intermediate hypersensitivity reaction to ethylene oxide used in the sterilization of new dialyzers. This reaction typically occurs soon after the initiation of a treatment (within the first few minutes) and can progress to full-blown anaphylaxis if the therapy is not promptly discontinued. Treatment with steroids or epinephrine may be needed if symptoms are severe. The type B reaction consists of a symptom complex of nonspecific chest and back pain, which appears to result from complement activation and cytokine release. These symptoms typically occur several minutes into the dialysis run and typically resolve over time with continued dialysis.

PERITONEAL DIALYSIS

In peritoneal dialysis, 1.5–3 L of a dextrose-containing solution is infused into the peritoneal cavity and allowed to dwell for a set period of time, usually 2–4 h. As with hemodialysis, metabolic byproducts are removed through a combination of convective clearance generated through ultrafiltration and diffusive clearance down a concentration gradient. The clearance of solutes and water during a peritoneal dialysis exchange depends on the balance between the movement of solute and water into the peritoneal cavity versus absorption from the peritoneal cavity. The rate of diffusion diminishes with time and eventually stops when equilibration between plasma and dialysate is reached. Absorption of solutes and water from the peritoneal cavity occurs across the peritoneal membrane into the peritoneal capillary circulation and via peritoneal lymphatics into the lymphatic circulation. The rate of peritoneal solute transport varies from patient to patient and may be altered by the presence of infection (peritonitis), drugs, and physical factors such as position and exercise.

FORMS OF PERITONEAL DIALYSIS

Peritoneal dialysis may be carried out as CAPD, CCPD, or a combination of both. In CAPD, dialysate is manually infused into the peritoneal cavity and exchanged three to five times during the day. A nighttime dwell is frequently instilled at bedtime and remains in the peritoneal cavity through the night. In CCPD, exchanges are performed in an automated fashion, usually at night; the patient is connected to an automated cycler that performs a series of exchange cycles while the patient sleeps. The number of exchange cycles required to optimize peritoneal solute clearance varies by the peritoneal membrane characteristics; as with hemodialysis, solute clearance should be tracked to ensure dialysis "adequacy."

Peritoneal dialysis solutions are available in volumes typically ranging from 1.5 to 3 L. The major difference between the dialysate used for peritoneal rather than hemodialysis is that the hypertonicity of peritoneal dialysis solutions drives solute and fluid removal, whereas solute removal in hemodialysis depends on concentration gradients, and fluid removal requires transmembrane pressure. Typically, dextrose at varying concentrations contributes to the hypertonicity of peritoneal dialysate. Icodextrin is a nonabsorbable carbohydrate that can be used in place of dextrose. Studies have demonstrated more efficient ultrafiltration with icodextrin than with dextrose-containing solutions. Icodextrin is typically used as the "last fill" for patients on CCPD or for the longest dwell in patients on CAPD. The most common additives to peritoneal dialysis solutions are heparin to prevent obstruction of the dialysis catheter lumen with fibrin and antibiotics during an episode of acute peritonitis. Insulin may also be added in patients with diabetes mellitus.

ACCESS TO THE PERITONEAL CAVITY

Access to the peritoneal cavity is obtained through a peritoneal catheter. Catheters used for maintenance peritoneal dialysis are flexible, being made of silicone rubber with numerous side holes at the distal end. These catheters usually have two Dacron cuffs. The scarring that occurs around the cuffs anchors the catheter and seals it from bacteria tracking from the skin surface into the peritoneal cavity; it also prevents the external leakage of fluid from the peritoneal cavity. The cuffs are placed in the preperitoneal plane and ~2 cm from the skin surface.

The *peritoneal equilibrium test* is a formal evaluation of peritoneal membrane characteristics that measures the transfer rates of creatinine and glucose across the peritoneal membrane. Patients are classified as low, low–average, high–average, and high transporters. Patients with rapid equilibration (i.e., high transporters) tend to absorb more glucose and lose efficiency of ultrafiltration with long daytime dwells. High transporters also tend to lose larger quantities of albumin and

other proteins across the peritoneal membrane. In general, patients with rapid transporting characteristics require more frequent, shorter dwell time exchanges, nearly always obligating use of a cycler. Slower (low and low–average) transporters tend to do well with fewer exchanges. The efficiency of solute clearance also depends on the volume of dialysate infused. Larger volumes allow for greater solute clearance, particularly with CAPD in patients with low and low–average transport characteristics.

As with hemodialysis, the optimal dose of peritoneal dialysis is unknown. Several observational studies have suggested that higher rates of urea and creatinine clearance (the latter generally measured in L/week) are associated with lower mortality rates and fewer uremic complications. However, a randomized clinical trial (Adequacy of Peritoneal Dialysis in Mexico [ADEMEX]) failed to show a significant reduction in mortality or complications with a relatively large increment in urea clearance. In general, patients on peritoneal dialysis do well when they retain residual kidney function. Rates of technique failure increase with years on dialysis and have been correlated with loss of residual function to a greater extent than loss of peritoneal membrane capacity. For some patients in whom CCPD does not provide sufficient solute clearance, a hybrid approach can be adopted where one or more daytime exchanges are added to the CCPD regimen. While this approach can enhance solute clearance and prolong a patient's capacity to remain on peritoneal dialysis, the burden of the hybrid approach can be overwhelming.

COMPLICATIONS DURING PERITONEAL DIALYSIS

The major complications of peritoneal dialysis are peritonitis, catheter-associated nonperitonitis infections, weight gain and other metabolic disturbances, and residual uremia (especially among patients with little or no residual kidney function).

Peritonitis typically develops when there has been a break in sterile technique during one or more of the exchange procedures. Peritonitis is usually defined by an elevated peritoneal fluid leukocyte count ($100/mm^3$, of which at least 50% are polymorphonuclear neutrophils); these cutoffs are lower than in spontaneous bacterial peritonitis because of the presence of dextrose in peritoneal dialysis solutions and rapid bacterial proliferation in this environment without antibiotic therapy. The clinical presentation typically consists of pain and cloudy dialysate, often with fever and other constitutional symptoms. The most common culprit organisms are gram-positive cocci, including *Staphylococcus,* reflecting the origin from the skin. Gram-negative rod infections are less common; fungal and mycobacterial infections can be seen in selected patients, particularly after antibacterial therapy. Most cases of peritonitis can be managed either with intraperitoneal or oral antibiotics, depending on the organism; many patients with peritonitis do not require hospitalization. In cases where peritonitis is due to hydrophilic gram-negative rods (e.g., *Pseudomonas* sp.) or yeast, antimicrobial therapy is usually not sufficient, and catheter removal is required to ensure complete eradication of infection. Nonperitonitis catheter-associated infections (often termed *tunnel infections*) vary widely in severity. Some cases can be managed with local antibiotic or silver nitrate administration, while others are severe enough to require parenteral antibiotic therapy and catheter removal.

Peritoneal dialysis is associated with a variety of metabolic complications. Albumin and other proteins can be lost across the peritoneal membrane in concert with the loss of metabolic wastes. Hypoproteinemia obligates a higher dietary protein intake in order to maintain nitrogen balance. Hyperglycemia and weight gain are also common complications of peritoneal dialysis. Several hundred calories in the form of dextrose are absorbed each day, depending on the concentration of dextrose employed. Patients receiving peritoneal dialysis, particularly those with diabetes mellitus, are prone to other complications of insulin resistance, including hypertriglyceridemia. On the positive side, the continuous nature of peritoneal dialysis usually allows for a more liberal diet, due to continuous removal of potassium and phosphorus—two major dietary components whose accumulation can be hazardous in ESRD.

LONG-TERM OUTCOMES IN ESRD

Cardiovascular disease constitutes the major cause of death in patients with ESRD. Cardiovascular mortality and event rates are higher in patients receiving dialysis than in patients posttransplantation, although rates are extraordinarily high in both populations. The underlying cause of cardiovascular disease is unclear but may be related to shared risk factors (e.g., diabetes mellitus, hypertension, atherosclerotic and arteriosclerotic vascular disease), chronic inflammation, massive changes in extracellular volume (especially with high interdialytic weight gains), inadequate treatment of hypertension, dyslipidemia, anemia, dystrophic (vascular) calcification, and, perhaps, alterations in cardiovascular dynamics during the dialysis treatment. Few studies have targeted cardiovascular risk reduction in ESRD patients; none have demonstrated consistent benefit. Two clinical trials of statin agents in ESRD demonstrated significant reductions in low-density lipoprotein (LDL) cholesterol concentrations but no significant reductions in death or cardiovascular events (Die Deutsche Diabetes Dialyse Studie [4D] and AURORA studies). The Study of Heart and Renal Protection (SHARP) which included patients on dialysis and others with nondialysis-requiring CKD showed a 17% reduction in the rate of major cardiovascular events or cardiovascular death with simvastatin-ezatamide treatment. Most experts recommend conventional cardioprotective strategies (e.g., lipid-lowering agents, aspirin, inhibitors of the renin-angiotensin-aldosterone system, and β-adrenergic antagonists) in patients receiving dialysis based on the patients' cardiovascular risk profile, which appears to be increased by more than an order of magnitude relative to persons unaffected by kidney disease. Other complications of ESRD include a high incidence of infection, progressive debility and frailty, protein-energy malnutrition, and impaired cognitive function.

GLOBAL PERSPECTIVE

The incidence of ESRD is increasing worldwide with longer life expectancies and improved care of infectious and cardiovascular diseases. The management of ESRD varies widely by country and within country by region, and it is influenced by economic and other major factors. In general, peritoneal dialysis is more commonly performed in poorer countries owing to its lower expense and the high cost of establishing in-center hemodialysis units.

FURTHER READING

Cooper BA et al: A randomized, controlled trial of early versus late initiation of dialysis. N Engl J Med 363:609, 2010.

Correa-Rotter R et al: Peritoneal dialysis, in *Brenner and Rector's The Kidney,* 9th ed, MW Taal, GM Chertow, PA Marsden, K Skorecki, and ASL Yu (eds). Philadelphia, Elsevier, 2011.

Fellstrom BC et al: Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 360:1395, 2009.

Flythe JE et al: Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. Kidney Int 79:250, 2011.

Foley RN et al: Long interdialytic interval and mortality among patients receiving hemodialysis. N Engl J Med 365:1099, 2011.

Frequent Hemodialysis Network Trial Group: In-center hemodialysis six times per week versus three times per week. N Engl J Med 363:2287, 2010.

National Kidney Foundation: Kidney disease quality initiative clinical practice guidelines: Hemodialysis and peritoneal dialysis adequacy, 2006. Available online: *http://www.kidney.org/professionals/kdoqi/guidelines.cfm.*

Rocco MV et al: The effects of frequent nocturnal home hemodialysis: The frequent hemodialysis network nocturnal trial. Kidney Int 80:1080, 2011.

U.S. Renal Data System: USRDS 2016 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease, 2016.

307 Transplantation in the Treatment of Renal Failure

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Transplantation of the human kidney is the treatment of choice for advanced chronic renal failure. Worldwide, tens of thousands of these procedures have been performed with >180,000 patients bearing functioning kidney transplants in the United States today. When azathioprine and prednisone initially were used as immunosuppressive drugs in the 1960s, the results with properly matched familial donors were superior to those with organs from deceased donors: 75–90% compared with 50–60% graft survival rates at 1 year. During the 1970s and 1980s, the success rate at the 1-year mark for deceased-donor transplants rose progressively. Currently, deceased-donor grafts have a 92% 1-year survival and living-donor grafts have a 97% 1-year survival. Although there has been improvement in long-term survival, it has not been as impressive as the short-term survival, and currently the "average" ($t1/2$) life expectancy of a living-donor graft is around 14 years and that of a deceased-donor graft is close to 10 years.

Mortality rates after transplantation are highest in the first year and are age-related: 2% for ages 18–34 years, 3% for ages 35–49 years, and 6.8% for ages ≥50–60 years. These rates compare favorably with those in the chronic dialysis population even after risk adjustments for age, diabetes, and cardiovascular status. While the loss of kidney transplant due to acute rejection is currently rare, most allografts succumb at varying rates to a chronic process consisting of interstitial fibrosis, tubular atrophy, vasculopathy, and glomerulopathy, the pathogenesis of which is incompletely understood. Overall, transplantation returns most patients to an improved lifestyle and an improved life expectancy compared with patients on dialysis.

RECENT ACTIVITY AND RESULTS

In 2014 there were more than 12,328 deceased-donor kidney transplants and 5574 living-donor transplants in the United States, with the ratio of deceased to living donors remaining stable over the last few years. The backlog of patients with end-stage renal disease (ESRD) has been increasing every year, and it always lags behind the number of available donors. As the number of patients with end-stage kidney disease increases, the demand for kidney transplants continues to increase. As of 2015, there were 50,692 active adult candidates on the waiting list, and <18,000 patients were transplanted. This imbalance is set to worsen over the coming years with the predicted increased rates of obesity and diabetes worldwide. In an attempt to increase utilization of marginal kidneys while insuring longevity-matching, a new allocation system was developed and recently implemented. The main rule is that patients expected to survive the longest receive the allografts expected to last the longest. For this purpose, the Kidney Donor Profile Index (KDPI) score from 0 to 100% has been introduced to quantify the potential risk of graft failure after kidney transplant based on 10 donor factors. The lower KDPI values are associated with higher expected post-transplant survival. Hence, kidneys with KDPI <20% are allocated to the 20% of the potential recipients with the highest expected post-transplant survival. The kidneys with KDPI >85% (previously called expanded criteria donor or ECD kidneys) are usually used for older patients who are expected to fare less well on dialysis. Kidneys from donors after cardiac death (DCD) are also been used to overcome the increasing demand on the waiting list **(Table 307-1)**.

The overall results of transplantation are presented in **Table 307-2** as the survival of grafts and of patients. At the 1-year mark, graft survival is higher for living-donor recipients, most likely because those grafts are not subject to as much ischemic injury. The more effective drugs now in use for immunosuppression have almost equalized the risk of graft rejection in all patients for the first year. At 5 and 10 years, however, there has been a steeper decline in survival of those with deceased-donor kidneys.

TABLE 307-1 Definition of a Non-Heart-Beating Donor (Donation After Cardiac Death[a] [DCD])

I: Brought in dead
II: Unsuccessful resuscitation
III: Awaiting cardiac arrest
IV: Cardiac arrest after brainstem death
V: Cardiac arrest in a hospital patient

[a]Kidneys can be used for transplantation from categories II–V but are commonly only used from categories III and IV. The survival of these kidneys has not been shown to be inferior to that of deceased-donor kidneys.

Note: Kidneys can both have a KDPI >85 % and be DCD. High KDPI kidneys have been shown to have a poorer survival, and there is a separate shorter waiting list for those kidneys. They are generally utilized for patients for whom the benefits of being transplanted earlier outweigh the associated risks of using a lower quality kidney.

RECIPIENT SELECTION

There are few absolute contraindications to renal transplantation. The transplant procedure is relatively noninvasive, as the organ is generally placed in the inguinal fossa without entering the peritoneal cavity. Recipients without perioperative complications often can be discharged from the hospital in excellent condition within 5 days of the operation.

Virtually all patients with ESRD who receive a transplant have a higher life expectancy than do risk-matched patients who remain on dialysis. Even though diabetic patients and older candidates have a higher mortality rate than other transplant recipients, their survival is improved with transplantation compared with those remaining on dialysis. This global benefit of transplantation as a treatment modality poses substantial ethical issues for policy makers, as the number of deceased donor kidneys available is far from sufficient to meet the current needs of the candidates. The current standard of care is that the candidate should have a life expectancy of >5 years to be put on a deceased organ wait list. Even for living donation, the candidate should have >5 years of life expectancy. This standard has been established because the benefits of kidney transplantation over dialysis are realized only after a perioperative period in which the mortality rate is higher in transplanted patients than in dialysis patients with comparable risk profiles.

All candidates must have a thorough risk-versus-benefit evaluation before being approved for transplantation. In particular, an aggressive approach to diagnosis of correctable coronary artery disease, presence of latent or indolent infection (HIV, hepatitis B or C, tuberculosis), and neoplasm should be a routine part of the candidate workup. Most transplant centers consider overt AIDS and active hepatitis absolute contraindications to transplantation because of the high risk of opportunistic infection. Some centers are now transplanting individuals with hepatitis and even HIV infection under strict protocols to determine whether the risks and benefits favor transplantation over dialysis. Over the last few years, new direct acting hepatitis C antiviral medications have been introduced and have been shown to be very effective therapies both pre- and posttransplant. Those medications are reshaping our approach to patients with hepatitis C.

Among the few absolute "immunologic" contraindications to transplantation is the presence of antibodies against the donor kidney at the time of the anticipated transplant that can cause hyperacute rejection. Those harmful antibodies include natural antibodies against the ABO blood group antigens and antibodies against human leukocyte antigen (HLA) class I (A, B, C) or class II (DR, DQ, DP) antigens. These antibodies are routinely excluded by proper screening of the candidate's ABO compatibility and direct cytotoxic cross-matching of candidate serum with lymphocytes of the donor.

TISSUE TYPING AND CLINICAL IMMUNOGENETICS

Matching for antigens of the HLA major histocompatibility gene complex **(Chap. 343)** is an important criterion for selection of donors for renal allografts. Each mammalian species has a single chromosomal

TABLE 307-2 Mean Rates of Graft and Patient Survival for Kidneys Transplanted in the United States from 1998 to 2008[a]

	1-YEAR FOLLOW-UP		5-YEAR FOLLOW-UP		10-YEAR FOLLOW-UP	
	GRAFTS, %	PATIENTS, %	GRAFTS, %	PATIENTS, %	GRAFTS, %	PATIENTS, %
Deceased donor	92	96	72	84	46	64
Living donor	96	99	81	91	59	77

[a]All patients transplanted are included, and the follow-up unadjusted survival data from the 1-, 5- , and 10-year periods are presented to show the attrition rates over time within the two types of organ donors.

Source: Data from Summary Tables, 2009 Annual Reports, Scientific Registry of Transplant Recipients.

region that encodes the strong, or major, transplantation antigens, and this region on the human sixth chromosome is called *HLA*. HLA antigens have been classically defined by serologic techniques, but methods to define specific nucleotide sequences in genomic DNA are increasingly being used. Other "minor" antigens may play crucial roles, in addition to the ABH(O) blood groups and endothelial antigens that are not shared with lymphocytes. The Rh system is not expressed on graft tissue. Evidence for designation of HLA as the genetic region that encodes major transplantation antigens comes from the success rate in living related donor renal and bone marrow transplantation, with superior results in HLA-identical sibling pairs. Nevertheless, 5% of HLA-identical renal allografts are rejected, often within the first weeks after transplantation. These failures represent states of prior sensitization to non-HLA antigens. Non-HLA minor antigens are relatively weak when initially encountered and are, therefore, suppressible by conventional immunosuppressive therapy. Once priming has occurred, however, secondary responses are much more refractory to treatment.

DONOR SELECTION

Donors can be deceased or volunteer living donors. When first-degree relatives are donors, graft survival rates at 1 year are 5–7% greater than those for deceased-donor grafts. The 5-year survival rates still favor a partially matched (3/6 HLA mismatched) family donor over a randomly selected cadaver donor. In addition, living donors provide the advantage of immediate availability. For both living and deceased donors, the 5-year outcomes are somewhat poorer if there is a complete (6/6) HLA mismatch.

The survival rate of living unrelated renal allografts is as high as that of perfectly HLA-matched cadaver renal transplants and comparable to that of kidneys from living relatives. This outcome is probably a consequence of both short cold ischemia time and the extra care taken to document that the condition and renal function of the donor are optimal before proceeding with a living unrelated donation. It is illegal in the United States to purchase organs for transplantation.

Living volunteer donors should be cleared of any medical conditions that may cause morbidity and mortality after kidney transplantation. Concern has been expressed about the potential risk to a volunteer kidney donor of premature renal failure after several years of increased blood flow and hyperfiltration per nephron in the remaining kidney. There are a few reports of the development of hypertension, proteinuria, and even lesions of focal segmental sclerosis in donors over long-term follow-up. It is also desirable to consider the risk of development of type 1 diabetes mellitus in a family member who is a potential donor to a diabetic renal failure patient. Anti-insulin and anti-islet cell antibodies should be measured, and glucose tolerance tests should be performed in such donors to exclude a prediabetic state. Selective renal arteriography should be performed on donors to rule out the presence of multiple or abnormal renal arteries, because the surgical procedure is difficult, and the ischemic time of the transplanted kidney is long when there are vascular abnormalities. Transplant surgeons commonly use a laparoscopic approach to isolate and remove the living donor's kidney. This operation has the advantage of less evident surgical scars, and, as there is less tissue trauma, laparoscopic donors have a substantially shorter hospital stay and less discomfort than those who undergo an open nephrectomy.

Deceased donors should be free of malignant neoplastic disease, hepatitis, and HIV owing to possible transmission to the recipient, although under certain circumstances hepatitis C- and HIV-positive organs may be used in previously infected recipients. Increased risk of graft failure exists when the donor is elderly or has acute renal failure or when the kidney has a prolonged period of ischemia.

In the United States, there is a coordinated national system of regulations, allocation support, and outcomes analysis for kidney transplantation called the Organ Procurement Transplant Network. It is now possible to remove deceased-donor kidneys and maintain them for up to 48 h on cold pulsatile perfusion or with simple flushing and cooling. Although generally an ischemic time of <24 h is preferred, this approach permits adequate time for typing, cross-matching, transportation, and selection problems to be solved.

PRESENSITIZATION

A positive cytotoxic cross-match of recipient serum with donor T lymphocytes indicates the presence of pre-formed donor specific anti-HLA class I antibodies and is usually predictive of an acute vasculitic event termed *hyperacute rejection*. This finding, along with ABO incompatibility, represents the only absolute immunologic contraindication for kidney transplantation. Recently, an increasing number of tissue typing laboratories have shifted to a flow cytometric-based crossmatch assay, which detects the presence of anti HLA antibodies that are not necessarily detected on a cytotoxic crossmatch assay and may not be an absolute contraindication to transplantation. The known sources of such sensitization are blood transfusion, a prior transplant, pregnancy, and vaccination/infection. Patients sustained by dialysis often show fluctuating antibody titers and specificity patterns. At the time of assignment of a cadaveric kidney, cross-matches are performed with at least a current serum. Previously analyzed antibody specificities and additional cross-matches are performed accordingly. Flow cytometry detects binding of anti-HLA antibodies of candidate serum by recipient's lymphocytes. This highly sensitive test can be useful for avoidance of accelerated, and often untreatable, early graft rejection in patients receiving second or third transplants.

For the purposes of crossmatching, donor T lymphocytes, which express class I but not class II antigens, are used as targets for detection of anti–class I (HLA-A and -B) antibodies that are expressed on all nucleated cells. Preformed anti–class II (HLA-DR and -DQ) antibodies against the donor also carry a higher risk of graft loss, particularly in recipients who have suffered early loss of a prior kidney transplant. B lymphocytes, which express both class I and class II antigens, are used as targets in these assays. Furthermore, donor-specific HLA antibodies that fix complements have been shown to strongly correlate with antibody mediated rejection and worse long-term outcome.

Some non-HLA antigens restricted in expression to endothelium and monocytes have been described, but their clinical relevance is not well established. A series of minor histocompatibility antigens do not elicit antibodies, and sensitization to these antigens is detectable only by cytotoxic T cells, an assay too cumbersome for routine use.

Desensitization before transplantation by reducing the level of anti-donor antibodies utilizing plasmapheresis and administration of pooled immunoglobulin, or both, has been useful in reducing the risk of hyperacute rejection following transplantation.

IMMUNOLOGY OF REJECTION

Both cellular and humoral (antibody-mediated) effector mechanisms can play roles in kidney transplant rejection.

Cellular rejection is mediated by lymphocytes that respond to HLA antigens expressed within the organ. The CD4+ lymphocyte responds to class II (HLA-DR) incompatibility by proliferating and releasing proinflammatory cytokines that augment the proliferative response of the immune system. CD8+ cytotoxic lymphocyte precursors respond primarily to class I (HLA-A, -B) antigens and mature into cytotoxic effector cells that cause organ damage through direct contact and

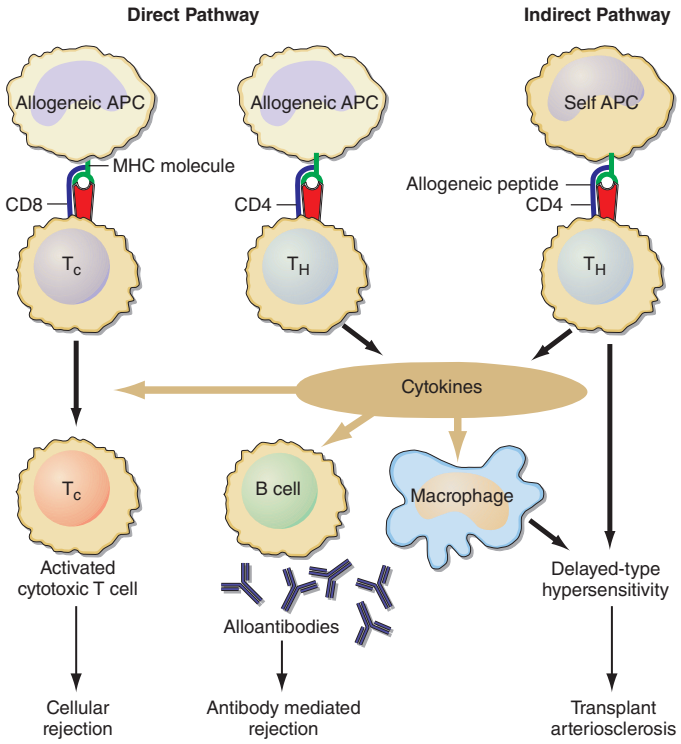


FIGURE 307-1 Recognition pathways for major histocompatibility complex (MHC) antigens. Graft rejection is initiated by CD4 helper T lymphocytes (TH) having antigen receptors that bind to specific complexes of peptides and MHC class II molecules on antigen-presenting cells (APC). In transplantation, in contrast to other immunologic responses, there are two sets of T cell clones involved in rejection. In the direct pathway the class II MHC of donor allogeneic APCs is recognized by CD4 TH cells that bind to the intact MHC molecule, and class I MHC allogeneic cells are recognized by CD8 T cells. The latter generally proliferate into cytotoxic cells (TC). In the indirect pathway, the incompatible MHC molecules are processed into peptides that are presented by the self-APCs of the recipient. The indirect, but not the direct, pathway is the normal physiologic process in T cell recognition of foreign antigens. Once TH cells are activated, they proliferate and, by secretion of cytokines and direct contact, exert strong helper effects on macrophages, TC, and B cells. *(From MH Sayegh, LH Turka: N Engl J Med, 338:1813, 1998. Copyright 1998, Massachusetts Medical Society. All rights reserved.)*

lysis of donor target cells. Full T cell activation requires not only T cell receptor binding to the allo-antigens presented by self or donor HLA molecules (indirect and direct presentation respectively), but also engaging costimulatory molecules such as CD28 on T cells and CD80 and CD86 ligands on antigen presenting cells (Fig. 307-1). Signaling through both of these pathways induces activation of the kinase activity of calcineurin which, in turn, activates transcription factors leading to upregulation of multiple genes, including interleukin-2 (IL-2) and interferon gamma. IL-2 signals through the target of rapamycin (TOR) to induce cell proliferation in an autocrine fashion. There is evidence that non-HLA antigens can also play a role in renal transplant rejection episodes. Recipients who receive a kidney from an HLA-identical sibling can have rejection episodes and require maintenance immunosuppression, whereas identical twin transplants require no immunosuppression. There are documented non-HLA antigens, such as an endothelial-specific antigen system with limited polymorphism and a tubular antigen, which can act as targets of humoral or cellular rejection responses, respectively.

IMMUNOSUPPRESSIVE TREATMENT

Immunosuppressive therapy, as currently available, generally suppresses all immune responses, including those to bacteria, fungi, and even malignant tumors. In general, all clinically useful drugs are more selective to primary than to memory immune responses. Agents to suppress the immune response are classically divided into induction and maintenance agents, and will be discussed in the following paragraphs. Those currently in clinical use are listed in Table 307-3.

INDUCTION THERAPY

Induction therapy is currently given to most kidney transplant recipients in the United States at the time of transplant to reduce the risk of early acute rejection and to minimize or eliminate the use of either steroids or calcineurin inhibitors and their associated toxicities. Induction therapy consists of antibodies that could be monoclonal or polyclonal, depletional or nondepletional.

Depleting Agents Anti-thymocyte globulin (ATG): peripheral human lymphocytes, thymocytes, or lymphocytes from spleens or thoracic duct fistulas are injected into horses, rabbits, or goats to produce anti-lymphocyte serum, from which the globulin fraction is then separated. Those polyclonal antibodies induce lymphocyte depletion, and the immune system may take several months to recover.

Monoclonal antibodies against defined lymphocyte subsets offer a more precise and standardized form of therapy. Alemtuzumab is directed to the CD52 protein, widely distributed on immune cells such as B and T cells, natural killer cells, macrophages, and some granulocytes.

Nondepleting Agents Another approach to more selective therapy is to target the 55-kDa alpha chain of the IL-2 receptor, which is expressed only on T cells that have been recently activated. This approach is used as prophylaxis for acute rejection in the immediate

TABLE 307-3 Maintenance Immunosuppressive Drugs

AGENT	PHARMACOLOGY	MECHANISMS	SIDE EFFECTS
Glucocorticoids	Increased bioavailability with hypoalbuminemia and liver disease; prednisone/prednisolone generally used	Binds cytosolic receptors and heat shock proteins. Blocks transcription of IL-1, -2, -3, -6, TNF-α, and IFN-γ	Hypertension, glucose intolerance, dyslipidemia, osteoporosis
Cyclosporine (CsA)	Lipid-soluble polypeptide, variable absorption, microemulsion more predictable	Trimolecular complex with cyclophilin and calcineurin → block in cytokine (e.g., IL-2) production; however, stimulates TGF-β production	Nephrotoxicity, hypertension, dyslipidemia, glucose intolerance, hirsutism/hyperplasia of gums
Tacrolimus	Macrolide, well absorbed	Trimolecular complex with FKBP-12 and calcineurin → block in cytokine (e.g., IL-2) production; may stimulate TGF-β production	Similar to CsA, but hirsutism/hyperplasia of gums unusual, and diabetes more likely
Azathioprine	Mercaptopurine analogue	Hepatic metabolites inhibit purine synthesis	Marrow suppression (WBC > RBC > platelets)
Mycophenolate mofetil/sodium	Metabolized to mycophenolic acid	Inhibits purine synthesis via inosine monophosphate dehydrogenase	Diarrhea/cramps; dose-related liver and marrow suppression is uncommon
Sirolimus/Everolimus	Macrolide, poor oral bioavailability	Complexes with FKBP-12 and then blocks p70 S6 kinase in the IL-2 receptor pathway for proliferation	Hyperlipidemia, thrombocytopenia
Belatacept	Fusion protein, intravenous injections	Binds CD80 and CD86, prevents CD28 binding and T cell activation	Posttransplant Lymphoproliferative Disease (PTLD)

Abbreviations: FKBP-12, FK506 binding protein 12; IFN, interferon; IL, interleukin; RBC, red blood cells; TGF, transforming growth factor; TNF, tumor necrosis factor; WBC, white blood cells.

posttransplant period, and is effective at decreasing the early acute rejection rate with few adverse side effects.

The next step in the evolution of this therapeutic strategy, which has already been achieved in the short term in small numbers of immunologically well-matched patients, is the elimination of all maintenance immunosuppression therapy.

MAINTENANCE THERAPY

All kidney transplant recipients should receive maintenance immunosuppressive therapies except identical twins. The most frequently used combination is triple therapy with prednisone, a calcineurin inhibitor, and an antimetabolite; mTOR inhibitors can replace one of the last two agents. More recently, the FDA approved a new costimulatory blocking antibody, belatacept, as a new strategy to prevent long-term CNI toxicity.

Antimetabolites *Azathioprine*, an analogue of mercaptopurine, was for two decades the keystone to immunosuppressive therapy in humans, but has given way to more effective agents. This agent can inhibit synthesis of DNA, RNA, or both. Azathioprine is administered in doses of 1.5–2 mg/kg per day. Reduction in the dose is required because of leukopenia and occasionally thrombocytopenia. Excessive amounts of azathioprine may also cause jaundice, anemia, and alopecia. If it is essential to administer allopurinol concurrently, the azathioprine dose must be reduced. As inhibition of xanthine oxidase delays degradation, this combination is best avoided.

Mycophenolate mofetil or mycophenolate sodium, both of which are metabolized to mycophenolic acid, is now used in place of azathioprine in most centers. It has a similar mode of action and a mild degree of gastrointestinal toxicity but produces less bone marrow suppression. Its advantage is its increased potency in preventing or reversing rejection.

Steroids *Glucocorticoids* are important adjuncts to immunosuppressive therapy. Among all the agents employed, prednisone has effects that are easiest to assess, and in large doses it is usually effective for the reversal of rejection. In general, 200–300 mg prednisone is given immediately before or at the time of transplantation, and the dose is reduced to 30 mg within a week. The side effects of the glucocorticoids, particularly impairment of wound healing and predisposition to infection, make it desirable to taper the dose as rapidly as possible in the immediate postoperative period. Many centers now have protocols for early discontinuance or avoidance of steroids because of long-term adverse effects on bone, skin, and glucose metabolism. For treatment of acute rejection, methylprednisolone, 0.5–1 g IV, is administered immediately upon diagnosis of beginning rejection and continued once daily for 3 days. Such "pulse" doses are not effective in chronic rejection. Most patients whose renal function is stable after 6 months or a year do not require large doses of prednisone; maintenance doses of 5–10 mg/d are the rule. A major effect of steroids is preventing the release of interleukin (IL) 6 and IL-1 by monocytes-macrophages.

Calcineurin Inhibitors *Cyclosporine* is a fungal peptide with potent immunosuppressive activity. It acts on the calcineurin pathway to block transcription of mRNA for IL-2 and other proinflammatory cytokines, thereby inhibiting T cell proliferation. Although it works alone, cyclosporine is more effective in conjunction with glucocorticoids and mycophenolate. Clinical results with tens of thousands of renal transplants have been impressive. Among its toxic effects (nephrotoxicity, hepatotoxicity, hirsutism, tremor, gingival hyperplasia, and diabetes), only nephrotoxicity presents a serious management problem and is further discussed below.

Tacrolimus (previously called FK506) is a fungal macrolide that has the same mode of action as cyclosporine as well as a similar side-effect profile; it does not, however, produce hirsutism or gingival hyperplasia. De novo diabetes mellitus is more common with tacrolimus. The drug was first used in liver transplantation and may substitute for cyclosporine entirely or as an alternative in renal patients whose rejections are poorly controlled by cyclosporine. An extended release formulation of tacrolimus is now available and is given once daily.

TOR Inhibitors *Sirolimus* (previously called rapamycin) is another fungal macrolide but has a different mode of action; i.e., it inhibits T cell growth factor signaling pathways, preventing the response to IL-2 and other cytokines. Sirolimus can be used in conjunction with cyclosporine or tacrolimus, or with mycophenolic acid, to avoid the use of calcineurin inhibitors.

Everolimus is another mTOR inhibitor with similar mechanism of action as *Sirolimus* but with better bioavailability.

Belatacept *Belatacept* is a fusion protein that binds costimulatory ligands (CD80 and CD86) present on antigen presenting cells, interrupting their binding to CD28 on T cells. This inhibition leads to T cell anergy and apoptosis. Belatacept is FDA-approved for kidney transplant recipients and is given monthly as an intravenous infusion. The 7 years follow-up of the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) showed higher patient and graft survival for the belatacept treated group compared to cyclosporine.

CLINICAL COURSE AND MANAGEMENT OF THE RECIPIENT

Adequate hemodialysis should be performed within 48 h of surgery as necessary, and care should be taken that the serum potassium level is not markedly elevated so that intraoperative cardiac arrhythmias can be averted. The diuresis that commonly occurs postoperatively must be carefully monitored. In some instances, it may be massive, reflecting the inability of ischemic tubules to regulate sodium and water excretion; with large diureses, large amounts of potassium may be lost. Most chronically uremic patients have some excess of extracellular fluid, and it is useful to maintain an expanded fluid volume in the immediate postoperative period. Acute tubular necrosis (ATN) due to ischemia may cause immediate oliguria or may follow an initial short period of graft function. Recovery usually occurs within 3 weeks, although periods as long as 6 weeks have been reported. Superimposition of rejection on ATN is common, and the differential diagnosis may be difficult without a graft biopsy. Cyclosporine therapy prolongs ATN, and some patients do not diurese until the dose is reduced drastically. Many centers avoid starting calcinenrins for the first several days, using ALG or a monoclonal antibody along with mycophenolic acid and prednisone until renal function is established. **Figure 307-2** illustrates an algorithm followed by many transplant centers for early posttransplant management of recipients at high or low risk of early renal dysfunction.

THE REJECTION EPISODE

Early diagnosis of rejection allows prompt institution of therapy to preserve renal function and prevent irreversible damage. Clinical evidence of rejection is rarely characterized by fever, swelling, and tenderness over the allograft. Rejection may present only with a rise in serum creatinine, with or without a reduction in urine volume. The focus should be on ruling out other causes of functional deterioration.

Doppler ultrasonography may be useful in ascertaining changes in the renal vasculature and in renal blood flow. Thrombosis of the renal vein occurs rarely; it may be reversible if it is caused by technical factors and intervention is prompt. Diagnostic ultrasound is the procedure of choice to rule out urinary obstruction or to confirm the presence of perirenal collections of urine, blood, or lymph. A rise in the serum creatinine level is a late marker of rejection, but it may be the only sign. Novel biomarkers are needed for early noninvasive detection of allograft rejection.

Calcineurin inhibitors (cyclosporine and tacrolimus) have an afferent arteriolar constrictor effect on the kidney, and may produce permanent vascular and interstitial injury after sustained high-dose therapy. This action will lead to a deterioration in renal function difficult to distinguish from rejection without a renal biopsy. Interstitial fibrosis, isometric tubular vacuolization, and thickening of arteriolar walls are suggestive of this side effect, but not diagnostic. Hence, if no rejection is detected on the biopsy, serum creatinine may respond to a reduction in dose. However, if cellular rejection activity is present in the biopsy, appropriate therapy is indicated. The first rejection episode is usually treated with IV administration of methylprednisolone, 500–1000 mg daily for 3 days. Failure to respond is an indication for antibody therapy, usually with antithymocyte globulin.

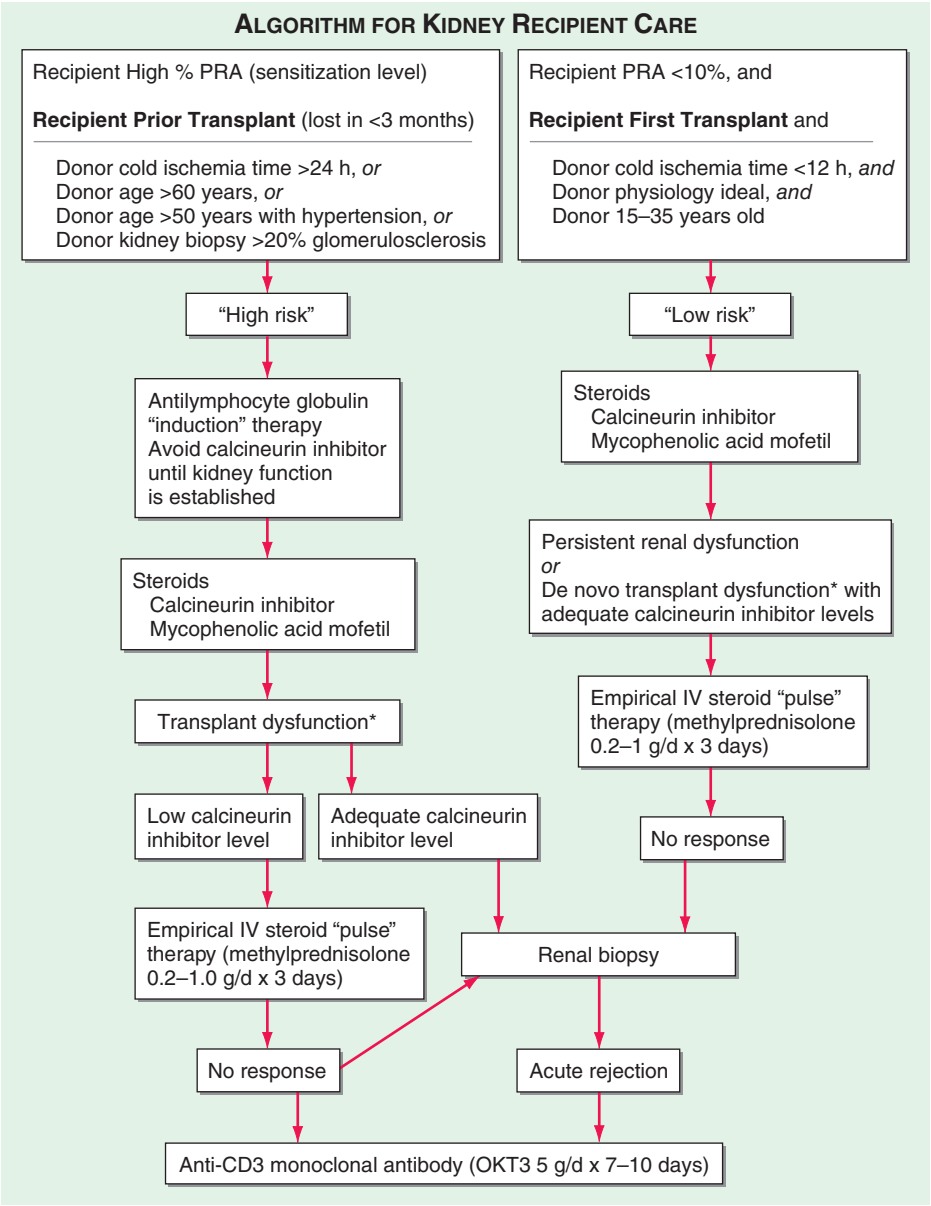


FIGURE 307-2 A typical algorithm for early posttransplant care of a kidney recipient. If any of the recipient or donor "high-risk" factors exist, more aggressive management is called for. Low-risk patients can be treated with a standard immunosuppressive regimen. Patients at higher risk of rejection or early ischemic and nephrotoxic transplant dysfunction are often induced with an antilymphocyte globulin to provide more potent early immunosuppression or to spare calcineurin nephrotoxicity. *When there is early transplant dysfunction, prerenal, obstructive, and vascular causes must be ruled out by ultrasonographic examination. The panel reactive antibody (PRA) is a quantitation of how much antibody is present in a candidate against a panel of cells representing the distribution of antigens in the donor pool. APC, antigen-presenting cell; MHC, major histocompatibility complex.

Evidence of antibody-mediated injury is present when endothelial injury and deposition of complement component c4d is detected by fluorescence labeling. This is usually accompanied by detection of the antibody in the recipient blood. The prognosis is poor, and aggressive use of plasmapheresis, immunoglobulin infusions, anti-CD20 monoclonal antibody (rituximab) to target B lymphocytes, bortezomib to target antibody producing plasma cells, and eculizumab to inhibit complement is indicated.

MANAGEMENT PROBLEMS

The typical times after transplantation when the most common opportunistic infections occur are shown in Table 307-4. Prophylaxis for cytomegalovirus (CMV) and Pneumocystis *Jirovecci* pneumonia is given for 6–12 months after transplantation.

The signs and symptoms of infection may be masked or distorted. Fever without obvious cause is common, and only after days or weeks may it become apparent that it has a viral or fungal origin. Bacterial infections are most common during the first month after transplantation. The importance of blood cultures in such patients cannot be overemphasized because systemic infection without obvious foci is common. Particularly ominous are rapidly occurring pulmonary lesions, which may result in death within 5 days of onset. When these lesions become apparent, immunosuppressive agents should be discontinued, except for maintenance doses of prednisone.

Aggressive diagnostic procedures, including transbronchial and open-lung biopsy, are frequently indicated. In the case of *Pneumocystis carinii* (Chap. 215) infection, trimethoprim-sulfamethoxazole (TMP-SMX) is the treatment of choice; amphotericin B has been used effectively in systemic fungal infections. Prophylaxis against *P. jirovecci* with daily or alternate-day low-dose TMP-SMX is very effective. Involvement of the oropharynx with *Candida* (Chap. 211) may be treated with local nystatin. Tissue-invasive fungal infections require treatment with systemic agents such as fluconazole. Small doses (a total of 300 mg) of amphotericin given over a period of 2 weeks may be effective in fungal infections refractory to fluconazole. Macrolide antibiotics, especially ketoconazole and erythromycin, and some calcium channel blockers (diltiazem, verapamil) compete with calcineurin inhibitors for P450 catabolism and cause elevated levels of these immunosuppressive drugs. Analeptics, such as phenytoin and carbamazepine, will increase catabolism to result in low levels. *Aspergillus* (Chap. 212), *Nocardia* (Chap. 169), and especially CMV (Chap. 190) infections also occur.

CMV is a common and dangerous DNA virus in transplant recipients. It does not generally appear until the end of the first posttransplant month. Active CMV infection is sometimes associated, or occasionally confused, with rejection episodes. Patients at highest risk for severe CMV disease are those without anti-CMV antibodies who receive a graft from a CMV antibody–positive donor (15% mortality). Valganciclovir is a cost-effective and bioavailable oral form of ganciclovir that has been proved effective in both prophylaxis and treatment of CMV disease.

TABLE 307-4 The Most Common Opportunistic Infections in Renal Transplant Recipients

Peritransplant (<1 month)	Late (>6 months)
Wound infections	*Aspergillus*
Herpesvirus	*Nocardia*
Oral candidiasis	BK virus (polyoma)
Urinary tract infection	Herpes zoster
Early (1–6 months)	Hepatitis B
Pneumocystis carinii	Hepatitis C
Cytomegalovirus	
Legionella	
Listeria	
Hepatitis B	
Hepatitis C	

Early diagnosis in a febrile patient with clinical suspicion of CMV disease can be made by determining CMV viral load in the blood. A rise in IgM antibodies to CMV is also diagnostic. Culture of CMV from blood may be less sensitive. Tissue invasion of CMV is common in the gastrointestinal tract and lungs. CMV retinopathy occurs late in the course, if untreated. Treatment of active CMV disease with valganciclovir is always indicated. In many patients immune to CMV, viral activation can occur with major immunosuppressive regimens.

The polyoma group (BK, JC, SV40) is another class of DNA viruses that can become dormant in kidneys and can be activated by immunosuppression. When reactivation occurs with BK, if left untreated, there is a 50% chance of progressive fibrosis and loss of the graft within 1 year by the activated virus. Risk of infection is associated with the overall degree of immunosuppression rather than the individual immunosuppressive drugs used. Renal biopsy is necessary for the diagnosis. There have been variable results with leflunomide, cidofovir, and quinolone anitibiotics (which are effective against polyoma helicase), but it is most important to reduce the immunosuppressive load.

The complications of glucocorticoid therapy are well known and include gastrointestinal bleeding, impairment of wound healing, osteoporosis, diabetes mellitus, cataract formation, and hemorrhagic pancreatitis. The treatment of unexplained jaundice in transplant patients should include cessation or reduction of immunosuppressive drugs if hepatitis or drug toxicity is suspected. Therapy in such circumstances often does not result in rejection of a graft, at least for several weeks. Acyclovir is effective in therapy for herpes simplex virus infections.

CHRONIC LESIONS OF THE TRANSPLANTED KIDNEY

Although 1-year transplant survival is excellent, most recipients experience progressive decline in kidney function over time thereafter. Chronic renal transplant dysfunction can be caused by recurrent disease, hypertension, cyclosporine or tacrolimus nephrotoxicity, chronic immunologic rejection, secondary focal glomerulosclerosis, or a combination of these pathophysiologies. Chronic vascular changes with intimal proliferation and medial hypertrophy are commonly found. Control of systemic and intrarenal hypertension with ACE inhibitors is thought to have a beneficial influence on the rate of progression of chronic renal transplant dysfunction. Renal biopsy can distinguish subacute cellular rejection from recurrent disease or secondary focal sclerosis.

MALIGNANCY

The incidence of tumors in patients on immunosuppressive therapy is 5–6%, or ~100 times greater than that in the general population in the same age range. The most common lesions are cancer of the skin and lips and carcinoma in situ of the cervix, as well as lymphomas such as non-Hodgkin's lymphoma. The risks are increased in proportion to the total immunosuppressive load administered and the time elapsed since transplantation. Surveillance for skin and cervical cancers is necessary.

OTHER COMPLICATIONS

Both chronic dialysis and renal transplant patients have a higher incidence of death from myocardial infarction and stroke than does the population at large, and this is particularly true in diabetic patients. Contributing factors are the use of glucocorticoids and sirolimus, as well as hypertension. Recipients of renal transplants have a high prevalence of coronary artery and peripheral vascular diseases. The percentage of deaths from these causes has been slowly rising as the numbers of transplanted diabetic patients and the average age of all recipients increase. More than 50% of renal recipient mortality is attributable to cardiovascular disease. In addition to strict control of blood pressure and blood lipid levels, close monitoring of patients for indications of further medical or surgical intervention is an important part of management.

Hypertension may be caused by (1) native kidney disease, (2) rejection activity in the transplant, (3) renal artery stenosis if an end-to-end anastomosis was constructed with an iliac artery branch, and (4) renal calcineurin inhibitor toxicity, which may improve with reduction in dose. Whereas ACE inhibitors may be useful, calcium channel blockers are more frequently used initially. Amelioration of hypertension to the range of 120–130/70–80 mmHg should be the goal in all patients.

Hypercalcemia after transplantation may indicate failure of hyperplastic parathyroid glands to regress. Aseptic necrosis of the head of the femur is probably due to preexisting hyperparathyroidism, with aggravation by glucocorticoid treatment. With improved management of calcium and phosphorus metabolism during chronic dialysis, the incidence of parathyroid-related complications has fallen dramatically. Persistent hyperparathyroid activity may require subtotal parathyroidectomy.

Although most transplant patients have robust production of erythropoietin and normalization of hemoglobin, *anemia* is commonly seen in the posttransplant period. Often the anemia is attributable to bone marrow–suppressant immunosuppressive medications such as azathioprine, mycophenolic acid, and sirolimus. Gastrointestinal bleeding is a common side effect of high-dose and long-term steroid administration. Many transplant patients have creatinine clearances of 30–50 mL/min and can be considered in the same way as other patients with chronic renal insufficiency for anemia management, including supplemental erythropoietin.

Chronic hepatitis, particularly when due to hepatitis B virus, can be a progressive, fatal disease over a decade or so. Patients who are persistently hepatitis B surface antigen–positive are at higher risk, according to some studies, but the presence of hepatitis C virus is also a concern when one embarks on a course of immunosuppression in a transplant recipient. However, the introduction of the new highly effective direct acting hepatitis C antiviral medications promises to reduce this risk significantly.

FURTHER READING

Birnbaum LM et al: Management of chronic allograft nephropathy: A systematic review. Clin J Am Soc Nephrol 4:860, 2009.

Briganti EM et al: Risk of renal allograft loss from recurrent glomerulonephritis. N Engl J Med 347:103, 2002.

Freeman RB Jr: Survival benefit: Quality versus quantity and tradeoffs in developing new renal allocation systems. Am J Transplant 7:1043, 2007.

Hirsch HH et al: Polyomavirus-associated nephropathy in renal transplantation: Interdisciplinary analyses and recommendations. Transplantation 79:1277, 2005.

Hodson EM et al: Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database Syst Rev CD003774, 2008.

Ibrahim HN et al: Long-term consequences of kidney donation. N Engl J Med 360:459, 2009.

KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 9 Suppl 3:S1, 2009.

Lentine KL et al: Incidence and predictors of myocardial infarction after kidney transplantation. J Am Soc Nephrol 16:496, 2005.

Loupy A et al: Complement-binding anti-HLA antibodies and kidney-allograft survival. N Engl J Med 369:1215, 2013.

Matas AJ et al: OPTN/SRTR 2013 Annual Data Report: Kidney. Am J Transplant 15 Suppl 2:1, 2015.

Riella LV, Sheridan AM: Testing for high-risk APOL1 alleles in potential living kidney donors. Am J Kidney Dis 66:396, 2015.

Sawinski D et al: Successful treatment of Hepatitis C in renal transplant recipients with direct-acting antiviral agents. Am J Transplant 16:1588, 2017.

Stegall MD: Clinical management of renal transplant patients with donor-specific alloantibody: The state of the art. Clin Transpl 307, 2010.

Stewart DE et al: Changes in deceased donor kidney transplantation one year after KAS implementation. Am J Transplant 16:1834, 2016.

Vincenti F et al: Belatacept and long-term outcomes in kidney transplantation. N Engl J Med 374:333, 2016.

Webster AC et al: Identifying high risk groups and quantifying absolute risk of cancer after kidney transplantation: a cohort study of 15,183 recipients. Am J Transplant 7:2140, 2007.

Wolfe RA et al: Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 341:1725, 1999.

308 Glomerular Diseases

Julia B. Lewis, Eric G. Neilson

Two human kidneys harbor nearly 1.8 million glomerular capillary tufts. Each glomerular tuft resides within Bowman's space. The capsule circumscribing this space is lined by parietal epithelial cells that transition into tubular epithelia forming the proximal nephron or migrate into the tuft to replenish podocytes. The glomerular capillary tuft derives from an afferent arteriole that forms a branching capillary bed embedded in mesangial matrix **(Fig. 308-1)**. This capillary network funnels into an efferent arteriole, which passes filtered blood into cortical peritubular capillaries or medullary vasa recta that supply and exchange with a folded tubular architecture. Hence the glomerular capillary tuft, fed and drained by arterioles, represents an arteriolar portal system. Fenestrated endothelial cells resting on a glomerular basement membrane (GBM) line glomerular capillaries. Delicate foot processes extending from epithelial podocytes shroud the outer surface of these capillaries, and adjacent podocytes interconnect to each other by slit-pore membranes forming a selective filtration barrier.

The glomerular capillaries filter 120–180 L/d of plasma water containing various solutes for reclamation or discharge by downstream tubules. Most large proteins and all cells are excluded from filtration by a physicochemical barrier governed by pore size and negative electrostatic charge. The mechanics of filtration and reclamation are quite complicated for many solutes **(Chap. 303)**. For example, in the case of serum albumin, the glomerulus is an imperfect barrier. Although albumin has a negative charge, which would tend to repel the negatively charged GBM, it only has a physical radius of 3.6 nm, while pores in the GBM and slit-pore membranes have a radius of 4 nm. Consequently, variable amounts of albumin inevitably cross the filtration barrier to be reclaimed by megalin and cubilin receptors along the proximal tubule. Remarkably, humans with normal nephrons excrete on average 8–10 mg of albumin in daily voided urine, ~20–60% of total excreted protein. This amount of albumin, and other proteins, can rise to gram quantities following glomerular injury.

The breadth of diseases affecting the glomerulus is expansive because the microenvironment supporting the glomerular capillaries can be injured in a variety of ways, producing many different lesions. Some order to this vast subject is brought by grouping all of these diseases into a smaller number of clinical syndromes.

PATHOGENESIS OF GLOMERULAR DISEASE

There are many forms of glomerular disease with pathogenesis variably linked to the presence of genetic mutations, infection, toxin exposure, autoimmunity, atherosclerosis, hypertension, emboli, thrombosis, or diabetes mellitus. Even after careful study, however, the cause often remains unknown, and the lesion is called *idiopathic*. Specific or unique features of pathogenesis are mentioned with the description of each of the glomerular diseases later in this chapter.

Some glomerular diseases result from genetic mutations producing familial disease or a founder effect: congenital nephrotic syndrome from mutations in *NPHS1* (nephrin) and *NPHS2* (podocin) affect the slit-pore membrane at birth, and *TRPC6* cation channel mutations produce *focal segmental glomerulosclerosis* (*FSGS*) in adulthood; polymorphisms in the gene encoding apolipoprotein L1, *APOL1*, are a major risk for nearly 70% of African Americans with nondiabetic end-stage renal disease (ESRD), particularly FSGS; mutations in complement factor H associate with *membranoproliferative glomerulonephritis* (*MPGN*), C_3 glomerulopathies, or *atypical hemolytic uremic syndrome* (*aHUS*), type II partial lipodystrophy from mutations in genes encoding lamin A/C, or PPARγ cause a metabolic syndrome associated with MPGN, or C_3 glomerulopathies, which is sometimes accompanied by dense deposits and C3 nephritic factor; Alport's syndrome, from mutations in the genes encoding for the α3, α4, or α5 chains of type IV collagen, produces *split-basement membranes* with *glomerulosclerosis*; and lysosomal storage diseases, such as α-galactosidase A deficiency causing Fabry's disease and *N* acetylneuraminic acid hydrolase deficiency causing nephrosialidosis, produce FSGS.

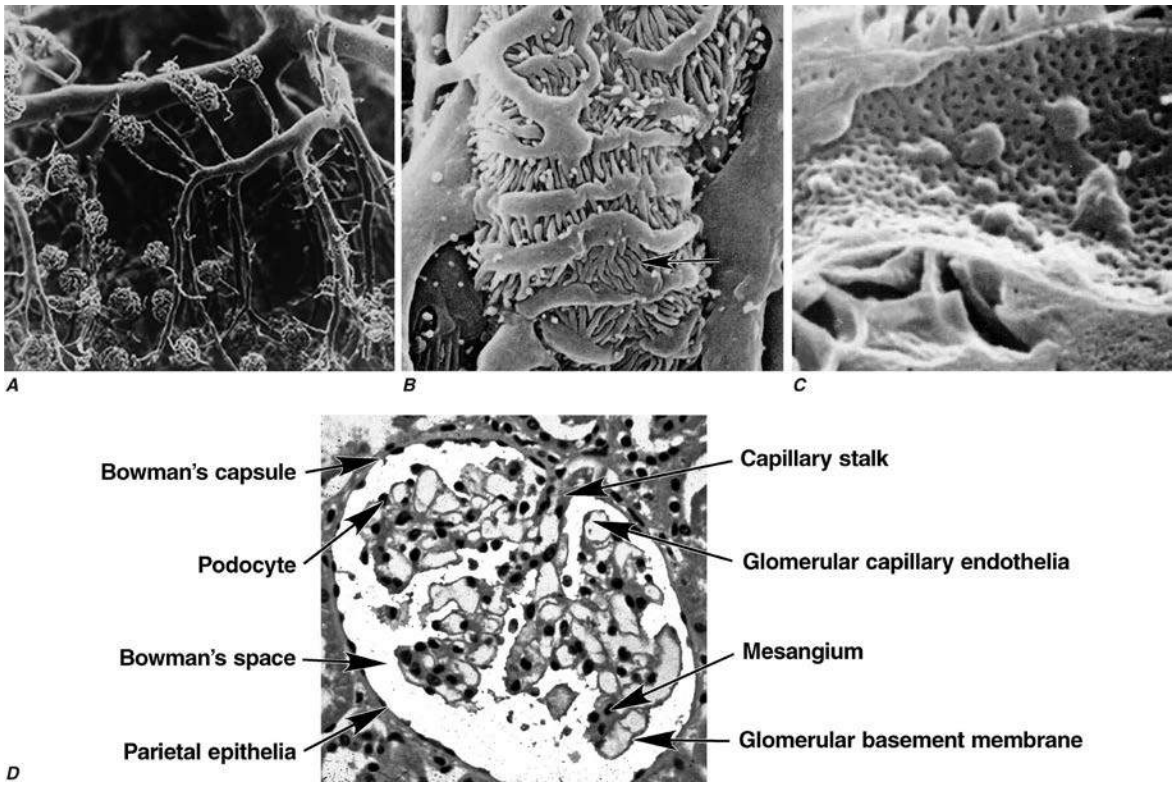


FIGURE 308-1 Glomerular architecture. ***A.*** The glomerular capillaries form from a branching network of renal arteries, arterioles, leading to an afferent arteriole, glomerular capillary bed (tuft), and a draining efferent arteriole. *(From VH Gattone II et al: Hypertension 5:8, 1983.)* ***B.*** Scanning electron micrograph of podocytes that line the outer surface of the glomerular capillaries (*arrow* shows foot process). ***C.*** Scanning electron micrograph of the fenestrated endothelia lining the glomerular capillary. ***D.*** The various normal regions of the glomerulus on light microscopy. *(A–C: Courtesy of Dr. Vincent Gattone, Indiana University; with permission.)*

Systemic hypertension and atherosclerosis can produce pressure stress, ischemia, or lipid oxidants that lead to *chronic glomerulosclerosis*. *Malignant hypertension* can quickly complicate glomerulosclerosis with fibrinoid necrosis of arterioles and glomeruli, thrombotic microangiopathy, and acute renal failure. *Diabetic nephropathy* is an acquired sclerotic injury associated with thickening of the GBM secondary to the long-standing effects of hyperglycemia, advanced glycosylation end products, and reactive oxygen species.

Inflammation of the glomerular capillaries is called *glomerulonephritis*. Most glomerular or mesangial antigens involved in *immune-mediated glomerulonephritis* are unknown **(Fig. 308-2)**. Glomerular epithelial or mesangial cells may shed or express epitopes that mimic other immunogenic proteins made elsewhere in the body. Bacteria, fungi, and viruses can directly infect the kidney producing their own antigens. Autoimmune diseases like idiopathic *membranous glomerulonephritis* (*MGN*) or MPGN are confined to the kidney, whereas systemic inflammatory diseases like *lupus nephritis* or *granulomatosis with polyangiitis* spread to the kidney, causing secondary glomerular injury. *Antiglomerular basement membrane disease* producing Goodpasture's syndrome primarily injures both the lung and kidney because of the narrow distribution of the α3 NC1 domain of type IV collagen that is the target antigen.

Local activation of Toll-like receptors on glomerular cells, deposition of immune complexes, or complement injury to glomerular structures induces mononuclear cell infiltration, which subsequently leads to an adaptive immune response attracted to the kidney by local release of chemokines. Neutrophils, macrophages, and T cells are drawn by chemokines into the glomerular tuft, where they react with antigens and epitopes on or near somatic cells or their structures, producing more cytokines and proteases that damage the mesangium, capillaries, and/or the GBM. While the adaptive immune response is similar to that of other tissues, early T cell activation plays an important role in the mechanism of glomerulonephritis. Antigens presented by class II major histocompatibility complex (MHC) molecules on macrophages

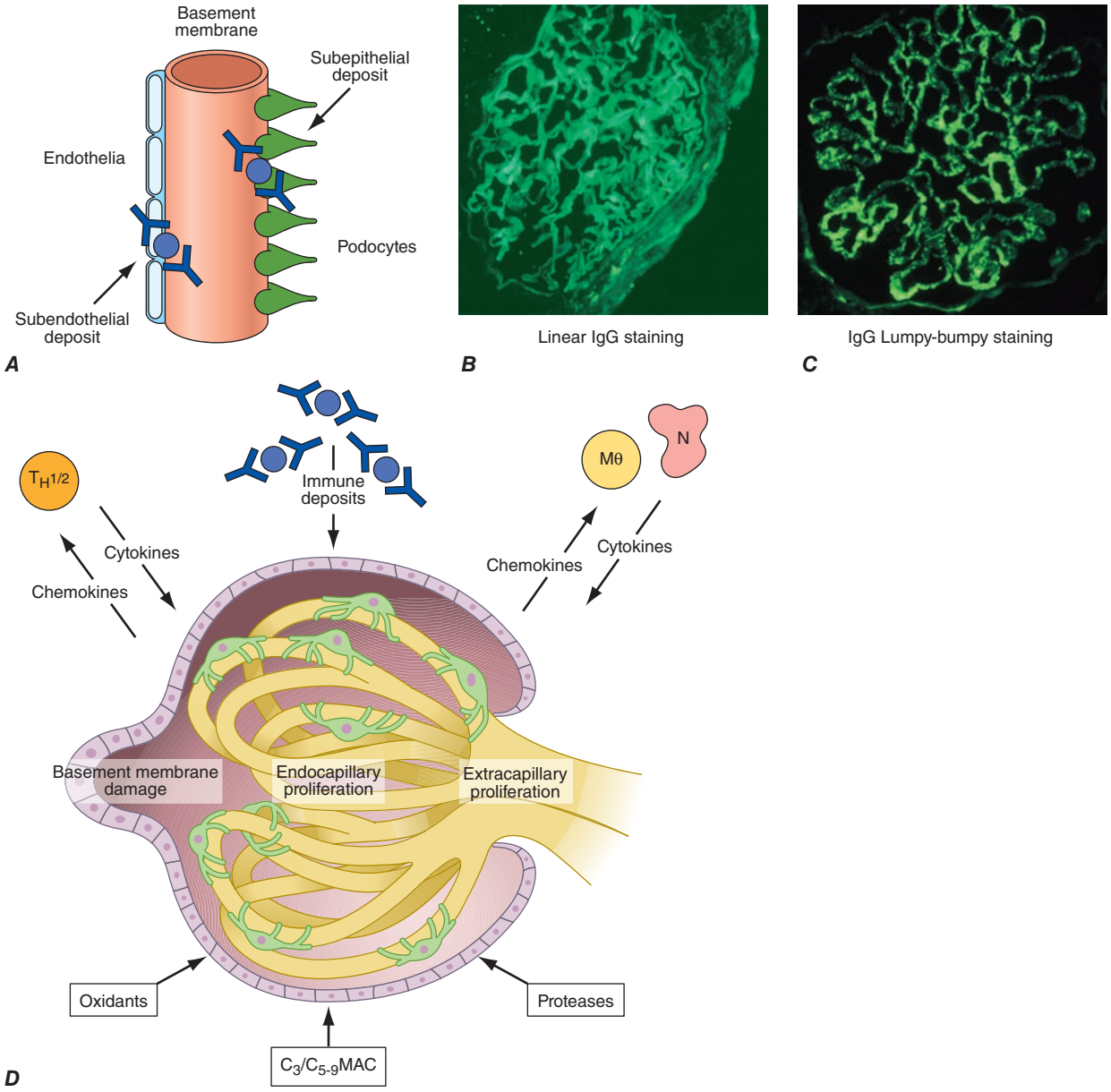


FIGURE 308-2 The glomerulus is injured by a variety of mechanisms. ***A.*** Preformed immune deposits can precipitate from the circulation and collect along the glomerular basement membrane (GBM) in the subendothelial space or can form in situ along the subepithelial space. ***B.*** Immunofluorescent staining of glomeruli with labeled anti-IgG demonstrating linear staining from a patient with anti-GBM disease or immune deposits from a patient with membranous glomerulonephritis. ***C.*** The mechanisms of glomerular injury have a complicated pathogenesis. Immune deposits and complement deposition classically draw macrophages and neutrophils into the glomerulus. T lymphocytes may follow to participate in the injury pattern as well. ***D.*** Amplification mediators as locally derived oxidants and proteases expand this inflammation, and, depending on the location of the target antigen and the genetic polymorphisms of the host, basement membranes are damaged with either endocapillary or extracapillary proliferation.

and dendritic cells in conjunction with associative recognition molecules engage the CD4/8 T cell repertoire.

Mononuclear cells by themselves can injure the kidney, but autoimmune events that damage glomeruli classically produce a humoral immune response. *Poststreptococcal glomerulonephritis, lupus nephritis*, and idiopathic *membranous nephritis* typically are associated with immune deposits along the GBM, while anti-GBM antibodies produce the linear binding of anti-GBM disease. Preformed circulating immune complexes can precipitate along the subendothelial side of the GBM, while other immune deposits form in situ on the subepithelial side. These latter deposits accumulate when circulating autoantibodies find their antigen trapped along the subepithelial edge of the GBM. Immune deposits in the glomerular mesangium may result from the deposition of preformed circulating complexes or in situ antigen-antibody interactions. Immune deposits stimulate the release of local proteases and activate the complement cascade, producing C_{5-9} attack complexes. In addition, local oxidants damage glomerular structures, producing proteinuria and effacement of the podocytes. Overlapping etiologies or pathophysiologic mechanisms can produce similar glomerular lesions, suggesting that downstream molecular and cellular responses often converge toward common patterns of injury.

PROGRESSION OF GLOMERULAR DISEASE

Persistent glomerulonephritis that worsens renal function is always accompanied by interstitial nephritis, renal fibrosis, and tubular atrophy **(see Fig. A3-27)**. What is not so obvious, however, is that renal failure in glomerulonephritis best correlates histologically with the appearance of tubulointerstitial nephritis rather than with the type of inciting glomerular injury.

Loss of renal function due to interstitial damage is explained hypothetically by several mechanisms. The simplest explanation is that urine flow is impeded by tubular obstruction as a result of interstitial inflammation and fibrosis. Thus, obstruction of the tubules with debris or by extrinsic compression functionally results in aglomerular nephrons. A second mechanism suggests that interstitial changes, including interstitial edema or fibrosis, alter tubular and vascular architecture and thereby compromise the normal tubular transport of solutes and water from tubular lumen to vascular space. This failure increases the solute and water content of the tubule fluid, resulting in isosthenuria and polyuria. Adaptive mechanisms related to tubuloglomerular feedback also fail, resulting in a reduction of renin output from the juxtaglomerular apparatus trapped by interstitial inflammation. Consequently, the local vasoconstrictive influence of angiotensin II on the glomerular arterioles decreases, and filtration drops owing to a generalized decrease in arteriolar tone. A third mechanism involves changes in vascular resistance due to damage of peritubular capillaries. The cross-sectional volume of these capillaries is decreased by interstitial inflammation, edema, or fibrosis. These structural alterations in vascular resistance affect renal function through two mechanisms. First, tubular cells are very metabolically active, and, as a result, decreased perfusion leads to tubular ischemic injury. Second, impairment of glomerular arteriolar outflow leads to increased intravascular hypertension in less-involved glomeruli; this selective intraglomerular hypertension aggravates and extends *mesangial sclerosis* and *glomerulosclerosis* to less-involved glomeruli. Regardless of the exact mechanism, early *acute tubulointerstitial nephritis* **(see Fig. A3-27)** suggests potentially recoverable renal function, whereas the development of *chronic interstitial fibrosis* prognosticates permanent loss **(see Fig. A3-30)**.

Persistent damage to glomerular capillaries spreads to the tubulointerstitium in association with proteinuria. There is a hypothesis that efferent arterioles leading from inflamed glomeruli carry forward inflammatory mediators, which induces downstream interstitial nephritis, resulting in fibrosis. Glomerular filtrate from injured glomerular capillaries adherent to Bowman's capsule may also be misdirected to the periglomerular interstitium. Most nephrologists believe, however, that proteinuric glomerular filtrate forming tubular fluid is the primary route to downstream tubulointerstitial injury, although none of these hypotheses are mutually exclusive.

The simplest explanation for the effect of proteinuria on the development of interstitial nephritis is that increasingly severe proteinuria, carrying activated cytokines and lipoproteins producing reactive oxygen species, triggers a downstream inflammatory cascade in and around epithelial cells lining the tubular nephron. These effects induce T lymphocyte and macrophage infiltrates in the interstitial spaces along with fibrosis and tubular atrophy.

Tubules disaggregate following direct damage to their basement membranes, leading to more interstitial fibroblasts and fibrosis at the site of injury; recent comprehensive evidence suggests that renal fibroblasts increase through several mechanisms: epithelial or endothelial-mesenchymal transitions (15%), bone marrow-derived fibrocytes (35%), and the proliferation of resident fibroblasts (50%). Transforming growth factor-β (TGF-β), fibroblast growth factor 2 (FGF-2), hypoxemia-inducible factor 1α (HIF-1α), and platelet-derived growth factor (PDGF) are particularly active in this transition. With persistent nephritis, fibroblasts multiply and lay down tenascin and a fibronectin scaffold for the polymerization of new interstitial collagen types I/III. These events form scar tissue through a process called fibrogenesis. In experimental studies, bone morphogenetic protein 7 and hepatocyte growth factor can reverse early fibrogenesis and preserve tubular architecture. When fibroblasts outdistance their survival factors, apoptosis occurs, and the permanent renal scar becomes acellular, leading to irreversible renal failure.

APPROACH TO THE PATIENT

Glomerular Disease

HEMATURIA, PROTEINURIA, AND PYURIA

Patients with glomerular disease usually have some hematuria with varying degrees of proteinuria. Hematuria is typically asymptomatic. As few as 3–5 red blood cells in the spun sediment from first-voided morning urine is suspicious. The diagnosis of glomerular injury can be delayed because patients will not realize they have *microscopic hematuria*, and only rarely with the exception of IgA nephropathy and sickle cell disease is *gross hematuria* present. When working up microscopic hematuria, perhaps accompanied by minimal proteinuria (<500 mg/24 h), it is important to exclude anatomic lesions, such as malignancy of the urinary tract, particularly in older men. Microscopic hematuria may also appear with the onset of benign prostatic hypertrophy, interstitial nephritis, papillary necrosis, hypercalciuria, renal stones, cystic kidney diseases, or renal vascular injury. However, when red blood cell casts **(see Fig. A3-34)** or dysmorphic red blood cells are found in the sediment, glomerulonephritis is likely. A mean of 8–10 mg/24 h of albumin appears in the urine in the absence of kidney disease. In early nephropathy, such as in diabetic nephropathy, proteinuria increases to 30–300 mg/24 h and is called microalbuminuria and represents the presence of renal disease. Greater than 300 mg/24 h of albuminuria represents frank proteinuria and more advanced renal disease **(Table 308-1)**.

TABLE 308-1 Urine Assays for Albuminuria/Proteinuria

	24-h ALBUMIN[a] (mg/24 h)	ALBUMIN[a]/CREATININE RATIO (mg/g)	DIPSTICK PROTEINURIA	24-h URINE PROTEIN[b] (mg/24 h)
Normal	8–10	<30	–	<150
Microalbuminuria	30–300	30–300	–/Trace/1+	–
Proteinuria	>300	>300	Trace–3+	>150

[a]Albumin detected by radioimmunoassay. [b]Albumin represents 20–60% of the total protein excreted in the urine.

Sustained proteinuria >1–2 g/24 h is also commonly associated with glomerular disease. Patients often will not know they have proteinuria unless they become edematous or notice foaming urine on voiding. *Sustained proteinuria* has to be distinguished from lesser amounts of so-called *benign proteinuria* in the normal population. (Table 308-1). This latter class of proteinuria is nonsustained, generally <1 g/24 h, and is sometimes called *functional* or *transient proteinuria*. Fever, exercise, obesity, sleep apnea, emotional stress, and congestive heart failure can explain transient proteinuria. Proteinuria only seen with upright posture is called *orthostatic proteinuria* and has a benign prognosis. Isolated proteinuria sustained over multiple clinic visits is found in many glomerular lesions. Proteinuria in most adults with glomerular disease is *nonselective*, containing albumin and a mixture of other serum proteins, whereas in children with *minimal change disease* (MCD), the proteinuria is *selective* and composed largely of albumin.

Some patients with inflammatory glomerular disease, such as acute poststreptococcal glomerulonephritis or MPGN, have *pyuria* characterized by the presence of considerable numbers of leukocytes. This latter finding has to be distinguished from urine infected with bacteria.

CLINICAL SYNDROMES

Various forms of glomerular injury can also be parsed into several distinct syndromes on clinical grounds **(Table 308-2)**. These syndromes, however, are not always mutually exclusive. There is an *acute nephritic syndrome* producing 1–2 g/24 h of proteinuria, hematuria with red blood cell casts, pyuria, hypertension, fluid retention, and a rise in serum creatinine associated with a reduction in glomerular filtration. If glomerular inflammation develops slowly, the serum creatinine will rise gradually over many weeks, but if the serum creatinine rises quickly, particularly over a few days, acute nephritis is sometimes called *rapidly progressive glomerulonephritis* (RPGN); the histopathologic term *crescentic glomerulonephritis* is the pathologic equivalent of the clinical presentation of RPGN. When patients with RPGN present with lung hemorrhage from Goodpasture's syndrome, antineutrophil cytoplasmic antibodies (ANCA)-associated small-vessel vasculitis, lupus erythematosus, or cryoglobulinemia, they are often diagnosed as having a *pulmonary-renal syndrome*. *Nephrotic syndrome* describes the onset of heavy proteinuria (>3.0 g/24 h), hypertension, hypercholesterolemia, hypoalbuminemia, edema/anasarca, and microscopic hematuria; if only large amounts of proteinuria are present without clinical manifestations,

TABLE 308-2 Patterns of Clinical Glomerulonephritis

GLOMERULAR SYNDROMES	PROTEINURIA	HEMATURIA	VASCULAR INJURY
Acute Nephritic Syndromes			
Poststreptococcal glomerulonephritis[a]	+/++	++/+++	–
Subacute bacterial endocarditis[a]	+/++	++	–
Lupus nephritis[a]	+/++	++/+++	+
Antiglomerular basement membrane disease[a]	++	++/+++	–
IgA nephropathy[a]	+/++	+++[c]	–
ANCA small-vessel vasculitis[a]			
Granulomatosis with polyangiitis (Wegener's)	+/++	++/+++	++++
Microscopic polyangiitis	+/++	++/+++	++++
Churg-Strauss syndrome	+/++	++/+++	++++
Henoch-Schönlein purpura[a]	+/++	++/+++	++++
Cryoglobulinemia[a]	+/++	++/+++	++++
Membranoproliferative glomerulonephritis[a]	++	++/+++	–
C_3 Glomerulopathies	++	++/+++	-
Mesangioproliferative glomerulonephritis	+	+/++	–
Pulmonary-Renal Syndromes			
Goodpasture's syndrome[a]	++	++/+++	–
ANCA small-vessel vasculitis[a]			
Granulomatosis with polyangiitis (Wegener's)	+/++	++/+++	++++
Microscopic polyangiitis	+/++	++/+++	++++
Churg-Strauss syndrome	+/++	++/+++	++++
Henoch-Schönlein purpura[a]	+/++	++/+++	++++
Cryoglobulinemia[a]	+/++	++/+++	++++
Nephrotic Syndromes			
Minimal change disease	++++	–	–
Focal segmental glomerulosclerosis	+++/++++	+	–
Membranous glomerulonephritis	++++	+	–
Diabetic nephropathy	++/++++	–/+	–
AL and AA amyloidosis	+++/++++	+	+/++
Light-chain deposition disease	+++	+	–
Fibrillary-immunotactoid disease	+++/++++	+	+
Fabry's disease	+	+	–
Basement Membrane Syndromes			
Anti-GBM disease[a]	++	++/+++	–
Alport's syndrome	++	++	–
Thin basement membrane disease	+	++	–
Nail-patella syndrome	++/+++	++	–

(*Continued*)

TABLE 308-2 Patterns of Clinical Glomerulonephritis (Continued)

GLOMERULAR SYNDROMES	PROTEINURIA	HEMATURIA	VASCULAR INJURY
Glomerular Vascular Syndromes			
Atherosclerotic nephropathy	+	+	+++
Hypertensive nephropathy[b]	+/++	+/++	++
Cholesterol emboli	+/++	++	+++
Sickle cell disease	+/++	+++[c]	+++
Thrombotic microangiopathies	++	++	+++
Antiphospholipid syndrome	++	++	+++
ANCA small-vessel vasculitis[a]			
Granulomatosis with polyangiitis (Wegener's)	+/++	++/+++	++++
Microscopic polyangiitis	+/++	++/+++	++++
Churg-Strauss syndrome	+++	++/+++	++++
Henoch-Schönlein purpura[a]	+/++	++/+++	++++
Cryoglobulinemia[a]	+/++	++/+++	++++
AL and AA amyloidosis	+++/++++	+	+/++
Infectious Disease–Associated Syndromes			
Poststreptococcal glomerulonephritis[a]	+/++	++/+++	–
Subacute bacterial endocarditis[a]	+/++	++	–
HIV	+++	+/++	–
Hepatitis B and C	+++	+/++	–
Syphilis	+++	+	–
Leprosy	+++	+	–
Malaria	+++	+/++	–
Schistosomiasis	+++	+/++	–

[a]Can present as rapidly progressive glomerulonephritis (RPGN); sometimes called crescentic glomerulonephritis. [b]Can present as a malignant hypertensive crisis producing an aggressive fibrinoid necrosis in arterioles and small arteries with microangiopathic hemolytic anemia. [c]Can present with gross hematuria.

Abbreviations: AA, amyloid A; AL, amyloid L; ANCA, antineutrophil cytoplasmic antibodies; GBM, glomerular basement membrane.

the condition is sometimes called *nephrotic-range proteinuria*. The glomerular filtration rate (GFR) in these patients may initially be normal or, rarely, higher than normal, but with persistent hyperfiltration and continued nephron loss, it typically declines over months to years. Patients with a *basement membrane syndrome* either have genetically abnormal basement membranes (Alport's syndrome) or an autoimmune response to basement membrane collagen IV (Goodpasture's syndrome) associated with microscopic hematuria, mild to heavy proteinuria, and hypertension with variable elevations in serum creatinine. *Glomerular–vascular syndrome* describes patients with vascular injury producing hematuria and moderate proteinuria. Affected individuals can have vasculitis, thrombotic microangiopathy, antiphospholipid syndrome, or, more commonly, a systemic disease such as atherosclerosis, cholesterol emboli, hypertension, sickle cell anemia, and autoimmunity. *Infectious disease–associated syndrome* is most important if one has a global perspective. Save for subacute bacterial endocarditis (SBE) in the Western Hemisphere, malaria, and schistosomiasis may be the most common causes of glomerulonephritis throughout the world, closely followed by HIV and chronic hepatitis B and C. These infectious diseases produce a variety of inflammatory reactions in glomerular capillaries, ranging from nephrotic syndrome to acute nephritic injury, and urinalyses that demonstrate a combination of hematuria and proteinuria.

These six general categories of syndromes are usually determined at the bedside with the help of a history and physical examination, blood chemistries, renal ultrasound, and urinalysis. These initial studies help frame further diagnostic workup that typically involves testing of the serum for the presence of various proteins (HIV and hepatitis B and C antigens), antibodies (anti-GBM, antiphospholipid, antistreptolysin O [ASO], anti-DNAse, antihyaluronidase, ANCA, anti-DNA, cryoglobulins, anti-HIV, and anti-hepatitis B and C antibodies) or depletion of complement components (C_3 and C_4). The bedside history and physical examination can also help determine whether the glomerulonephritis is isolated to the kidney (*primary glomerulonephritis*) or is part of a systemic disease (*secondary glomerulonephritis*).

When confronted with an abnormal urinalysis and elevated serum creatinine, with or without edema or congestive heart failure, one must consider whether the glomerulonephritis is *acute* or *chronic*. This assessment is best made by careful history (last known urinalysis or serum creatinine during pregnancy or insurance physical, evidence of infection, or use of medication or recreational drugs); the size of the kidneys on renal ultrasound examination; and how the patient feels at presentation. Chronic glomerular disease often presents with decreased kidney size. Patients who quickly develop renal failure are fatigued and weak and often have uremic symptoms associated with nausea, vomiting, fluid retention, and somnolence. Primary glomerulonephritis presenting with renal failure that has progressed slowly, however, can be remarkably asymptomatic, as are patients with acute glomerulonephritis without much loss in renal function. Once this initial information is collected, selected patients who are clinically stable, have adequate blood clotting parameters, and are willing and able to receive treatment are encouraged to have a renal biopsy.

RENAL PATHOLOGY

A renal biopsy in the setting of glomerulonephritis quickly identifies the type of glomerular injury and often suggests a course of treatment. The biopsy is processed for light microscopy using stains for *hematoxylin and eosin* (*H&E*) to assess cellularity and architecture, *periodic acid–Schiff* (*PAS*) to stain carbohydrate moieties in the membranes of the glomerular tuft and tubules, *Jones-methenamine silver* to enhance basement membrane structure, *Congo red* for amyloid deposits, and *Masson's trichrome* to identify collagen deposition and assess the degree of glomerulosclerosis and interstitial fibrosis. Biopsies are also processed for direct immunofluorescence using conjugated antibodies against IgG, IgM, and IgA to detect the presence of "lumpy-bumpy" immune deposits or "linear" IgG or IgA antibodies bound to GBM, antibodies against trapped complement proteins (C_3 and C_4), or specific antibodies against

a relevant antigen. High-resolution electron microscopy can clarify the principal location of immune deposits and the status of the basement membrane.

Each region of a renal biopsy is assessed separately. By light microscopy, glomeruli (ideally 20) are reviewed individually for discrete lesions; <50% involvement is considered *focal*, and >50% is *diffuse*. Injury in each glomerular tuft can be *segmental,* involving a portion of the tuft, or *global,* involving most of the glomerulus. Glomeruli having *proliferative* characteristics show increased cellularity. When cells in the capillary tuft proliferate, it is called *endocapillary*, and when cellular proliferation extends into Bowman's space, it is called *extracapillary. Synechiae* are formed when epithelial podocytes attach to Bowman's capsule in the setting of glomerular injury; *crescents*, which in some cases may be the extension of synechiae, develop when fibrocellular/fibrin collections fill all or part of Bowman's space; and *sclerotic* glomeruli show acellular, amorphous accumulations of proteinaceous material throughout the tuft with loss of functional capillaries and normal mesangium. Since *age-related glomerulosclerosis* is common in adults, one can estimate the background percentage of sclerosis by dividing the patient's age in half and subtracting 10. Immunofluorescent and electron microscopy can detect the presence and location of *subepithelial, subendothelial, or mesangial* immune deposits, or *reduplication* or *splitting* of the basement membrane. In the other regions of the biopsy, the vasculature surrounding glomeruli and tubules can show *angiopathy, vasculitis*, the presence of *fibrils*, or *thrombi*. The tubules can be assessed for adjacency to one another; separation can be the result of edema, tubular dropout, or collagen deposition resulting from interstitial fibrosis. Interstitial fibrosis is an ominous sign of irreversibility and progression to renal failure.

ACUTE NEPHRITIC SYNDROMES

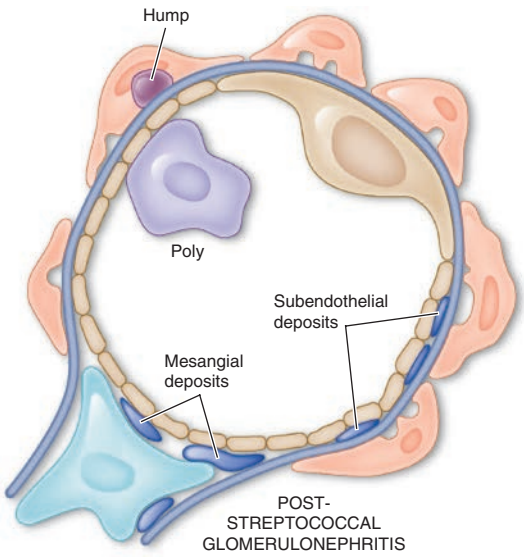
Acute nephritic syndromes classically present with hypertension, hematuria, red blood cell casts, pyuria, and mild to moderate proteinuria. Extensive inflammatory damage to glomeruli causes a fall in GFR and eventually produces uremic symptoms with salt and water retention, leading to edema and hypertension.

POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

Poststreptococcal glomerulonephritis is prototypical for *acute endocapillary proliferative glomerulonephritis*. The incidence of poststreptococcal glomerulonephritis has dramatically decreased in developed countries and in these locations is typically sporadic. Acute poststreptococcal glomerulonephritis in underdeveloped countries is epidemic and usually affects children between the ages of 2 and 14 years, but in developed countries is more typical in the elderly, especially in association with debilitating conditions. It is more common in males, and the familial or cohabitant incidence is as high as 40%. Skin and throat infections with particular M types of streptococci (nephritogenic strains) antedate glomerular disease; M types 47, 49, 55, 2, 60, and 57 are seen following impetigo and M types 1, 2, 4, 3, 25, 49, and 12 with pharyngitis. Poststreptococcal glomerulonephritis due to impetigo develops 2–6 weeks after skin infection and 1–3 weeks after streptococcal pharyngitis.

The renal biopsy in poststreptococcal glomerulonephritis demonstrates hypercellularity of mesangial and endothelial cells, glomerular infiltrates of polymorphonuclear leukocytes, granular subendothelial immune deposits of IgG, IgM, C_3, C_4, and C_{5-9}, and subepithelial deposits (which appear as "humps") **(see Fig. A3-6)**. **(See Glomerular Schematic 1.)** Poststreptococcal glomerulonephritis is an immune-mediated disease involving putative streptococcal antigens, circulating immune complexes, and activation of complement in association with cell-mediated injury. Many candidate antigens have been proposed over the years; candidates from nephritogenic streptococci of interest at the moment are: a cationic cysteine proteinase known as streptococcal pyrogenic exotoxin B (SPEB) that is generated by proteolysis of a zymogen precursor (zSPEB), and NAPlr, the nephritis-associated plasmin receptor. These two antigens have biochemical affinity for plasmin, bind as complexes facilitated by this relationship, and activate the alternate complement pathway. The nephritogenic antigen, SPEB, has been demonstrated inside the subepithelial "humps" on biopsy.

Glomerular schematic 1



The classic presentation is an acute nephritic picture with hematuria, pyuria, red blood cell casts, edema, hypertension, and oliguric renal failure, which may be severe enough to appear as RPGN. Systemic symptoms of headache, malaise, anorexia, and flank pain (due to swelling of the renal capsule) are reported in as many as 50% of cases. Five percent of children and 20% of adults have proteinuria in the nephrotic range. In the first week of symptoms, 90% of patients will have a depressed CH_{50} and decreased levels of C_3 with normal levels of C_4. Positive rheumatoid factor (30–40%), cryoglobulins and circulating immune complexes (60–70%), and ANCA against myeloperoxidase (10%) are also reported. Positive cultures for streptococcal infection are inconsistently present (10–70%), but increased titers of ASO (30%), anti-DNAse (70%), or antihyaluronidase antibodies (40%) can help confirm the diagnosis. Consequently, the diagnosis of poststreptococcal glomerulonephritis rarely requires a renal biopsy. A subclinical disease is reported in some series to be 4–5 times as common as clinical nephritis, and these latter cases are characterized by asymptomatic microscopic hematuria with low serum C_3 complement levels.

Treatment is supportive, with control of hypertension, edema, and dialysis as needed. Antibiotic treatment for streptococcal infection should be given to all patients and their cohabitants. There is no role for immunosuppressive therapy, even in the setting of crescents. Recurrent poststreptococcal glomerulonephritis is rare despite repeated streptococcal infections. Early death is rare in children but does occur in the elderly. Overall, the prognosis is good, with permanent renal failure being reported as very uncommon in the past (<1%) but with recent reports of an increased risk of chronic kidney disease in adulthood. Complete resolution of the hematuria and proteinuria in the majority of children occurs within 3–6 weeks of the onset of nephritis but 3–10% of children may have persistent microscopic hematuria, nonnephrotic proteinuria, or hypertension. The prognosis in elderly patients is worse with a high incidence of azotemia (up to 60%), nephrotic-range proteinuria, and ESRD.

SUBACUTE BACTERIAL ENDOCARDITIS

Endocarditis-associated glomerulonephritis is typically a complication of SBE, particularly in patients who remain untreated for a long time, have negative blood cultures, or have right-sided endocarditis. Common comorbidities are valvular heart disease, intravenous drug use, hepatitis C, and diabetes mellitus. Glomerulonephritis is unusual in acute bacterial endocarditis because it takes 10–14 days to develop immune complex–mediated injury, by which time the patient has been treated, often with emergent surgery. Grossly, the kidneys in SBE have subcapsular hemorrhages with a "flea-bitten" appearance, and microscopy on renal biopsy reveals focal proliferation around foci of necrosis associated with abundant mesangial, subendothelial, and subepithelial

immune deposits of IgG, IgM, and C_3. Commonly patients present with a clinical picture of RPGN and have crescents on biopsy. Embolic infarcts or septic abscesses may also be present. The pathogenesis hinges on the renal deposition of circulating immune complexes in the kidney with complement activation. Patients present with gross or microscopic hematuria, pyuria, and mild proteinuria, acute kidney injury or, RPGN with rapid loss of renal function. A normocytic anemia, elevated erythrocyte sedimentation rate, hypocomplementemia, high titers of rheumatoid factor, type III cryoglobulins, circulating immune complexes, and ANCAs may be present. Levels of serum creatinine may be elevated at diagnosis, but with modern therapy there is little progression to chronic renal failure. Primary treatment is eradication of the infection with 4–6 weeks of antibiotics, and if accomplished expeditiously, the prognosis for renal recovery is good. ANCA-associated vasculitis sometimes accompanies or is confused with SBE and should be ruled out, as the treatment is different.

As variants of persistent bacterial infection in blood-associated glomerulonephritis, postinfectious glomerulonephritis can occur in patients with ventriculoatrial and ventriculoperitoneal shunts; pulmonary, intraabdominal, pelvic, or cutaneous infections; and infected vascular prostheses. In developed countries, a significant proportion of cases afflict adults, especially the immunocompromised, and the predominant organism is *Staphylococcus*. The clinical presentation of these conditions is variable and includes proteinuria, microscopic hematuria, acute renal failure, and hypertension. Serum complement levels are low, and there may be elevated levels of C-reactive proteins, rheumatoid factor, antinuclear antibodies, and cryoglobulins. Renal lesions include MPGN, diffuse proliferative and exudative glomerulonephritis (DPGN), or mesangioproliferative glomerulonephritis, sometimes leading to RPGN. Treatment focuses on eradicating the infection, with most patients treated as if they have endocarditis. The prognosis is guarded.

LUPUS NEPHRITIS

Lupus nephritis is a common and serious complication of systemic lupus erythematosus (SLE) and most severe in African-American female adolescents. Thirty to 50% of patients will have clinical manifestations of renal disease at the time of diagnosis, and 60% of adults and 80% of children develop renal abnormalities at some point in the course of their disease. Lupus nephritis results from the deposition of circulating immune complexes, which activate the complement cascade leading to complement-mediated damage, leukocyte infiltration, activation of procoagulant factors, and release of various cytokines. In situ immune complex formation following glomerular binding of nuclear antigens, particularly necrotic nucleosomes, also plays a role in renal injury. The presence of antiphospholipid antibodies may also trigger a thrombotic microangiopathy in a minority of patients.

The clinical manifestations, course of disease, and treatment of lupus nephritis are closely linked to renal pathology. The most common clinical sign of renal disease is proteinuria, but hematuria, hypertension, varying degrees of renal failure, and active urine sediment with red blood cell casts can all be present. Although significant renal pathology can be found on biopsy even in the absence of major abnormalities in the urinalysis, most nephrologists do not biopsy patients until the urinalysis is convincingly abnormal. The extrarenal manifestations of lupus are important in establishing a firm diagnosis of systemic lupus because, while serologic abnormalities are common in lupus nephritis, they are not diagnostic. Anti-dsDNA antibodies that fix complement correlate best with the presence of renal disease. Hypocomplementemia is common in patients with acute lupus nephritis (70–90%) and declining complement levels may herald a flare. Although urinary biomarkers of lupus nephritis are being identified to assist in predicting renal flares, renal biopsy is the only reliable method of identifying the morphologic variants of lupus nephritis.

The World Health Organization (WHO) workshop in 1974 first outlined several distinct patterns of lupus-related glomerular injury; these were modified in 1982. In 2004 the International Society of Nephrology in conjunction with the Renal Pathology Society again updated the classification. This latest version of lesions seen on biopsy **(Table 308-3)** forms the basis for modern treatment recommendations. Class I nephritis describes normal glomerular histology by any technique or normal light microscopy with minimal mesangial deposits on immunofluorescent or electron microscopy. Class II designates mesangial immune complexes with *mesangial proliferation*. Both class I and II lesions are typically associated with minimal renal manifestation and normal renal function; nephrotic syndrome is rare. Patients with lesions limited to the renal mesangium have an excellent prognosis and generally do not need therapy for their lupus nephritis.

TABLE 308-3 Classification for Lupus Nephritis

Class I	Minimal mesangial	Normal histology with mesangial deposits
Class II	Mesangial proliferation	Mesangial hypercellularity with expansion of the mesangial matrix
Class III	Focal nephritis	Focal endocapillary ± extracapillary proliferation with focal subendothelial immune deposits and mild mesangial expansion
Class IV	Diffuse nephritis	Diffuse endocapillary ± extracapillary proliferation with diffuse subendothelial immune deposits and mesangial alterations
Class V	Membranous nephritis	Thickened basement membranes with diffuse subepithelial immune deposits; may occur with class III or IV lesions and is sometimes called mixed membranous and proliferative nephritis
Class VI	Sclerotic nephritis	Global sclerosis of nearly all glomerular capillaries

Note: Revised in 2004 by the International Society of Nephrology-Renal Pathology Society Study Group.

The subject of lupus nephritis is presented under acute nephritic syndromes because of the aggressive and important proliferative lesions seen in class III–V renal diseases. Class III describes *focal lesions with proliferation or scarring*, often involving only a segment of the glomerulus **(see Fig. A3-12)**. Class III lesions have the most varied course. Hypertension, an active urinary sediment, and proteinuria are common with nephrotic-range proteinuria in 25–33% of patients. Elevated serum creatinine is present in 25% of patients. Patients with mild proliferation involving a small percentage of glomeruli respond well to therapy with steroids alone, and fewer than 5% progress to renal failure over 5 years. Patients with more severe proliferation involving a greater percentage of glomeruli have a far worse prognosis and lower remission rates. Treatment of those patients is the same as that for class IV lesions. Many nephrologists believe that class III lesions are simply an early presentation of class IV disease. Others believe severe class III disease is a discrete vasculitic lesion requiring aggressive therapy. Class IV describes *global, diffuse proliferative lesions* involving the vast majority of glomeruli. Patients with class IV lesions commonly have high anti-DNA antibody titers, low serum complement, hematuria, red blood cell casts, proteinuria, hypertension, and decreased renal function; 50% of patients have nephrotic-range proteinuria. Patients with crescents on biopsy often have a rapidly progressive decline in renal function **(see Fig. A3-12)**. Without treatment, this aggressive lesion has the worst renal prognosis. However, if a remission—defined as a return to near-normal renal function and proteinuria ≤330 mg/dL per day—is achieved with treatment, renal outcomes are excellent. Current evidence suggests that inducing a remission with administration of high-dose steroids and either cyclophosphamide or mycophenolate mofetil for 2–6 months, followed by maintenance therapy with lower doses of steroids and mycophenolate mofetil or azathioprine, best balances the likelihood of successful remission with the side effects of therapy. There is no consensus on use of high-dose intravenous methylprednisolone versus oral prednisone, monthly intravenous cyclophosphamide versus daily oral cyclophosphamide, or other immunosuppressants such as cyclosporine, tacrolimus, rituximab, or belimumab. Nephrologists tend to avoid prolonged use of cyclophosphamide in patients of childbearing age without first banking eggs or sperm.

The class V lesion describes subepithelial immune deposits producing a *membranous pattern*; a subcategory of class V lesions is associated with proliferative lesions and is sometimes called *mixed membranous and proliferative disease* **(see Fig. A3-11)**; this category of injury is treated like class IV glomerulonephritis. Sixty percent of patients present with nephrotic syndrome or lesser amounts of proteinuria. Patients with lupus nephritis class V, like patients with *idiopathic membranous nephropathy* (IMN), are predisposed to renal-vein thrombosis and other thrombotic complications. A minority of patients with class V will present with hypertension and renal dysfunction. There are conflicting data on the clinical course, prognosis, and appropriate therapy for patients with class V disease, which may reflect the heterogeneity of this group of patients. Patients with severe nephrotic syndrome, elevated serum creatinine, and a progressive course will probably benefit from therapy with steroids in combination with other immunosuppressive agents. Therapy with inhibitors of the renin-angiotensin system also may attenuate the proteinuria. Antiphospholipid antibodies present in lupus may result in glomerular microthromboses and complicate the course in up to 20% of lupus nephritis patients. The renal prognosis is worse despite anticoagulant therapy.

Patients with any of the above lesions also can transform to another lesion; hence patients often require reevaluation, including repeat renal biopsy. Lupus patients with class VI lesions have >90% *sclerotic glomeruli* and ESRD with interstitial fibrosis. As a group, ~20% of patients with lupus nephritis will reach end-stage disease, requiring dialysis or transplantation. Patients with lupus nephritis have a markedly increased mortality compared with the general population. Renal transplantation in renal failure from lupus, usually performed after ~6 months of inactive disease, results in allograft survival rates comparable to patients transplanted for other reasons.

ANTIGLOMERULAR BASEMENT MEMBRANE DISEASE

Patients who develop autoantibodies directed against glomerular basement antigens frequently develop a glomerulonephritis termed *antiglomerular basement membrane* (*anti-GBM*) *disease*. When they present with lung hemorrhage and glomerulonephritis, they have a pulmonary-renal syndrome called *Goodpasture's syndrome*. The target epitopes for this autoimmune disease lie in the quaternary structure of α3 NC1 domain of collagen IV. Indeed, anti-GBM disease may be considered an autoimmune "conformeropathy" that involves the perturbation of quaternary structure of the α 345NC1 hexamer. MHC-restricted T cells initiate the autoantibody response because humans are not tolerant to the epitopes created by this quaternary structure. The epitopes are normally sequestered in the collagen IV hexamer and can be exposed by infection, smoking, oxidants, or solvents. Goodpasture's syndrome appears in two age groups: in young men in their late twenties and in men and women in their sixties and seventies. Disease in the younger age group is usually explosive, with hemoptysis, a sudden fall in hemoglobin, fever, dyspnea, and hematuria. Hemoptysis is largely confined to smokers, and those who present with lung hemorrhage as a group do better than older populations who have prolonged, asymptomatic renal injury; presentation with oliguria is often associated with a particularly bad outcome. The performance of an urgent kidney biopsy is important in suspected cases of Goodpasture's syndrome to confirm the diagnosis and assess prognosis. Renal biopsies typically show *focal or segmental necrosis* that later, with aggressive destruction of the capillaries by cellular proliferation, leads to crescent formation in Bowman's space **(see Fig. A3-14)**. As these lesions progress, there is concomitant interstitial nephritis with fibrosis and tubular atrophy.

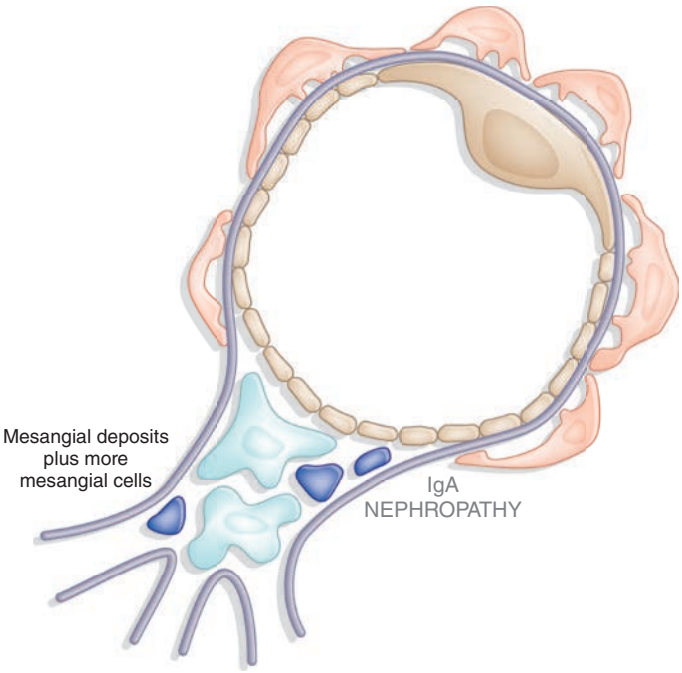
The presence of anti-GBM antibodies and complement is recognized on biopsy by linear immunofluorescent staining for IgG (rarely IgA). In testing serum for anti-GBM antibodies, it is particularly important that the α3 NC1 domain of collagen IV alone be used as the target. This is because nonnephritic antibodies against the α1 NC1 domain are seen in paraneoplastic syndromes and cannot be discerned from assays that use whole basement membrane fragments as the binding target. Between 10 and 15% of sera from patients with Goodpasture's syndrome also contain ANCA antibodies against myeloperoxidase. This subset of patients has a vasculitis-associated variant, which has a surprisingly good prognosis with treatment. Prognosis at presentation is worse if there are >50% crescents on renal biopsy with advanced fibrosis, if serum creatinine is >5–6 mg/dL, if oliguria is present, or if there is a need for acute dialysis. Although frequently attempted, most of these latter patients will not respond to plasmapheresis and steroids. Patients with advanced renal failure who present with hemoptysis should still be treated for their lung hemorrhage, as it responds to plasmapheresis and can be lifesaving. Treated patients with less severe disease typically respond to 8–10 treatments of plasmapheresis accompanied by oral prednisone and cyclophosphamide in the first 2 weeks. Kidney transplantation is possible, but because there is risk of recurrence, experience suggests that patients should wait for 6 months and until serum antibodies are undetectable.

IgA NEPHROPATHY

Berger first described the glomerulonephritis now termed *IgA nephropathy*. It is classically characterized by episodic hematuria associated with the deposition of IgA in the mesangium. IgA nephropathy is one of the most common forms of glomerulonephritis worldwide. There is a male preponderance, a peak incidence in the second and third decades of life, and rare familial clustering. There are geographic differences in the prevalence of IgA nephropathy, with 30% prevalence along the Asian and Pacific Rim and 20% in southern Europe, compared to a much lower prevalence in northern Europe and North America. It was initially hypothesized that variation in detection, in part, accounted for regional differences. With clinical care in nephrology becoming more uniform, this variation in prevalence more likely reflects true differences among racial and ethnic groups.

IgA nephropathy is predominantly a sporadic disease but susceptibility to it has been shown uncommonly to have a genetic component depending on geography and the existence of "founder effects." Familial forms of IgA nephropathy are more common in northern Italy and eastern Kentucky. No single causal gene has been identified. Clinical and laboratory evidence suggests close similarities between Henoch-Schönlein purpura and IgA nephropathy. Henoch-Schönlein purpura is distinguished clinically from IgA nephropathy by prominent systemic symptoms, a younger age (<20 years old), preceding infection, and abdominal complaints. Deposits of IgA are also found in the glomerular mesangium in a variety of systemic diseases, including chronic liver disease, Crohn's disease, gastrointestinal adenocarcinoma, chronic bronchiectasis, idiopathic interstitial pneumonia, dermatitis herpetiformis, mycosis fungoides, leprosy, ankylosing spondylitis, relapsing polychondritis, and Sjögren's syndrome. IgA deposition in these entities is not usually associated with clinically significant glomerular inflammation or renal dysfunction and thus is not called IgA nephropathy.

IgA nephropathy is an immune complex–mediated glomerulonephritis defined by the presence of diffuse mesangial IgA deposits often associated with mesangial hypercellularity. **(See Glomerular Schematic 2.)** IgM, IgG, C_3, or immunoglobulin light chains may be codistributed with IgA. IgA deposited in the mesangium is typically polymeric and of the IgA1 subclass, the pathogenic significance of which is not clear. Abnormalities have been described in IgA production by plasma cells; in IgA clearance, by the liver and in mesangial IgA clearance and receptors for IgA. Currently, however, abnormalities in the *O* glycosylation of the hinge region of primarily polymeric IgA1 seem to best account for the pathogenesis of sporadic IgA nephropathy. Synthesis of poorly galactosylated IgA1 results in exposure of N-acetyl-galactosomine in truncated IgA1 hinge regions which is recognized by IgG or IgA1 antibodies leading to formation of immune complexes in the circulation or in situ after glomerular deposition of galactose-deficient IgA1. The galactose-deficient IgA1 may evade liver catabolism and preferentially deposit in the mesangium. A second hit, such as a viral or other antigen exposure, may be necessary for disease manifestation. Despite the presence of elevated serum IgA levels in 20–50% of patients, and IgA deposition in skin biopsies in 15–55% of patients, a renal biopsy is necessary to confirm the diagnosis. Although the immunofluorescent pattern of IgA on renal biopsy defines IgA nephropathy in the proper



clinical context, a variety of histologic lesions may be seen on light microscopy **(see Fig. A3-8)**, including DPGN; *segmental sclerosis*; and, rarely, *segmental necrosis with cellular crescent formation*, which typically presents as RPGN.

The two most common presentations of IgA nephropathy are recurrent episodes of macroscopic hematuria during or immediately following an upper respiratory infection often accompanied by proteinuria or persistent asymptomatic microscopic hematuria. Nephrotic syndrome is uncommon. Proteinuria can also first appear late in the course of the disease. Rarely patients present with acute renal failure and a rapidly progressive clinical picture. IgA nephropathy is a benign disease for the majority of patients, and 5–30% of patients may go into a complete remission, with others having hematuria but well preserved renal function. In the minority of patients who have progressive disease, progression is slow, with renal failure seen in only 25–30% of patients with IgA nephropathy over 20–25 years. This risk varies considerably among populations. Cumulatively, risk factors for the loss of renal function identified thus far account for <50% of the variation in observed outcome but include the presence of hypertension or proteinuria, the absence of episodes of macroscopic hematuria, male sex, older age of onset, and extensive glomerulosclerosis or interstitial fibrosis on renal biopsy. Several analyses in large populations of patients found persistent proteinuria for 6 months or longer to have the greatest predictive power for adverse renal outcomes.

There is no agreement on optimal treatment. Both large studies that include patients with multiple glomerular diseases and small studies of patients with IgA nephropathy support the use of angiotensin-converting enzyme (ACE) inhibitors in patients with proteinuria or declining renal function. In patients with persistent proteinuria after ACE inhibitor therapy, steroid treatment or other immunosuppressives have demonstrated conflicting results. Tonsillectomy and fish oil have also been suggested in small studies to benefit select patients. When presenting as RPGN, patients typically receive steroids, cytotoxic agents, and plasmapheresis.

ANCA SMALL-VESSEL VASCULITIS

A group of patients with small-vessel vasculitis (arterioles, capillaries, and venules; rarely small arteries) and glomerulonephritis have serum ANCA; the antibodies are of two types, anti-proteinase 3 (PR3) or anti-myeloperoxidase (MPO) **(Chap. 356)**; Lamp-2 antibodies have also been reported experimentally as potentially pathogenic. ANCA are produced with the help of T cells and activate leukocytes and monocytes, which together damage the walls of small vessels. Endothelial injury also attracts more leukocytes and extends the inflammation. Granulomatosis with polyangiitis, microscopic polyangiitis, Churg-Strauss syndrome, and renal-limited vasculitis belong to this group because they are ANCA-positive and have a *pauci-immune glomerulonephritis* with few immune complexes in small vessels and glomerular capillaries. Patients with any of these diseases can have any combination of the above serum antibodies, but anti-PR3 antibodies are more common in granulomatosis with polyangiitis and anti-MPO antibodies are more common in microscopic polyangiitis or Churg-Strauss. Although each of these diseases has some unique clinical features, most features do not predict relapse or progression, and as a group, they are generally treated in the same way. Once diagnosed ANCA monitoring has limited value, but targeted determination of ANCA levels may be useful if a relapse is clinically suspected. Since mortality is high without treatment, virtually all patients receive urgent treatment. Induction therapy usually includes glucocorticoids and either cyclophosphamide or rituximab. Plasmapheresis is recommended in rapidly progressive renal failure or pulmonary hemorrhage. Monthly "pulse" IV cyclophosphamide to induce remission of ANCA-associated vasculitis is as effective as daily oral cyclophosphamide but may be associated with increased relapses. Steroids are tapered soon after acute inflammation subsides, and patients are maintained on cyclophosphamide or less toxic agents such as azathioprine, methotrexate, or rituximab for up to a year to minimize the risk of relapse.

Granulomatosis with Polyangiitis Patients with this disease classically present with fever, purulent rhinorrhea, nasal ulcers, sinus pain, polyarthralgias/arthritis, cough, hemoptysis, shortness of breath, microscopic hematuria, and 0.5–1 g/24 h of proteinuria; occasionally there may be cutaneous purpura and mononeuritis multiplex. Presentation without renal involvement is termed *limited granulomatosis with polyangiitis*, although some of these patients will show signs of renal injury later. Chest x-ray often reveals nodules and persistent infiltrates, sometimes with cavities. Biopsy of involved tissue will show a small-vessel vasculitis and adjacent noncaseating granulomas. Renal biopsies during active disease demonstrate *segmental necrotizing glomerulonephritis* without immune deposits and have been classified as focal, mixed, crescentic or sclerotic **(see Fig. A3-13)**. The disease is more common in patients exposed to silica dust and those with α_1-antitrypsin deficiency, which is an inhibitor of PR3. Relapse after achieving remission is common and is more common in patients with granulomatosis with polyangiitis than the other ANCA-associated vasculitis, necessitating diligent follow-up care. Although associated with an unacceptable high mortality rate without treatment, the greatest threat to patients, especially elderly patients in the first year of therapy, is from adverse events, which are often secondary to treatment, rather than active vasculitis. Patients should also be monitored long term for malignancy after immunosuppressive therapy.

Microscopic Polyangiitis Clinically, these patients look somewhat similar to those with granulomatosis with polyangiitis, except they rarely have significant lung disease or destructive sinusitis. The distinction is made on biopsy, where the vasculitis in microscopic polyangiitis is without granulomas. Some patients will also have injury limited to the capillaries and venules.

Churg-Strauss Syndrome When small-vessel vasculitis is associated with peripheral eosinophilia, cutaneous purpura, mononeuritis, asthma, and allergic rhinitis, a diagnosis of Churg-Strauss syndrome is considered. Hypergammaglobulinemia, elevated levels of serum IgE, or the presence of rheumatoid factor sometimes accompanies the allergic state. Lung inflammation, including fleeting cough and pulmonary infiltrates, often precedes the systemic manifestations of disease by years; lung manifestations are rarely absent. A third of patients may have exudative pleural effusions associated with eosinophils. Small-vessel vasculitis and *focal segmental necrotizing glomerulonephritis* can be seen on renal biopsy, usually absent eosinophils or granulomas. The cause of Churg-Strauss syndrome is autoimmune, but the inciting factors are unknown.

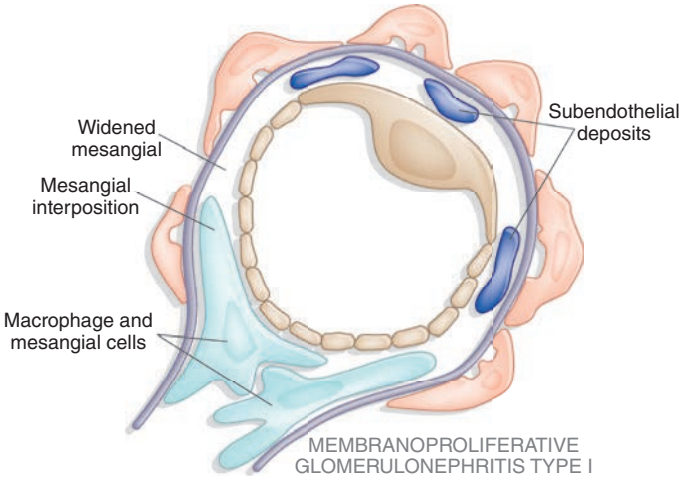
TABLE 308-4 Membranoproliferative Glomerulonephritis: Immunoglobulin-Mediated
Type I Disease—Most Common
Idiopathic
Subacute bacterial endocarditis
Systemic lupus erythematosus
Hepatitis C and cryoglobulinemia
Mixed cryoglobulinemia
Hepatitis C
Cancer: lung, breast and ovary (germinal)
Type II Disease
Idiopathic
Dense Deposit Disease (immunoglobulin-mediated)
Type III Disease
Idiopathic
C_3 Glomerulopathy: C_3 Dominant, Non-Immunoglobulin-mediated
Dense Deposit Disease (C_3 dominant)
Idiopathic
Specific genetic mutations and/or autoantibodies to alternate complement pathway factors or regulatory factors of alternate complement pathway
C_3 Glomerulonephritis
Specific genetic mutations and/or autoantibodies to alternate complement pathway factors or regulatory factors of alternate complement pathway

C_3 Glomerulopathies C_3 glomerulopathy is a recent disease classification that is defined by the glomerular accumulation of C_3 with little or no immunoglobulin and encompasses dense deposit disease (DDD), formerly MPGN type II (see below), and C_3 glomerulonephritis (C_3GN), **(Table 308-4)**. DDD is defined morphologically with dense deposits forming ribbons in the GBM. In the absence of this specific morphology the entity is categorized as C_3GN. Both are associated with the presence of a complement mutation believed to cause the renal pathology, including mutations in the complement factor H regulatory proteins (CFHR's) genes. DDD is primarily a disease of children and young adults while the other C_3 glomerulopathies are reported to present in an older age group (mean age 30). By definition kidneys with C_3 glomerulopathy show sole or dominant staining for C_3 but can have variable light microscopy with mesangial proliferative or membranoproliferative patterns seen most commonly. Morphologically, many cases are not distinguishable from recovering post-infections GN. Patients with DDD present with proteinuria and/or hematuria with nephrotic range proteinuria in up to 2/3 of patients. Partial lipodystrophy and Drusen bodies in the retina may also be present. Prognosis is poor with 50% of patients progressing to ESRD. C_3GN patients are clinically less well defined but ~2/3 have hematuria and 1/3 proteinuria. In addition to renal biopsy serological and genetic evaluation may be indicated including measurement of C_3 levels which are typically low with normal C_4 levels, C_3 nephritic factor, Factor H, paraprotein detection and specific CFHR genetic mutations. The optimal therapies remain undefined but include inhibition of the renin-angiotensin system, anticoagulants, steroids and other immunosuppressants. Increasing evidence suggests a benefit of therapy with eculizumab, a monoclonal antibody directed at C_5 which is activated by C_3.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

MPGN is sometimes called *mesangiocapillary glomerulonephritis* or *lobar glomerulonephritis*. It is an immune-mediated glomerulonephritis characterized by thickening of the GBM with mesangioproliferative changes; 70% of patients have hypocomplementemia. MPGN is rare in African Americans, and idiopathic disease usually presents in childhood or young adulthood. MPGN has been subdivided pathologically into type I, type II, and type III disease. *Type I MPGN* is commonly associated with persistent hepatitis C infections, autoimmune diseases like lupus or cryoglobulinemia, or neoplastic diseases (Table 308-4). A minority of cases of MPGN type I have C_3 but not immunoglobulin deposits on biopsy and are best considered as in the category of a C_3 glomerulopathy. *Types II and III MPGN* can be idiopathic, and immunoglobulin-mediated disease (driven by the classical complement pathway) but the majority of cases formerly defined as MPGN type II and III are non-immunoglobulin-mediated and driven by the alternate complement pathway.

Glomerular schematic 3



Type I MPGN, the most proliferative of the three types, shows mesangial proliferation with lobular segmentation on renal biopsy and mesangial interposition between the capillary basement membrane and endothelial cells, producing a double contour sometimes called *tram-tracking* **(see Fig. A3-9). (See Glomerular Schematic 3.)** Subendothelial deposits with low serum levels of C_3 are typical, although 50% of patients have normal levels of C_3 and occasional intramesangial deposits. Low serum C_3 and a dense thickening of the GBM containing ribbons of dense deposits and C_3 characterize type II MPGN, *dense deposit disease* **(see Fig. A3-10)**. Classically, the glomerular tuft has a lobular appearance; intramesangial deposits are rarely present and subendothelial deposits are generally absent. Proliferation in type III MPGN is less common than the other two types and is often focal; mesangial interposition is rare, and subepithelial deposits can occur along widened segments of the GBM that appear laminated and disrupted.

Classic type I MPGN is secondary to glomerular deposition of circulating immune complexes or their in situ formation. Patients with MPGN present with proteinuria, hematuria, and pyuria (30%); systemic symptoms of fatigue and malaise that are most common in children with type I disease; or an acute nephritic picture with RPGN and a speedy deterioration in renal function in up to 25% of patients. Low serum C_3 levels are common. Fifty percent of patients with MPGN develop ESRD 10 years after diagnosis, and 90% have renal insufficiency after 20 years. Nephrotic syndrome, hypertension, and renal insufficiency all predict poor outcome. In the presence of proteinuria, treatment with inhibitors of the renin-angiotensin system is prudent. Evidence for treatment with dipyridamole, Coumadin (warfarin), or cyclophosphamide is not strongly established. There is some evidence supporting the efficacy of treatment of *primary MPGN* with steroids, particularly in children, as well as reports of efficacy with plasma exchange and other immunosuppressive drugs. If defects in the complement pathway are found, treatment with eculizumab is of hypothetical but unproven benefit. In *secondary MPGN*, treating the associated infection, autoimmune disease, or neoplasms is of demonstrated benefit. In particular, pegylated interferon and ribavirin are useful in reducing viral load. Although all primary renal diseases can recur over time in transplanted renal allografts, patients with MPGN are well known to be at risk for not only a histologic recurrence but also a clinically significant recurrence with loss of graft function.

MESANGIOPROLIFERATIVE GLOMERULONEPHRITIS

Mesangioproliferative glomerulonephritis is characterized by expansion of the mesangium, sometimes associated with mesangial hypercellularity; thin, single contoured capillary walls; and mesangial immune deposits. Clinically, it can present with varying degrees of proteinuria and, commonly, hematuria. Mesangioproliferative disease may be seen in IgA nephropathy, *Plasmodium falciparum* malaria, resolving postinfectious glomerulonephritis, and class II nephritis from lupus, all of which can have a similar histologic appearance. With these secondary entities excluded, the diagnosis of *primary mesangioproliferative glomerulonephritis* is made in <15% of renal biopsies. As an immune-mediated renal lesion with deposits of IgM, C1q, and C_3, the clinical course is variable. Patients with isolated hematuria may have a very benign course, and those with heavy proteinuria occasionally progress to renal failure. There is little agreement on treatment, but some clinical reports suggest benefit from use of inhibitors of the renin-angiotensin system, steroid therapy, and even cytotoxic agents.

NEPHROTIC SYNDROME

Nephrotic syndrome classically presents with heavy proteinuria, minimal hematuria, hypoalbuminemia, hypercholesterolemia, edema, and hypertension. If left undiagnosed or untreated, some of these syndromes will progressively damage enough glomeruli to cause a fall in GFR, producing renal failure. Multiple studies have noted that the higher the 24-h urine protein excretion, the more rapid is the decline in GFR.

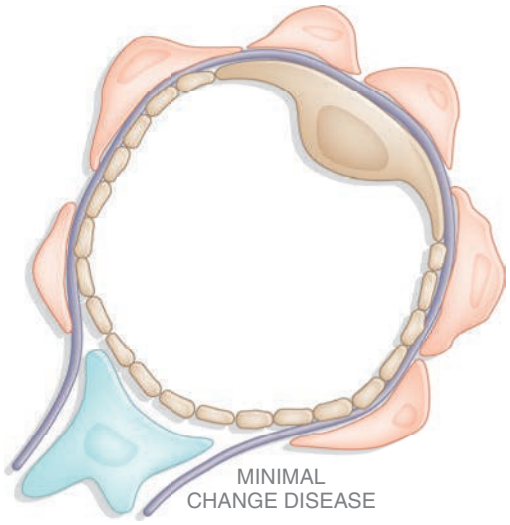
Therapies for various causes of nephrotic syndrome are noted under individual disease headings below. In general, all patients with hypercholesterolemia secondary to nephrotic syndrome should be treated with lipid-lowering agents because they are at increased risk for cardiovascular disease. Edema secondary to salt and water retention can be controlled with the judicious use of diuretics, avoiding intravascular volume depletion. Venous complications secondary to the hypercoagulable state associated with nephrotic syndrome can be treated with anticoagulants. The losses of various serum binding proteins, such as thyroid-binding globulin, lead to alterations in functional tests. Lastly, proteinuria itself is hypothesized to be nephrotoxic, and treatment of proteinuria with inhibitors of the renin-angiotensin system can lower urinary protein excretion.

MINIMAL CHANGE DISEASE

MCD, sometimes known as *nil lesion*, causes 70–90% of nephrotic syndrome in childhood but only 10–15% of nephrotic syndrome in adults. MCD usually presents as a primary renal disease but can be associated with several other conditions, including Hodgkin's disease, allergies, or use of nonsteroidal anti-inflammatory agents; significant interstitial nephritis often accompanies cases associated with nonsteroidal drug use. MCD on renal biopsy shows no obvious glomerular lesion by light microscopy and is negative for deposits by immunofluorescent microscopy, or occasionally shows small amounts of IgM in the mesangium **(see Fig. A3-1). (See Glomerular Schematic 4.)** Electron microscopy, however, consistently demonstrates an effacement of the foot processes supporting the epithelial podocytes with weakening of slit-pore membranes. The pathophysiology of this lesion is uncertain. Most agree there is a circulating cytokine, perhaps related to a T cell response that alters capillary charge and podocyte integrity. The evidence for cytokine-related immune injury is circumstantial and is suggested by the presence of preceding allergies, altered cell-mediated immunity during viral infections, and the high frequency of remissions with steroids.

MCD presents clinically with the abrupt onset of edema and nephrotic syndrome accompanied by acellular urinary sediment. Average urine protein excretion reported in 24 h is 10 g with severe hypoalbuminemia. Less common clinical features include hypertension (30% in children, 50% in adults), microscopic hematuria (20% in children, 33% in adults), atopy or allergic symptoms (40% in children, 30% in adults), and decreased renal function (<5% in children, 30% in adults). The appearance of acute renal failure in adults is often seen more commonly in patients with low serum albumin and intrarenal edema

Glomerular schematic 4



(nephrosarca) that is responsive to intravenous albumin and diuretics. This presentation must be distinguished from acute renal failure secondary to hypovolemia. Acute tubular necrosis and interstitial inflammation are also reported. In children, the abnormal urine principally contains albumin with minimal amounts of higher-molecular-weight proteins, and is sometimes called *selective proteinuria*. Although up to 30% of children have a spontaneous remission, all children today are treated with steroids; only children who are nonresponders are biopsied in this setting. Primary responders are patients who have a complete remission (<0.2 mg/24 h of proteinuria) after a single course of prednisone; steroid-dependent patients relapse as their steroid dose is tapered. Frequent relapsers have two or more relapses in the 6 months following taper, and steroid-resistant patients fail to respond to steroid therapy. Adults are not considered steroid-resistant until after 4 months of therapy. Ninety to 95% of children will develop a complete remission after 8 weeks of steroid therapy, and 80–85% of adults will achieve complete remission, but only after a longer course of 20–24 weeks. Patients with steroid resistance may have FSGS on repeat biopsy. Some hypothesize that if the first renal biopsy does not have a sample of deeper corticomedullary glomeruli, then the correct diagnosis of FSGS may be missed.

Relapses occur in 70–75% of children after the first remission, and early relapse predicts multiple subsequent relapses, as do high levels of basal proteinuria. The frequency of relapses decreases after puberty. There is an increased risk of relapse following the rapid tapering of steroids in all groups. Relapses are less common in adults but are more resistant to subsequent therapy. Prednisone is first-line therapy, either given daily or on alternate days. Other immunosuppressive drugs, such as cyclophosphamide, chlorambucil, and mycophenolate mofetil, are saved for frequent relapsers, steroid-dependent patients, or steroid-resistant patients. Cyclosporine can induce remission, but relapse is also common when cyclosporine is withdrawn. The long-term prognosis in adults is less favorable when acute renal failure or steroid resistance occurs.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

FSGS refers to a pattern of renal injury characterized by segmental glomerular scars that involve some but not all glomeruli; the clinical findings of FSGS largely manifest as proteinuria. When the secondary causes of FSGS are eliminated **(Table 308-5)**, the remaining patients are considered to have primary FSGS. The incidence of this disease is increasing, and it now represents up to one-third of cases of nephrotic syndrome in adults and one-half of cases of nephrotic syndrome in African Americans, in whom it is seen more commonly. The pathogenesis of FSGS is probably multifactorial. Possible mechanisms include a T cell–mediated circulating permeability factor, increased soluble urokinase receptor levels, TGF-β–mediated cellular proliferation and

TABLE 308-5 Focal Segmental Glomerulosclerosis

Primary focal segmental glomerulosclerosis
Secondary focal segmental glomerulosclerosis
Viruses: HIV/hepatitis B/parvovirus
Hypertensive nephropathy
Reflux nephropathy
Cholesterol emboli
Drugs: Heroin/analgesics/bisphosphonates/ecstasy
Oligomeganephronia
Renal dysgenesis
Alport's syndrome
Sickle cell disease
Lymphoma
Radiation nephritis
Familial podocytopathies
NPHS1 mutation/nephrin
NPHS2 mutation/podocin
TRPC6 mutation/cation channel
ACTN4 mutation/actinin
α-Galactosidase A deficiency/Fabry's disease
N acetylneuraminic acid hydrolase deficiency/nephrosialidosis

matrix synthesis, and podocyte abnormalities associated with genetic mutations. Risk polymorphisms at the *APOL1* locus encoding apolipoprotein L1 expressed in podocytes substantially explain the increased burden of FSGS among African Americans with or without HIV-associated disease.

The pathologic changes of FSGS are most prominent in glomeruli located at the corticomedullary junction **(see Fig. A3-2)**, so if the renal biopsy specimen is from superficial tissue, the lesions can be missed, which sometimes leads to a misdiagnosis of MCD. In addition to focal and segmental scarring, other variants have been described, including cellular lesions with *endocapillary hypercellularity* and heavy proteinuria; *collapsing glomerulopathy* **(see Fig. A3-3)** with segmental or global glomerular collapse and a rapid decline in renal function; a hilar stalk lesion **(see Fig. A3-4)**; or the *glomerular tip lesion* **(see Fig. A3-5)**, which may have a better prognosis. **(See Glomerular Schematic 5.)**

FSGS can present with hematuria, hypertension, any level of proteinuria, or renal insufficiency. Nephrotic-range proteinuria, African-American race, and renal insufficiency are associated with a poor outcome, with 50% of patients reaching renal failure in 6–8 years. FSGS rarely remits spontaneously, but treatment-induced remission of proteinuria significantly improves prognosis. Treatment of patients with *primary FSGS* should include inhibitors of the renin-angiotensin system. Based on retrospective studies, patients with nephrotic-range proteinuria can be treated with steroids but respond far less often and after a longer course of therapy than patients with MCD. Proteinuria remits in only 20–45% of patients receiving a course of steroids over 6–9 months. Limited evidence suggests the use of cyclosporine in steroid-responsive patients helps ensure remissions. Relapse frequently occurs after cessation of cyclosporine therapy, and cyclosporine itself can lead to a deterioration of renal function due to its nephrotoxic effects. A role for other agents that suppress the immune system such as rituximab or mycophenolate mofetil has not been firmly established. Primary FSGS recurs in 25–40% of patients given allografts at ESRD, leading to graft loss in half of those cases. In recurrent post-transplant FSGS many patients will achieve a full or partial remission with plasmapheresis. The treatment of *secondary FSGS* typically involves treating

Glomerular schematic 5

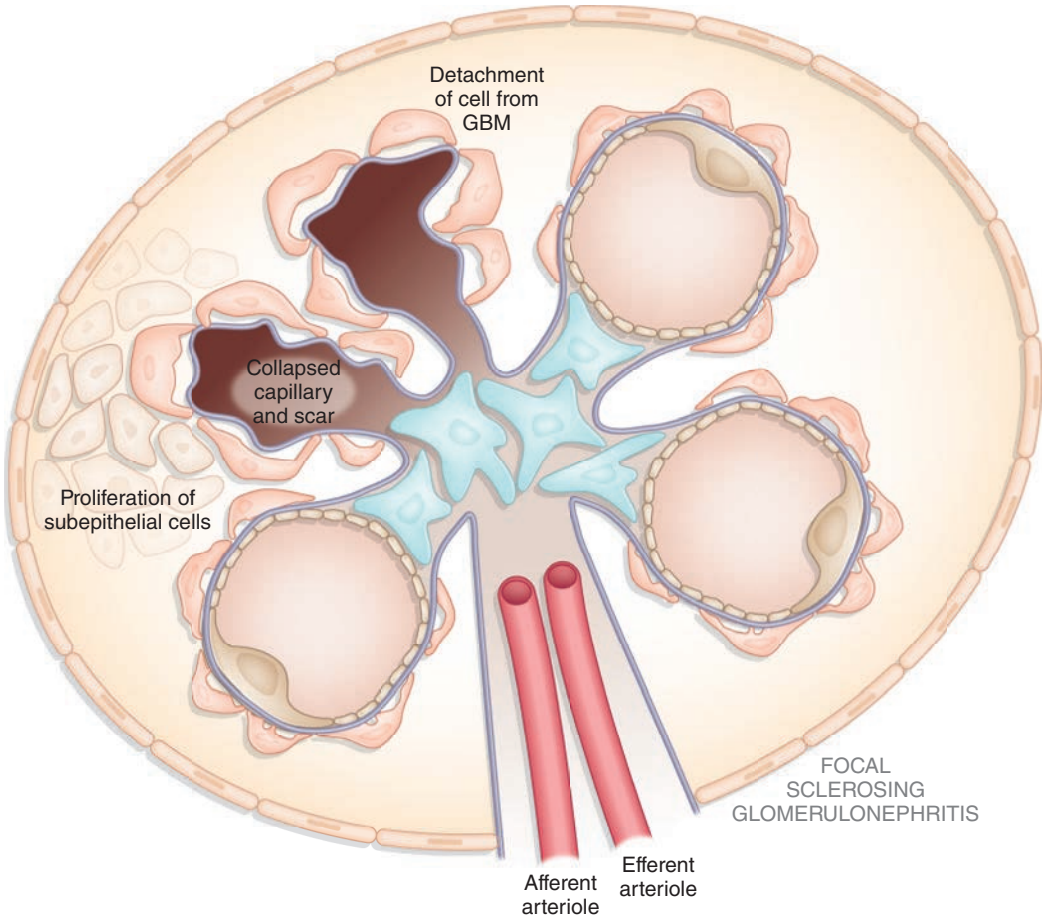


TABLE 308-6 Membranous Glomerulonephritis

Primary/idiopathic membranous glomerulonephritis
Secondary membranous glomerulonephritis
Infection: Hepatitis B and C, syphilis, malaria, schistosomiasis, leprosy, filariasis
Cancer: Breast, colon, lung, stomach, kidney, esophagus, neuroblastoma
Drugs: Gold, mercury, penicillamine, nonsteroidal anti-inflammatory agents, probenecid
Autoimmune diseases: Systemic lupus erythematosus, rheumatoid arthritis, primary biliary cirrhosis, dermatitis herpetiformis, bullous pemphigoid, myasthenia gravis, Sjögren's syndrome, Hashimoto's thyroiditis
Other systemic diseases: Fanconi's syndrome, sickle cell anemia, diabetes, Crohn's disease, sarcoidosis, Guillain-Barré syndrome, Weber-Christian disease, angiofollicular lymph node hyperplasia

the underlying cause and controlling proteinuria. There is no role for steroids or other immunosuppressive agents in secondary FSGS.

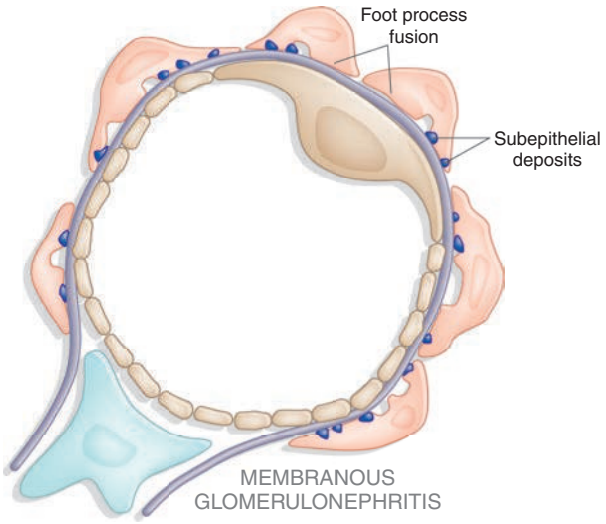
MEMBRANOUS GLOMERULONEPHRITIS

MGN, or *membranous nephropathy* as it is sometimes called, accounts for ~20% of cases of nephrotic syndrome in adults, with a peak incidence between the ages of 30 and 50 years and a male to female ratio of 2:1. IMN is rare in childhood and the most common cause of nephrotic syndrome in the elderly. In 20–30% of cases, MGN is secondary and is associated with a malignancy (solid tumors of the breast, lung, colon), infection (hepatitis B, syphilis, malaria, schistosomiasis), rheumatologic disorders like lupus, rheumatoid arthritis, IgG4 diseases or drug exposure **(Table 308-6)**.

Uniform thickening of the basement membrane along the peripheral capillary loops is seen by light microscopy on renal biopsy **(see Fig. A3-7)**; this thickening needs to be distinguished from that seen in diabetes and amyloidosis. **(See Glomerular Schematic 6.)** Immunofluorescence demonstrates diffuse granular deposits of IgG and C_3, and electron microscopy typically reveals electron-dense subepithelial deposits. While different stages (I–V) of progressive membranous lesions have been described, some published analyses indicate the degree of tubular atrophy or interstitial fibrosis is more predictive of progression than is the stage of glomerular disease. The presence of subendothelial deposits or the presence of tubuloreticular inclusions strongly points to a diagnosis of membranous lupus nephritis, which may precede the extrarenal manifestations of lupus. In 70% of cases of IMN, autoantibodies against the M-type phospholipase A_2 receptor circulate and bind to a conformational epitope present in the PLA2R on human podocytes, producing characteristic in situ deposits. 5–10% of IMN patients alternatively have autoantibodies to thrombospondin type-1 domain containing 7A. Both antigens co-localize within glomerular subepithelial deposits with IgG4 (PLA2R). Other renal diseases do not involve these autoantibodies. In most cases of secondary membranous nephropathy, these autoantibodies are absent with rare reports of autoantibodies to PLA2R in membranous glomerulopathy associated with hepatitis B and sarcoidosis. Circulating deposits and glomerular deposits of these autoantibodies have correlated with the likelihood of a spontaneous remission, severity of IMN, and the response to therapy. Eighty percent of patients with MGN present with nephrotic syndrome and nonselective proteinuria. Microscopic hematuria is seen but less commonly than in IgA nephropathy or FSGS. Spontaneous remissions occur in 20–33% of patients and often occur late in the course which make treatment decisions difficult. Low or absent levels of autoantibodies to PLA2R assist in predicting both spontaneous and treatment associated remissions. One-third of patients continue to have relapsing nephrotic syndrome but maintain normal renal function, and approximately another third of patients develop renal failure or die from the complications of nephrotic syndrome. Male gender, older age, hypertension, and the persistence of proteinuria are associated with worse prognosis. Although thrombotic complications are a feature of all nephrotic syndromes, MGN has the highest reported incidences of renal vein thrombosis, pulmonary embolism, and deep-vein thrombosis. Prophylactic anticoagulation is controversial but has been recommended for patients with severe or prolonged proteinuria in the absence of risk factors for bleeding.

In addition to the treatment of edema, dyslipidemia, and hypertension, inhibition of the renin-angiotensin system is recommended. Therapy with immunosuppressive drugs is also recommended for patients with primary MGN and persistent proteinuria (>3.0 g/24 h). The choice of immunosuppressive drugs for therapy is controversial, but current recommendations are to treat with steroids and cyclophosphamide, chlorambucil, mycophenolate mofetil, or cyclosporine or rituximab, an anti-CD20 antibody directed at B cells.

Glomerular schematic 6



DIABETIC NEPHROPATHY

Diabetic nephropathy is the single most common cause of chronic renal failure in the United States, accounting for 45% of patients receiving renal replacement therapy, and is a rapidly growing problem worldwide. The dramatic increase in the number of patients with diabetic nephropathy reflects the epidemic increase in obesity, metabolic syndrome, and type 2 diabetes mellitus. Approximately 40% of patients with types 1 or 2 diabetes develop nephropathy, but due to the higher prevalence of type 2 diabetes (90%) compared to type 1 (10%), the majority of patients with diabetic nephropathy have type 2 disease. Renal lesions are more common in African-American, Native American, Polynesian, and Maori populations. Risk factors for the development of diabetic nephropathy include hyperglycemia, hypertension, dyslipidemia, smoking, a family history of diabetic nephropathy, and gene polymorphisms affecting the activity of the renin-angiotensin-aldosterone axis.

Within 1–2 years after the onset of clinical diabetes, morphologic changes appear in the kidney. Thickening of the GBM is a sensitive indicator for the presence of diabetes but correlates poorly with the presence or absence of clinically significant nephropathy. The composition of the GBM is altered notably with a loss of heparan sulfate moieties that form the negatively charged filtration barrier. This change results in increased filtration of serum proteins into the urine, predominately negatively charged albumin. The expansion of the mesangium due to the accumulation of extracellular matrix correlates with the clinical manifestations of diabetic nephropathy **(see stages in Fig. A3-20)**. This expansion in mesangial matrix is associated with the development of *mesangial sclerosis*. Some patients also develop eosinophilic, PAS^+ nodules called *nodular glomerulosclerosis* or *Kimmelstiel-Wilson nodules*. Immunofluorescence microscopy often reveals the nonspecific deposition of IgG (at times in a linear pattern) or complement staining without immune deposits on electron microscopy. Prominent vascular changes are frequently seen with hyaline and hypertensive arteriosclerosis. This is associated with varying degrees of chronic glomerulosclerosis and

tubulointerstitial changes. Renal biopsies from patients with types 1 and 2 diabetes are largely indistinguishable.

These pathologic changes are the result of a number of postulated factors. Multiple lines of evidence support an important role for increases in glomerular capillary pressure (intraglomerular hypertension) in alterations in renal structure and function. Direct effects of hyperglycemia on the actin cytoskeleton of renal mesangial and vascular smooth-muscle cells as well as diabetes-associated changes in circulating factors such as atrial natriuretic factor, angiotensin II, and insulin-like growth factor (IGF) may account for this. Sustained glomerular hypertension increases matrix production, alterations in the GBM with disruption in the filtration barrier (and hence proteinuria), and glomerulosclerosis. A number of factors have also been identified that alter matrix production, including the accumulation of advanced glycosylation end products, circulating factors including growth hormone, IGF-I, angiotensin II, connective tissue growth factor, TGF-β, and dyslipidemia.

The natural history of diabetic nephropathy in patients with types 1 and 2 diabetes is similar. However, since the onset of type 1 diabetes is readily identifiable and the onset of type 2 diabetes is not, a patient newly diagnosed with type 2 diabetes may present with *advanced diabetic nephropathy*. At the onset of diabetes, renal hypertrophy and glomerular hyperfiltration are present. The degree of glomerular hyperfiltration correlates with the subsequent risk of clinically significant nephropathy. In the ~40% of patients with diabetes who develop diabetic nephropathy, the earliest manifestation is an increase in albuminuria detected by sensitive radioimmunoassay. Albuminuria in the range of 30–300 mg/24 h is called *microalbuminuria* (Table 308-1). Microalbuminuria appears 5–10 years after the onset of diabetes. It is currently recommended to test patients with type 1 disease for microalbuminuria 5 years after diagnosis of diabetes and yearly thereafter and, because the time of onset of type 2 diabetes is often unknown, to test type 2 patients at the time of diagnosis of diabetes and yearly thereafter.

Patients with small increases in albuminuria increase their levels of urinary albumin excretion, typically reaching dipstick positive levels of proteinuria (>300 mg albuminuria) 5–10 years after the onset of early albuminuria. Microalbuminuria is a potent risk factor for cardiovascular events and death in patients with type 2 diabetes. Many patients with type 2 diabetes and microalbuminuria succumb to cardiovascular events before they progress to proteinuria or renal failure. Proteinuria in frank diabetic nephropathy can be variable, ranging from 500 mg to 25 g/24 h, and is often associated with nephrotic syndrome. More than 90% of patients with type 1 diabetes and nephropathy have diabetic retinopathy, so the absence of retinopathy in type 1 patients with proteinuria should prompt consideration of a diagnosis other than diabetic nephropathy; only 60% of patients with type 2 diabetes with nephropathy have diabetic retinopathy. There is a significant correlation between the presence of retinopathy and the presence of Kimmelstiel-Wilson nodules **(see Fig. A3-20)**. Also, characteristically, patients with advanced diabetic nephropathy have normal to enlarged kidneys, in contrast to many other glomerular diseases where kidney size is usually decreased. Using the above epidemiologic and clinical data, and in the absence of other clinical or serologic data suggesting another disease, diabetic nephropathy is usually diagnosed without a renal biopsy. After the onset of proteinuria, renal function inexorably declines, with 50% of patients reaching renal failure over another 5–10 years; thus, from the earliest stages of microalbuminuria, it usually takes 10–20 years to reach ESRD. However, up to 20–25% of patients with type 2 diabetes and chronic kidney disease have never had albuminuria documented. It is not known if this represents an altered natural history of diabetic nephropathy or another kidney disease that happens to occur in a patient with diabetes. Once renal failure appears, survival on dialysis is shorter for patients with diabetes compared to other dialysis patients. Survival is best for patients who receive a transplant from a living related donor.

Good evidence supports the benefits of blood sugar and blood pressure control as well as inhibition of the renin-angiotensin system in retarding the progression of diabetic nephropathy. In patients with type 1 diabetes, intensive control of blood sugar clearly prevents the development or progression of diabetic nephropathy. The evidence for benefit of intensive blood glucose control in patients with type 2 diabetes is less certain, with current studies reporting conflicting results.

Controlling systemic blood pressure decreases renal and cardiovascular adverse events in this high-risk population. The vast majority of patients with diabetic nephropathy require three or more antihypertensive drugs including ACE inhibitors or angiotensin receptor blockers (ARB) to achieve this goal. Drugs that inhibit the renin-angiotensin system, independent of their effects on systemic blood pressure, have been shown in numerous large clinical trials to slow the progression of diabetic nephropathy at early (microalbuminuria) and late (proteinuria with reduced glomerular filtration) stages. Since angiotensin II increases efferent arteriolar resistance and, hence, glomerular capillary pressure, one key mechanism for the efficacy of inhibitors of the renin angiotensin system is reducing glomerular hypertension. Evidence suggests increased risk for cardiovascular adverse events with little evidence of efficacy in some patients with a combination of two drugs (ACE inhibitors, ARBs, or renin inhibitors) that suppress several components of the renin-angiotensin system. Ongoing trials are examining the hypotheses that other agents may be of benefit including sodium glucose transport 2 inhibitors, endothelin antagonists, and aldosterone antagonists.

GLOMERULAR DEPOSITION DISEASES

Plasma cell dyscrasias producing excess light chain immunoglobulin sometimes lead to the formation of glomerular and tubular deposits that cause heavy proteinuria and renal failure; the same is true for the accumulation of serum amyloid A protein fragments seen in several inflammatory diseases. This broad group of proteinuric patients has *glomerular deposition disease*.

Light Chain Deposition Disease The biochemical characteristics of nephrotoxic light chains produced in patients with light chain malignancies often confer a specific pattern of renal injury; that of either *cast nephropathy* **(see Fig. A3-17)**, which causes renal failure but not heavy proteinuria or amyloidosis, or light chain deposition disease **(see Fig. A3-16)**, which produces nephrotic syndrome with renal failure. These latter patients produce kappa light chains that do not have the biochemical features necessary to form amyloid fibrils. Instead, they self-aggregate and form granular deposits along the glomerular capillary and mesangium, tubular basement membrane, and Bowman's capsule. When predominant in glomeruli, nephrotic syndrome develops, and about 70% of patients progress to dialysis. Light-chain deposits are not fibrillar and do not stain with Congo red, but they are easily detected with anti–light chain antibody using immunofluorescence or as granular deposits on electron microscopy. A combination of the light chain rearrangement, self-aggregating properties at neutral pH, and abnormal metabolism probably contribute to the deposition. Treatment for light chain deposition disease is treatment of the primary disease and, if possible, autologous stem cell transplantation.

Renal Amyloidosis Most *renal amyloidosis* is either the result of primary fibrillar deposits of immunoglobulin light chains known as amyloid L (AL), or secondary to fibrillar deposits of serum amyloid A (AA) protein fragments **(Chap. 108)**. Even though both occur for different reasons, their clinicopathophysiology is quite similar and will be discussed together. Amyloid infiltrates the liver, heart, peripheral nerves, carpal tunnel, upper pharynx, and kidney, producing restrictive cardiomyopathy, hepatomegaly, macroglossia, and heavy proteinuria sometimes associated with renal vein thrombosis. In systemic AL amyloidosis, also called *primary amyloidosis,* light chains produced in excess by clonal plasma cell dyscrasias are made into fragments by macrophages so they can self-aggregate at acid pH. A disproportionate number of these light chains (75%) are of the *lambda* class. About 10% of these patients have overt myeloma with lytic bone lesions and infiltration of the bone marrow with >30% plasma cells; nephrotic syndrome is common, and about 20% of patients progress to dialysis. AA amyloidosis is sometimes called *secondary amyloidosis* and also presents as nephrotic syndrome. It is due to deposition of β-pleated sheets of

serum amyloid A protein, an acute phase reactant whose physiologic functions include cholesterol transport, immune cell attraction, and metalloproteases activation. Forty percent of patients with AA amyloid have rheumatoid arthritis, and another 10% have ankylosing spondylitis or psoriatic arthritis; the rest derive from other lesser causes. Less common in Western countries but more common in Mediterranean regions, particularly in Sephardic and Iraqi Jews, is familial Mediterranean fever (FMF). FMF is caused by a mutation in the gene encoding pyrin, whereas Muckle-Wells syndrome, a related disorder, results from a mutation in cryopyrin; both proteins are important in the apoptosis of leukocytes early in inflammation; such proteins with pyrin domains are part of a pathway called the *inflammasome*. Receptor mutations in tumor necrosis factor receptor 1 (TNFR1)-associated periodic syndrome also produce chronic inflammation and secondary amyloidosis. Fragments of serum amyloid A protein increase and self-aggregate by attaching to receptors for advanced glycation end products in the extracellular environment; nephrotic syndrome is common, and about 40–60% of patient's progress to dialysis. AA and AL amyloid fibrils are detectable with Congo red or in more detail with electron microscopy **(see Fig. A3-15)**. Serum-free light chain nephelometry assays are useful in the early diagnosis and follow-up of disease progression. Biopsy of involved liver or kidney is diagnostic 90% of the time when the pretest probability is high; abdominal fat pad aspirates are positive about 70% of the time, but apparently less so when looking for AA amyloid. Amyloid deposits are distributed along blood vessels and in the mesangial regions of the kidney. The treatment for primary amyloidosis, melphalan, and autologous hematopoietic stem cell transplantation can delay the course of disease in about 30% of patients. Secondary amyloidosis is also relentless unless the primary disease can be controlled. Some new drugs in development that disrupt the formation of fibrils may be available in the future.

Fibrillary-Immunotactoid Glomerulopathy Fibrillary-immunotactoid glomerulopathy is a rare (<1.0% of renal biopsies), morphologically defined disease characterized by glomerular accumulation of nonbranching randomly arranged fibrils. Some classify amyloid and nonamyloid fibril-associated renal diseases all as fibrillary glomerulopathies with immunotactoid glomerulopathy reserved for nonamyloid fibrillary disease not associated with a systemic illness. Others define fibrillary glomerulonephritis as a nonamyloid fibrillary disease with fibrils 12–24 nm and immunotactoid glomerulonephritis with fibrils >30 nm. In either case, fibrillar/microtubular deposits of oligoclonal or oligotypic immunoglobulins and complement appear in the mesangium and along the glomerular capillary wall. Congo red stains are negative. The cause of this "nonamyloid" glomerulopathy is mostly idiopathic; reports of immunotactoid glomerulonephritis describe an occasional association with chronic lymphocytic leukemia or B cell lymphoma. Both disorders appear in adults in the fourth decade with moderate to heavy proteinuria, hematuria, and a wide variety of histologic lesions, including DPGN, MPGN, MGN, or mesangioproliferative glomerulonephritis. Nearly half of patients develop renal failure over a few years. There is no consensus on treatment of this uncommon disorder. The disease has been reported to recur following renal transplantation in a minority of cases.

FABRY'S DISEASE

Fabry's disease is an X-linked inborn error of globotriaosylceramide metabolism secondary to deficient lysosomal α-galactosidase A activity, resulting in excessive intracellular storage of globotriaosylceramide. Affected organs include the vascular endothelium, heart, brain, and kidneys. Classically, Fabry's disease presents in childhood in males with acroparesthesias, angiokeratoma, and hypohidrosis. Over time male patients develop cardiomyopathy, cerebrovascular disease, and renal injury, with an average age of death around 50 years of age. Hemizygotes with hypomorphic mutations sometimes present in the fourth to sixth decade with single-organ involvement. Rarely, dominant-negative α-galactosidase A mutations or female heterozygotes with unfavorable X inactivation present with mild single-organ involvement. Rare females develop severe manifestations including renal failure but do so later in life than males. Renal biopsy reveals enlarged glomerular visceral epithelial cells packed with small clear vacuoles containing globotriaosylceramide; vacuoles may also be found in parietal and tubular epithelia **(see Fig. A3-18)**. These vacuoles of electron-dense materials in parallel arrays (zebra bodies) are easily seen on electron microscopy. Ultimately, renal biopsies reveal FSGS. The nephropathy of Fabry's disease typically presents in the third decade as mild to moderate proteinuria, sometimes with microscopic hematuria or nephrotic syndrome. Urinalysis may reveal oval fat bodies and birefringent glycolipid globules under polarized light (Maltese cross). Renal biopsy is necessary for definitive diagnosis. Progression to renal failure occurs by the fourth or fifth decade. Treatment with inhibitors of the renin-angiotensin system is recommended. Treatment with recombinant α-galactosidase A clears microvascular endothelial deposits of globotriaosylceramide from the kidneys, heart, and skin. In patients with advanced organ involvement including chronic kidney disease, progression of disease occurs despite enzyme replacement therapy. Variable responses to enzyme therapy may be due to the occurrence of neutralizing antibodies or differences in uptake of the enzyme. Graft and patient survival following renal transplantation in patients with Fabry's are similar to other causes of ESRD.

PULMONARY-RENAL SYNDROMES

Several diseases can present with catastrophic hemoptysis and glomerulonephritis associated with varying degrees of renal failure. The usual causes include Goodpasture's syndrome, granulomatosis with polyangiitis, microscopic polyangiitis, Churg-Strauss vasculitis, and, rarely, Henoch-Schönlein purpura or cryoglobulinemia. Each of these diseases can also present without hemoptysis and are discussed in detail earlier in "Acute Nephritic Syndromes." **(See Glomerular Schematic 7.)** Pulmonary bleeding in this setting is life-threatening and often results in airway intubation, and acute renal failure requires dialysis. Diagnosis is difficult initially because biopsies and serologic testing take time. Treatment with plasmapheresis and methylprednisolone is often empirical and temporizing until results of testing are available.

BASEMENT MEMBRANE SYNDROMES

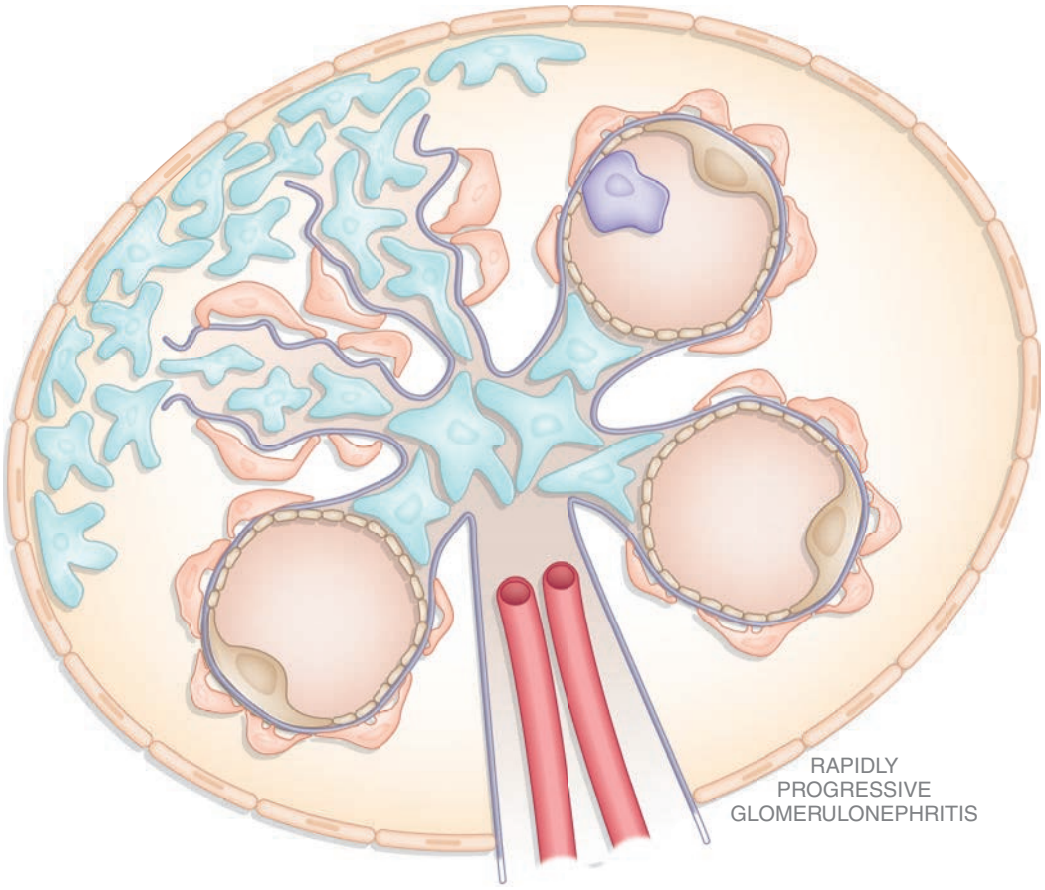
All kidney epithelia, including podocytes, rest on basement membranes assembled into a planar surface through the interweaving of collagen IV with laminins, nidogen, and sulfated proteoglycans. Structural abnormalities in GBM associated with hematuria are characteristic of several familial disorders related to the expression of collagen IV genes. The extended family of collagen IV contains six chains, which are expressed in different tissues at different stages of embryonic development. All epithelial basement membranes early in human development are composed of interconnected triple-helical protomers rich in α1.α1.α2(IV) collagen. Some specialized tissues undergo a developmental switch replacing α1.α1.α2(IV) protomers with an α3.α4.α5(IV) collagen network; this switch occurs in the kidney (glomerular and tubular basement membrane), lung, testis, cochlea, and eye, while an α5.α5.α6(IV) network appears in skin, smooth muscle, and esophagus and along Bowman's capsule in the kidney. This switch probably occurs because the α3.α4.α5(IV) network is more resistant to proteases and ensures the structural longevity of critical tissues. When basement membranes are the target of glomerular disease, they produce moderate proteinuria, some hematuria, and progressive renal failure.

ANTI-GBM DISEASE

Autoimmune disease where antibodies are directed against the α3 NC1 domain of collagen IV produces an *anti-GBM disease* often associated with RPGN and/or a pulmonary-renal syndrome called *Goodpasture's syndrome*. Discussion of this disease is covered earlier in "Acute Nephritic Syndromes."

ALPORT'S SYNDROME

Classically, patients with Alport's syndrome develop hematuria, thinning and splitting of the GBMs, mild proteinuria (<1–2 g/24 h), which appears late in the course, followed by chronic glomerulosclerosis leading to renal failure in association with sensorineural deafness.



Some patients develop lenticonus of the anterior lens capsule, "dot and fleck" retinopathy, and rarely, mental retardation or leiomyomatosis. Approximately 85% of patients with Alport's syndrome have an X-linked inheritance of mutations in the α5(IV) collagen chain on chromosome Xq22–24. Female carriers have variable penetrance depending on the type of mutation or the degree of mosaicism created by X inactivation. Fifteen percent of patients have autosomal recessive disease of the α3(IV) or α4(IV) chains on chromosome 2q35–37. Rarely, some kindred have an autosomal dominant inheritance of dominant-negative mutations in α3(IV) or α4(IV) chains.

Pedigrees with the X-linked syndrome are quite variable in their rate and frequency of tissue damage leading to organ failure. Seventy percent of patients have the juvenile form with nonsense or missense mutations, reading frame shifts, or large deletions and generally develop renal failure and sensorineural deafness by age 30. Patients with splice variants, exon skipping, or missense mutations of α-helical glycines generally deteriorate after the age of 30 (adult form) with mild or late deafness. Early severe deafness, lenticonus, or proteinuria suggests a poorer prognosis. Usually females from X-linked pedigrees have only microhematuria, but up to 25% of carrier females have been reported to have more severe renal manifestations. Pedigrees with the autosomal recessive form of the disease have severe early disease in both females and males with asymptomatic parents.

Clinical evaluation should include a careful eye examination and hearing tests. However, the absence of extrarenal symptoms does not rule out the diagnosis. Since α5(IV) collagen is expressed in the skin, some X-linked Alport's patients can be diagnosed with a skin biopsy revealing the lack of the α5(IV) collagen chain on immunofluorescent analysis. Patients with mutations in α3(IV) or α4(IV) require a renal biopsy. Genetic testing can be used for the diagnosis of Alport's syndrome and the demonstration of the mode of inheritance. Early in their disease, Alport's patients typically have thin basement membranes on renal biopsy **(see Fig. A3-19)**, which thicken over time into multilamellations surrounding lucent areas that often contain granules of varying density—the so-called split basement membrane. In any Alport's kidney, there are areas of thinning mixed with splitting of the GBM. Tubules drop out, glomeruli scar, and the kidney eventually succumbs to interstitial fibrosis. All affected members of a family with X-linked Alport's syndrome should be identified and followed, including mothers of affected males. Primary treatment is control of systemic hypertension and use of ACE inhibitors to slow renal progression. Although patients who receive renal allografts usually develop anti-GBM antibodies directed toward the collagen epitopes absent in their native kidney, overt Goodpasture's syndrome is rare and graft survival is good.

THIN BASEMENT MEMBRANE DISEASE

Thin basement membrane disease (TBMD) characterized by persistent or recurrent hematuria is not typically associated with proteinuria, hypertension, or loss of renal function or extrarenal disease. Although not all cases are familial (perhaps a founder effect), it usually presents in childhood in multiple family members and is also called *benign familial hematuria*. Cases of TBMD have genetic defects in type IV collagen but in contrast to Alport behave as an autosomal dominant disorder that in ~40% of families segregates with the *COL(IV) α3/COL(IV) α4* loci. Mutations in these loci can result in a spectrum of disease ranging from TBMD to autosomal dominant or recessive Alport's. The GBM shows diffuse thinning compared to normal values for the patient's age in otherwise normal biopsies **(see Fig. A3-19)**. The vast majority of patients have a benign course.

NAIL-PATELLA SYNDROME

Patients with nail-patella syndrome develop iliac horns on the pelvis and dysplasia of the dorsal limbs involving the patella, elbows, and nails, variably associated with neural-sensory hearing impairment, glaucoma, and abnormalities of the GBM and podocytes, leading to

hematuria, proteinuria, and FSGS. The syndrome is autosomal dominant, with haploinsufficiency for the *LIM* homeodomain transcription factor LMX1B; pedigrees are extremely variable in the penetrance for all features of the disease. LMX1B regulates the expression of genes encoding α3 and α4 chains of collagen IV, interstitial type III collagen, podocin, and CD2AP that help form the slit-pore membranes connecting podocytes. Mutations in the LIM domain region of *LMX1B* associate with glomerulopathy, and renal failure appears in as many as 30% of patients. Proteinuria or isolated hematuria is discovered throughout life, but usually by the third decade, and is inexplicably more common in females. On renal biopsy there is focal sclerosing glomerulonephritis with specific lucent damage to the lamina densa of the GBM, an increase in collagen III fibrils along glomerular capillaries and in the mesangium, and damage to the slit-pore membrane, producing heavy proteinuria not unlike that seen in congenital nephrotic syndrome. Patients with renal failure do well with transplantation.

GLOMERULAR-VASCULAR SYNDROMES

A variety of diseases result in classic vascular injury to the glomerular capillaries. Most of these processes also damage blood vessels elsewhere in the body. The group of diseases discussed here lead to vasculitis, renal endothelial injury, thrombosis, ischemia, and/or lipid-based occlusions.

ATHEROSCLEROTIC NEPHROPATHY

Aging in the developed world is commonly associated with the occlusion of coronary and systemic blood vessels. The reasons for this include obesity, insulin resistance, smoking, hypertension, and diets rich in lipids that deposit in the arterial and arteriolar circulation, producing local inflammation and fibrosis of small blood vessels. When the renal arterial circulation is involved, the glomerular microcirculation is damaged, leading to *chronic nephrosclerosis*. Patients with GFRs <60 mL/min have more cardiovascular events and hospitalizations than those with higher filtration rates. Several aggressive lipid disorders can accelerate this process, but most of the time atherosclerotic progression to chronic nephrosclerosis is associated with poorly controlled hypertension. Approximately 10% of glomeruli are normally sclerotic by age 40, rising to 20% by age 60 and 30% by age 80. Serum lipid profiles in humans are greatly affected by *apolipoprotein E* polymorphisms; the E4 allele is accompanied by increases in serum cholesterol and is more closely associated with atherogenic profiles in patients with renal failure. Mutations in E2 alleles, particularly in Japanese patients, produce a specific renal abnormality called *lipoprotein glomerulopathy* associated with glomerular lipoprotein thrombi and capillary dilation.

HYPERTENSIVE NEPHROSCLEROSIS

Systemic hypertension causes permanent damage to the kidneys in about 6% of patients with elevated blood pressure. As many as 27% of patients with end-stage kidney disease have hypertension as a primary cause. Although there is not a clear correlation between the extent or duration of hypertension and the risk of end-organ damage, *hypertensive nephrosclerosis* is fivefold more frequent in African Americans than whites. Risk alleles associated with *APOL1*, a functional gene for apolipoprotein L1 expressed in podocytes, substantially explains the increased burden of ESRD among African Americans. Associated risk factors for progression to end-stage kidney disease include increased age, male gender, race, smoking, hypercholesterolemia, duration of hypertension, low birth weight, and preexisting renal injury. Kidney biopsies in patients with hypertension, microhematuria, and moderate proteinuria demonstrate arteriolosclerosis, chronic nephrosclerosis, and interstitial fibrosis in the absence of immune deposits **(see Fig. A3-21)**. Today, based on a careful history, physical examination, urinalysis, and some serologic testing, the diagnosis of chronic nephrosclerosis is usually inferred without a biopsy. Recent studies suggest, in the absence of diabetes, adults with hypertension and cardiovascular risk factors benefit from achieving a systolic BP <120 mmHg compared to <140 mmHg. In the presence of kidney disease, most patients begin antihypertensive therapy with two drugs, classically a thiazide diuretic and an ACE inhibitor; most will require three drugs. There is strong evidence in African Americans with hypertensive nephrosclerosis that therapy initiated with an ACE inhibitor can slow the rate of decline in renal function independent of effects on systemic blood pressure. Malignant acceleration of hypertension complicates the course of chronic nephrosclerosis, particularly in the setting of scleroderma or cocaine use **(see Fig. A3-24)**. The hemodynamic stress of malignant hypertension leads to fibrinoid necrosis of small blood vessels, thrombotic microangiography, a nephritic urinalysis, and acute renal failure. In the setting of renal failure, chest pain, or papilledema, the condition is treated as a hypertensive emergency.

CHOLESTEROL EMBOLI

Aging patients with clinical complications from atherosclerosis sometimes shower cholesterol crystals into the circulation—either spontaneously or, more commonly, following an endovascular procedure with manipulation of the aorta—or with use of systemic anticoagulation. Spontaneous emboli may shower acutely or shower subacutely and somewhat more silently. Irregular emboli trapped in the microcirculation produce ischemic damage that induces an inflammatory reaction. Depending on the location of the atherosclerotic plaques releasing these cholesterol fragments, one may see cerebral transient ischemic attacks; livedo reticularis in the lower extremities; Hollenhorst plaques in the retina with visual field cuts; necrosis of the toes; and acute glomerular capillary injury leading to FSGS sometimes associated with hematuria, mild proteinuria, and loss of renal function, which typically progresses over a few years. Occasional patients have fever, eosinophilia, or eosinophiluria. A skin biopsy of an involved area may be diagnostic. Since tissue fixation dissolves the cholesterol, one typically sees only residual, biconvex clefts in involved vessels **(see Fig. A3-22)**. There is no therapy to reverse embolic occlusions, and steroids do not help. Controlling blood pressure and lipids and cessation of smoking are usually recommended for prevention.

SICKLE CELL DISEASE

Although individuals with SA-hemoglobin are usually asymptomatic, most will gradually develop hyposthenuria due to subclinical infarction of the renal medulla, thus predisposing them to volume depletion. There is an unexpectedly high prevalence of sickle trait among dialysis patients who are African American. Patients with homozygous SS-sickle cell disease and less commonly SC-sickle cell disease develop chronic vasoocclusive disease in many organs. Polymers of deoxygenated SS-hemoglobin distort the shape of red blood cells. These cells attach to endothelia and obstruct small blood vessels, producing frequent and painful sickle cell crises over time. Vessel occlusions in the kidney produce glomerular hypertension, FSGS, interstitial nephritis, and renal infarction associated with hyposthenuria, microscopic hematuria, and even gross hematuria; some patients also present with MPGN. Renal function can be overestimated due to the increased tubular secretion of creatinine seen in many patients with SS-sickle cell. By the second or third decade of life, persistent vasoocclusive disease in the kidney leads to varying degrees of renal failure, and some patients end up on dialysis. Their prognosis on dialysis is poor and anemia management with erythropoiesis-stimulating agents complicated. Treatment is directed to reducing the frequency of painful crises and administering ACE inhibitors in the hope of delaying a progressive decline in renal function. In sickle cell patients undergoing renal transplantation, renal graft survival is comparable to African Americans in the general transplant population.

THROMBOTIC MICROANGIOPATHIES

Thrombotic thrombocytopenic purpura (TTP) and *hemolytic-uremic syndrome* (HUS) represent a spectrum of thrombotic microangiopathies. TTP and HUS share the general features of idiopathic thrombocytopenic purpura, hemolytic anemia, fever, renal failure, and neurologic disturbances. When patients, particularly children, have more evidence of renal injury, their condition tends to be called HUS. In adults with neurologic disease, it is considered to be TTP. In adults there is often a mixture of both, which is why they are often referred to as having TTP/HUS. On examination of kidney tissue, there is evidence of *glomerular capillary endotheliosis* associated with platelet thrombi, damage to the

capillary wall, and formation of fibrin material in and around glomeruli (see Fig. A3-23). These tissue findings are similar to what is seen in preeclampsia/HELLP (*h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelet count syndrome), malignant hypertension, and the antiphospholipid syndrome. TTP/HUS is also seen in pregnancy; with the use of oral contraceptives or quinine; in renal transplant patients given OKT3 for rejection; in patients taking the calcineurin inhibitors, cyclosporine and tacrolimus, or in patients taking the antiplatelet agents, ticlopidine and clopidogrel; or following HIV infection.

Although there is no agreement on how much they share a final common pathophysiology, two general groups of patients are recognized: childhood HUS associated with enterohemorrhagic diarrhea and TTP/HUS in adults. Childhood HUS is caused by a toxin released by *Escherichia coli* 0157:H7 and occasionally by *Shigella dysenteriae*. This shiga toxin (verotoxin) directly injures endothelia, enterocytes, and renal cells, causing apoptosis, platelet clumping, and intravascular hemolysis by binding to the glycolipid receptors (Gb3). These receptors are more abundant along endothelia in children compared to adults. Shiga toxin also inhibits the endothelial production of ADAMTS13. In familial cases of adult TTP/HUS, there is a genetic deficiency of the ADAMTS13 metalloprotease that cleaves large multimers of von Willebrand's factor. Absent ADAMTS13, these large multimers cause platelet clumping and intravascular hemolysis. An antibody to ADAMTS13 is found in many sporadic cases of adult TTP/HUS, but not all; many patients also have antibodies to the thrombospondin receptor on selected endothelial cells in small vessels or increased levels of plasminogen-activator inhibitor 1 (PAI-1). Patients can be tested for ADAMTS13 activity and, if low, the presence of antibodies to ADAMTS13 distinguishes the deficiency from the immune-mediated disease. Some children with complement protein deficiencies express atypical HUS (aHUS), which can be treated with liver transplant. The treatment of adult TTP/HUS with ADAMTS13 antibodies is daily plasmapheresis, which can be lifesaving. Plasmapheresis with fresh frozen plasma is given until the platelet count rises, but in relapsing patients it normally is continued well after the platelet count improves, and in resistant patients twice-daily exchange may be helpful. Most patients respond within 2 weeks of daily plasmapheresis. Since TTP/HUS often has an autoimmune basis, there is an anecdotal role in relapsing patients for using splenectomy, steroids, immunosuppressive drugs, bortezomib, or rituximab, an anti-CD20 antibody. Patients without antibodies and a genetic deficiency of ADAMTS13 production can potentially be treated with fresh frozen plasma alone. Patients with childhood HUS from infectious diarrhea are not given antibiotics, because antibiotics are thought to accelerate the release of the toxin and the diarrhea is usually self-limited. No intervention appears superior to supportive therapy in children with postdiarrheal HUS.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME (SEE CHAP. 350)

GLOBAL CONSIDERATIONS

INFECTIOUS DISEASE–ASSOCIATED SYNDROMES

A number of infectious diseases will injure the glomerular capillaries as part of a systemic reaction producing an immune response or from direct infection of renal tissue. Evidence of this immune response is collected by glomeruli in the form of immune deposits that damage the kidney, producing moderate proteinuria and hematuria. A high prevalence of many of these infectious diseases in developing countries results in infection-associated renal disease being the most common cause of glomerulonephritis in many parts of the world.

Poststreptococcal Glomerulonephritis This form of glomerulonephritis is one of the classic complications of streptococcal infection. The discussion of this disease can be found earlier, in the section "Acute Nephritic Syndromes."

Subacute Bacterial Endocarditis Renal injury from persistent bacteremia absent the continued presence of a foreign body, regardless of cause, is treated presumptively as if the patient has endocarditis. The discussion of this disease can be found earlier, in the section "Acute Nephritic Syndromes."

Human Immunodeficiency Virus Renal disease is an important complication of HIV disease. The risk of development of ESRD is much higher in HIV-infected African Americans than in HIV-infected whites. About 50% of HIV-infected patients with kidney disease have HIV-associated nephropathy (HIVAN) on biopsy. The lesion in HIVAN is FSGS, characteristically revealing a collapsing glomerulopathy (see Fig. A3-3) with visceral epithelial cell swelling, microcystic dilatation of renal tubules, and tubuloreticular inclusion. Renal epithelial cells express replicating HIV virus, but host immune responses also play a role in the pathogenesis. HIVAN develops almost exclusively in patients of black race origin who have the APOL1 variant. HIVICK, HIV immune complex kidney disease is a group of immune complex-mediated glomerular lesions seen in HIV patients, and on biopsy can look like a constellation of other glomerular lesions, including postinfectious glomerulonephritis, MGN, MPGN, DPGN, MCD, and IgA nephropathy. The HIVICK effect is a complication of active HIV viremia.

HIV patients with FSGS typically present with nephrotic-range proteinuria and hypoalbuminemia, but unlike patients with other etiologies for nephrotic syndrome, they do not commonly have hypertension, edema, or hyperlipidemia. Renal ultrasound also reveals large, echogenic kidneys despite the finding that renal function in some patients declines rapidly. Treatment with inhibitors of the renin-angiotensin system decreases the proteinuria. Effective antiretroviral therapy benefits both the patient and the kidney and improves survival of HIV-infected patients with HIVAN and in some cases HIVICK-associated chronic kidney disease or ESRD. In HIV-infected patients not yet on therapy, the presence of HIVAN is an indication to initiate therapy. Following the introduction of antiretroviral therapy, survival on dialysis for the HIV-infected patient has improved dramatically. Renal transplantations in HIV-infected patients without detectable viral loads or histories of opportunistic infections provide a better survival benefit over dialysis. Following transplantation, patient and graft survival are similar to the general transplant population despite frequent rejections.

Hepatitis B and C Typically, infected patients present with microscopic hematuria, nonnephrotic or nephrotic-range proteinuria, and hypertension. There is a close association between hepatitis B infection and polyarteritis nodosa with vasculitis appearing generally in the first 6 months following infection. Renal manifestations include renal artery aneurysms, renal infarction, and ischemic scars. Alternatively, the hepatitis B carrier state can produce a MGN with predominant IgG1 deposition that is more common in children than adults, or MPGN that is more common in adults than in children. Renal histology is indistinguishable from idiopathic MGN, type I or type 3 MPGN. Viral antigens most commonly, HBeAG, are found in the renal deposits. Cryoglobulinemic glomerulonephritis has also been reported. There are no good treatment guidelines, but interferon α-2b and antiviral agents which consist of either nucleotide or nucleoside reverse transcription inhibitors have been used to some effect. Children have a good prognosis, with 60–65% achieving spontaneous remission within 4 years. In contrast, 30% of adults have renal insufficiency and 10% have renal failure 5 years after diagnosis.

Up to 30% of patients with chronic hepatitis C infection have some renal manifestations. Patients often present with type II mixed cryoglobulinemia, nephrotic syndrome, microscopic hematuria, abnormal liver function tests, depressed C3 levels, anti–hepatitis C virus (HCV) antibodies, and viral RNA in the blood. The renal lesions most commonly seen, in order of decreasing frequency, are cryoglobulinemic glomerulonephritis, MGN, and type I MPGN but PAN, IgA and FSGS have been reported. With the availability of direct-acting antivirals, including ledipasvir/sofosbuvir which can achieve a viral remission in >95% of patients, the prevalence of glomerular disease in HCV patients should decline. These drugs are currently the treatment of choice for patients with HCV-related MPGN or PAN.

Other Viruses Other viral infections are occasionally associated with glomerular lesions, but cause and effect are not well established.

These viral infections and their respective glomerular lesions include: cytomegalovirus producing MPGN or FSGS; influenza and anti-GBM disease; measles-associated endocapillary proliferative glomerulonephritis, with measles antigen in the capillary loops and mesangium; parvovirus causing mild proliferative or mesangioproliferative glomerulonephritis or FSGS; mumps and mesangioproliferative glomerulonephritis; Epstein-Barr virus producing MPGN, diffuse proliferative nephritis, or IgA nephropathy; dengue hemorrhagic fever causing endocapillary proliferative glomerulonephritis; Hanta virus and mesangial proliferative glomerulonephritis and coxsackievirus producing *focal glomerulonephritis* or DPGN.

Syphilis Secondary syphilis, with rash and constitutional symptoms, develops weeks to months after the chancre first appears and occasionally presents with the nephrotic syndrome from MGN caused by subepithelial immune deposits containing treponemal antigens. Other lesions have also rarely been described including interstitial syphilitic nephritis. The diagnosis is confirmed with nontreponemal and treponemal tests for *Treponema pallidum*. The renal lesion responds to treatment with penicillin or an alternative drug, if allergic. Additional testing for other sexually transmitted diseases is an important part of disease management.

Leprosy Despite aggressive eradication programs, ~400,000 new cases of leprosy appear annually worldwide. The diagnosis is best made in patients with multiple skin lesions accompanied by sensory loss in affected areas, using skin smears showing paucibacillary or multibacillary infection (WHO criteria). Leprosy is caused by infection with *Mycobacterium leprae* and can be classified by Ridley-Jopling criteria into various types: tuberculoid, borderline tuberculoid, mid-borderline and borderline lepromatous, and lepromatous. Renal involvement in leprosy is related to the quantity of bacilli in the body, and the kidney is one of the target organs during splanchnic localization. In some series, all cases with borderline lepromatous and lepromatous types of leprosy have various forms of renal involvement including FSGS, mesangioproliferative glomerulonephritis, or renal amyloidosis; much less common are the renal lesions of DPGN and MPGN. Treatment of the infection with multi-drug therapy can reduce the incidence of renal disease or produce remission of the renal disease.

Malaria There are 300–500 million incident cases of malaria each year worldwide, and the kidney is commonly involved. Glomerulonephritis is due to immune complexes containing malarial antigens that are implanted in the glomerulus. In malaria from *P. falciparum*, mild proteinuria is associated with subendothelial deposits, mesangial deposits, and mesangioproliferative glomerulonephritis that usually resolve with treatment. In quartan malaria from infection with *Plasmodium malariae*, children are more commonly affected and renal involvement is more severe. Transient proteinuria and microscopic hematuria can resolve with treatment of the infection. However, resistant nephrotic syndrome with progression to renal failure over 3–5 years does happen, as <50% of patients respond to steroid therapy. Affected patients with nephrotic syndrome have thickening of the glomerular capillary walls, with subendothelial deposits of IgG, IgM, and C_3 associated with a sparse membranoproliferative lesion. The rare mesangioproliferative glomerulonephritis reported with *Plasmodium vivax* or *Plasmodium ovale* typically has a benign course. Acute kidney injury can often complicate these glomerulopathies.

Schistosomiasis Schistosomiasis affects >300 million people worldwide and primarily involves the urinary and gastrointestinal tracts. Glomerular involvement varies with the specific strain of schistosomiasis; *Schistosoma mansoni* is most commonly associated with clinical renal disease, and the glomerular lesions can be classified: Class I is a *mesangioproliferative glomerulonephritis*; class II is an *extracapillary proliferative glomerulonephritis*; class III is a *membranoproliferative glomerulonephritis*; class IV is a *focal segmental glomerulonephritis*; and class V is *amyloidosis*. Classes I–II often remit with treatment of the infection, but classes III and IV lesions are associated with IgA immune deposits and progress despite antiparasitic and/or immunosuppressive therapy.

Other Parasites Renal involvement with toxoplasmosis infections is rare. When it occurs, patients present with nephrotic syndrome and have a histologic picture of MPGN. Fifty percent of patients with leishmaniasis will have mild to moderate proteinuria and microscopic hematuria, but renal insufficiency is rare. Acute DPGN, MGN, and mesangioproliferative glomerulonephritis have all been observed on biopsy. Filariasis and trichinosis are caused by nematodes and are sometimes associated with glomerular injury presenting with proteinuria, hematuria, and a variety of histologic lesions that typically resolve with eradication of the infection.

FURTHER READING

The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia): Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. Lancet 349:1857, 1997.

Kopp JB et al: APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. J Am Soc Nephrol 22:2129, 2011.

Kupin WL: Viral-associated GN: Hepatitis C and HIV. Clin J Am Soc Nephrol 12:1337, 2017.

Lewis EJ et al: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 345:851, 2001.

Pickering MC et al: C_3 glomerulopathy: Consensus report. Kidney Int 84:1079, 2013.

Ronco P, Debiec H: Membranous nephropathy: A fairy tale for immunopathologists, nephrologists and patients. Mol Immunol 68:57, 2015.

309 Polycystic Kidney Disease and Other Inherited Disorders of Tubule Growth and Development

Jing Zhou, Martin R. Pollak

The polycystic kidney diseases are a group of genetically heterogeneous disorders and a leading cause of kidney failure. The autosomal dominant form of polycystic kidney disease (ADPKD) is the most common life-threatening monogenic disease, affecting 12 million people worldwide. The autosomal recessive form of polycystic kidney disease (ARPKD) is rarer but affects the pediatric population. Kidney cysts are often seen in a wide range of syndromic diseases. Recent studies have shown that defects in the structure or function of the primary cilia may underline this group of genetic diseases collectively termed *ciliopathies* **(Table 309-1)**.

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Etiology and Pathogenesis (Fig. 309-1) ADPDK is characterized by progressive formation of epithelial lined cysts in the kidney. Although cysts only occur in 5% of the tubules in the kidney, the enormous growth of these cysts ultimately leads to the loss of normal surrounding tissues and loss of renal function. The cellular defects in ADPKD that have been known for a long time are increased cell proliferation and fluid secretion, decreased cell differentiation, and abnormal extracellular matrix. ADPKD is caused by mutations in *PKD1* and *PKD2* which, respectively, code for polycystin-1 (PC1) and polycystin-2 (PC2). PC1 is a large 11- transmembrane protein that functions like a G-protein coupled receptor. PC2 is a calcium-permeable six transmembrane protein that structurally belongs to the transient

TABLE 309-1 Inherited Diseases Commonly Associated with a Cystic Phenotype

DISEASE	MODE OF INHERITANCE	RENAL ABNORMALITIES	OTHER CLINICAL FEATURES	GENES
Autosomal dominant polycystic kidney disease	AD	Cortical and medullary cysts	Liver, pancreatic cysts, hypertension, subarachnoid hemorrhage	*PKD1, PKD2*
Autosomal recessive polycystic kidney disease	AR	Distal and collecting duct cysts	Oligohydramnios if severe, hypertension, ascending cholangitis, liver fibrosis	*PKHD1*
Medullary cystic kidney (Autosomal dominant tubulointerstital kidney disease)	AD	Small fibrotic kidneys; medullary cysts	In adults, gout	*UMOD* *MUC1* *REN*
Nephronophthisis	AR	Small fibrotic kidneys; medullary cysts	Growth retardation, anemia, (visual loss, liver fibrosis, cerebellar ataxia if associated with another syndrome)	*NPHP1-20, IQCB1, CEP290, GLIS2, RPGRIP1L, NEK8, SDCCAG8, TMEM67, TTC21B*
Senior-Loken syndrome	AR	Renal cysts	Juvenile nephronophthisis, Leber amaurosis	*NPHP1-6, SDCCAG8*
Leber congenital amaurosis	AR	Renal cysts	Visual impairment in first year of life; pigmentary retinopathy	*GUCY2D, RPE65, LCA3-14* (including *LCA10, CEP290*)
Meckel-Gruber syndrome	AR	Cortical and medullary cysts	CNS anomalies, polydactyly, congenital heart defects	*MKS1, TMEM216, TMEM67, CEP290, RPGRIP1L, CC2D2A, TCTN2, B9D1, B9D2, NPHP3*
Bardet-Biedl syndrome	AR	Renal cysts	Obesity, polydactyly, retinitis pigmentosa, anosmia, congenital heart defects, mental retardation	*BBS1, 2, ARL6, BBS4,5, MKKS, BBS7, TTC8, BBS9, 10, TRIM32, BBS12, MKS1, CEP290, C2ORF86; modifiers MKS1, MKS3, CCDC28B*
Oral-facial-digital syndrome type I	AR	Renal cysts	Oral cavity, face, and digit anomalies; CNS abnormalities; cystic kidney disease; X-linked with male lethality, primary ciliary dyskinesia	*OFD1*
Cranioectodermal dysplasia (Sensenbrenner syndrome)	AR	Renal cysts	Skeletal dysplasia; thoracic deformities; polydactyly; renal cysts; retinitis pigmentosa	*IFT80*
Tuberous sclerosis	AD	Renal cysts	Angiomyolipomas; renal cell carcinoma Facial angiofibromas; CNS hamartomas	*TSC1, TSC2*
Von Hippel-Lindau disease	AD	Renal cysts	Renal cell carcinoma, retinal angiomas; CNS hemangioblastomas; pheochromocytomas	*VHL*

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system.

receptor potential (TRP) cation channel family. PC1 and PC2 are widely expressed in almost all tissues and organs. PC1 expression is high in development and low in the adult, whereas PC2 expression is relatively constant. PC1/2 are found on the primary cilium, a hair-like structure present on the apical membrane of a cell, in addition to the cell membranes and cell-cell junctions of tubular epithelial cells. Defects in the primary cilia are linked to a wide spectrum of human diseases, collectively termed ciliopathies. The most common phenotype shared by many ciliopathies is kidney cysts. PC1 and PC2 bind to each other via their respective C-terminal tails to form a receptor-channel complex and regulate each other's function. The PC1/2 protein complex serves as a mechanosensor or chemical sensor and regulates calcium and G-protein signaling. The PC1/2 protein complex may also directly regulate a number of cellular functions including the cell cycle, the actin cytoskeleton, planar cell polarity (PCP), and cell migration. This protein complex has also been implicated in regulating a number of signaling pathways, including Wnt, mammalian target of rapamycin (mTOR), STAT3, cMET, phosphoinositide 3-kinase (PI3K/Akt), G protein–coupled receptor (GPCR), and epidermal growth factor receptor (EGFR), as well as in the localization and activity of cystic fibrosis transmembrane conductance regulator (CFTR). One hypothesis is that loss of ciliary function of PC1 and PC2 leads to aberrant calcium signaling and a subsequent increase of adenylyl cyclase activity and decrease of phosphodiesterase activity, which, in turn, causes increased cellular cAMP. Increased cAMP promotes protein kinase A activity, among other effectors, and, in turn, leads to cyst growth by promoting proliferation and fluid secretion of cyst-lining cells through chloride and aquarporin channels in ADPKD kidneys.

ADPKD is inherited as an autosomal dominant trait with complete penetrance, but variable expressivity. The disease affects all ethnic groups worldwide with an estimated prevalence of 1:1000 to 1:400. Only half of the patients with ADPKD are clinically diagnosed during their lifetime. ADPKD is genetically heterogeneous. The first disease gene (*PKD1*) was localized to the region of the alpha-globin gene on chromosome 16p13 in 1985, and a second disease gene (*PKD2*) locus was mapped to chromosome 4q21-q23 in 1993. Mutations of *PKD1* and *PKD2* are responsible for ~85% and ~15% of ADPKD cases, respectively. However, patients with *PKD2* mutations may be >15% because they tend to have milder clinical disease and, as a result, under-diagnosed. Embryonic lethality of *Pkd1* and *Pkd2* knockout mice suggest human homozygotes may be lethal, thus not clinically recognized.

PKD1 is comprised of 46 exons occupying ~52 kb of genomic DNA. It produces a ~14 kb transcript that encodes polycystin-1, a protein of ~4300 amino acids. A feature of the *PKD1* gene is that the 5′ three-quarters of *PKD1* have been duplicated at six other sites on chromosome 16p, and many of them produce mRNA transcripts, which provides a major challenge for genetic analysis of the duplicated region. *PKD2* is a single-copy gene with 15 exons producing a ~5.3 kb mRNA transcript that encodes polycystin-2, a protein of 968 amino acids. A third gene *GANAB*, encoding the glucosidase IIa subunit, was recently reported to cause ADPKD, but patients with mutations in this gene all appear to have polycystic liver disease, and their kidney disease is milder than that in classic ADPKD.

In ADPKD patients, every cell carries a germline mutant allele of either *PKD1* or *PKD2*. However, cysts develop in only a small fraction of the nephrons. Cysts are thought to originate from clonal growth of single cells that have received a somatic "second hit" mutation in the "normal" allele of the *PKD1* or *PKD2* gene. Accumulating evidence in mouse models now shows that partial loss of function of the second allele of *Pkd1* in a proliferative environment is sufficient for cystogenesis, suggesting that a critical amount of *PKD1* is needed in a cell. Somatic inactivation of the second allele of *Pkd1* in adult mice results

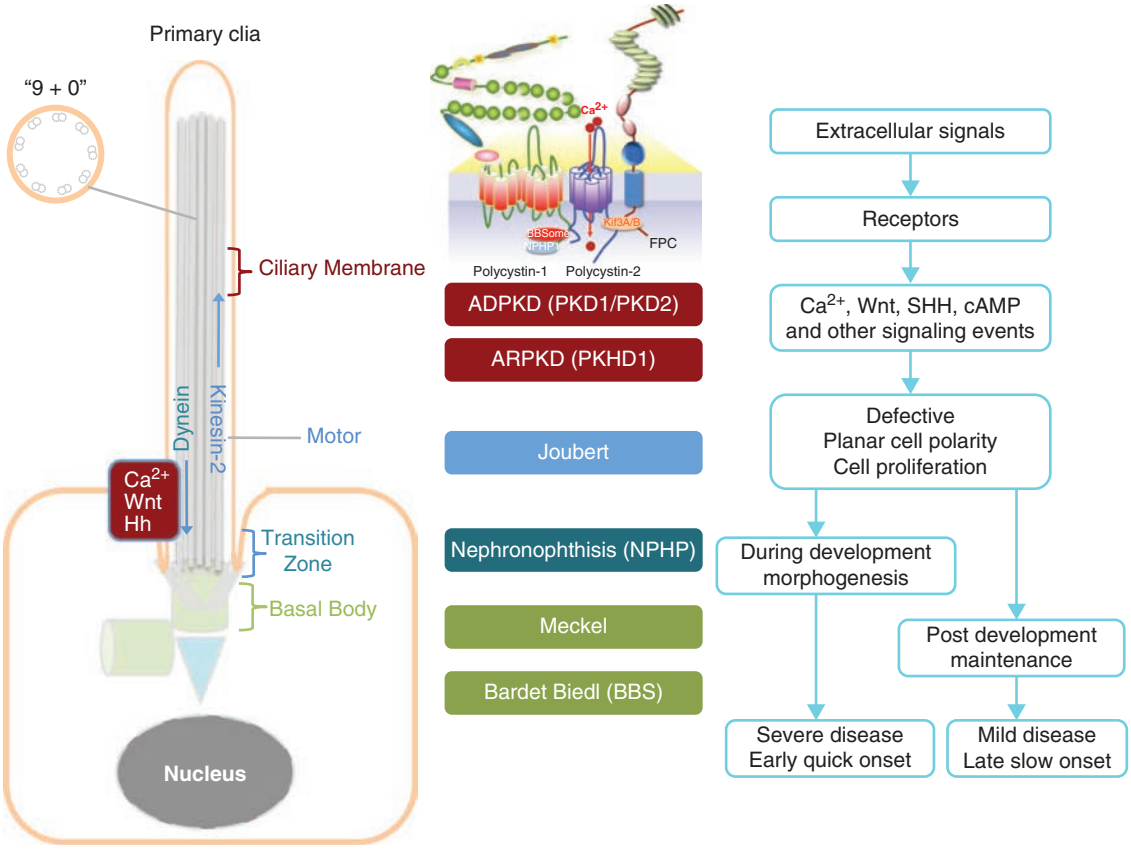


FIGURE 309-1 Scheme of the primary cilium and cystic kidney disease proteins. ***Left:*** a scheme of the primary cilium. Primary cilia share a "9+0" organization of microtubule doublets. Proteins are transported into the cilium by motor protein kinesin 2 and transported out of the cilium by dynein. The cilium is connected to the basal body through the transition zone. ***Middle:*** topology of ADPKD and ARPKD proteins polycystin 1, polycystin 2, and FPC are shown. Localization of disease proteins in the cilium, the transition zone and the basal body are color coded. ***Right:*** potential disease mechanisms due to cilium mediated signaling events.

in very slow onset of cyst development in the kidney, but a "third hit" such as an additional genetic or epigenetic event, the inactivation of a growth suppressor gene, the activation of a growth promoting gene(s), or an event like renal injury that activates the developmental program, may promote rapid cyst formation.

Clinical Manifestations ADPKD is characterized by the progressive bilateral formation of renal cysts. Focal renal cysts are typically detected in affected subjects aged <30 years. Hundreds to thousands of cysts are usually present in the kidneys of most patients in the fifth decade **(Fig. 309-2)**. Enlarged kidneys can each reach a fourfold increase in length, and weigh up to 20 times the normal weight. The clinical presentations of ADPKD are highly variable. While many patients are asymptomatic until the fourth to fifth decade of life and are diagnosed by incidental discoveries of hypertension or abdominal masses, back or flank pain is a frequent symptom in ~60% of patients with ADPKD. The pain may result from renal cyst infection, hemorrhage, or nephrolithiasis. Gross hematuria resulting from cyst rupture occurs in ~ 40% of patients during the course of their disease, and many of them will have recurrent episodes. Flank pain and hematuria may coexist if the cyst that ruptures is connected with the collecting system. Proteinuria is usually a minor feature of ADPKD. Infection is the second most common cause of death for patients with ADPKD. Up to half of patients with ADPKD will have one or more episodes of renal infection during their lifetime. An infected cyst and acute pyelonephritis are the most common renal infections often due to gram-negative bacteria, which are associated with fever and flank pain, with or without bacteremia. These complications and renal insufficiency often correlate with structural abnormality of the renal parenchyma. Kidney stones occur in ~20% of patients with ADPKD. Different from the general population, more than half of the stones in patients with ADPKD are composed of uric acid, with the remainder due to calcium oxalate. Distal acidification defects, abnormal ammonium transport, low urine pH, and hypocitraturia may be important in the pathogenesis of renal stones in ADPKD. Renal cell carcinoma is a rare complication of ADPKD with no apparent increased frequency compared to the general population. However, in ADPKD these tumors are more often bilateral at presentation, multicentric, and sarcomatoid in type. Radiological imaging is often not helpful in distinguishing cyst infection and cyst hemorrhage because of their complexity. CT scan and magnetic resonance imaging (MRI) are often useful in distinguishing a malignancy from a complex cyst. Cardiovascular complications are the major cause of mortality in patients with ADPKD. Hypertension is common, and typically occurs before any reduction in glomerular filtration rate (GFR). Hypertension is a risk factor for both cardiovascular and kidney disease progression in ADPKD. Notably, some normotensive patients with ADPKD may also have left ventricular hypertrophy. Hypertension in ADPKD may result from the increased activation of the renin-angiotensin-aldosterone system, increased sympathetic nerve activity, and impaired endothelial cilium function-dependent relaxation of small resistant blood vessels.

The progression of ADPKD has striking inter- and intrafamilial variability. The disease can present as early as *in utero*, but end-stage renal disease (ESRD) typically occurs in late middle age. Risk factors include early diagnosis of ADPKD, hypertension, gross hematuria, multiple pregnancies, and large kidney size. Liver cysts derived from the biliary epithelia are the most common extrarenal complication. Polycystic liver disease associated with ADPKD is different from autosomal dominant polycystic liver disease (ADPLD), which is caused by mutations in at least two distinct genes (*PRKCSH* and *SEC63*) and does not progress to renal failure. Massive polycystic liver disease occurs almost exclusively in women with ADPKD, particularly those with multiple pregnancies. Heterozygous loss-of-function variants in *PKHD1*, *ALG8*, *GANAB*, and *SEC61B* are now found in ADPLD. *ALG8*, *GANAB*, and *SEC61B*, all encode ER proteins that are involved in the same pathway as GIIβ and SEC63, and each appears to affect PC1 biogenesis.

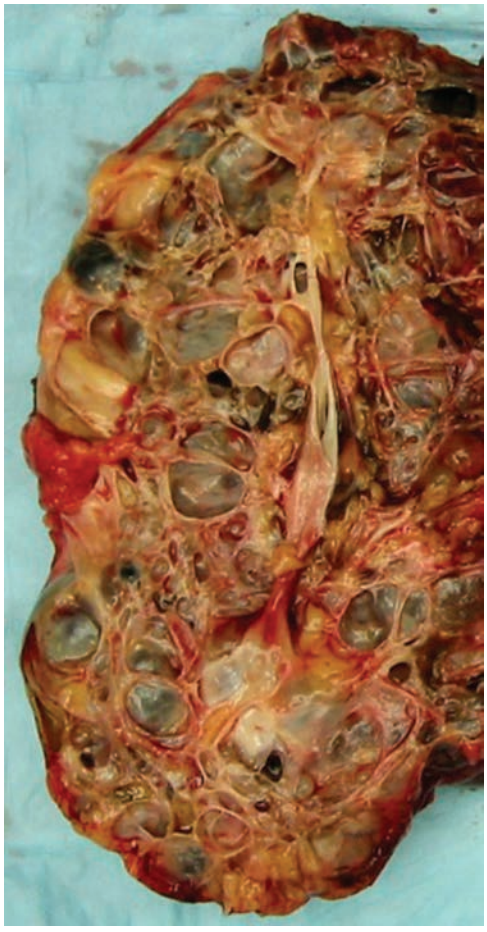


FIGURE 309-2 Photograph showing a kidney from a patient with autosomal dominant polycystic kidney disease. The kidney has been cut open to expose the parenchyma and internal aspects of cysts.

Intracranial aneurysm (ICA) occurs four to five times more frequent in APDKD patients than that seen in the general population and cause high mortality. The disease gene products PC1 and PC2 may be directly responsible for defects in arterial smooth muscle cells and myofibroblasts. The focal nature and the natural history of ICA in ADPKD remain unclear. A family history of ICA is a risk factor of aneurysm rupture in ADPKD, whether hypertension and cigarette smoking are independent risk factors is not clear. About 20–50% of patients may experience "warning headaches" preceding the index episode of subarachnoid hemorrhage due to ruptured ICA. A CT scan is generally used as the first diagnostic test. A lumbar puncture may be used to confirm the diagnosis. The role of radiological screening for ICA in asymptomatic patients with ADPKD remains unclear. ADPKD patients with a positive family history of ICAs may undergo pre-symptomatic screening of ICAs by MR angiography. Other vascular abnormalities in ADPKD patients include diffuse arterial dolichoectasias of the anterior and posterior cerebral circulation, which can predispose to arterial dissection and stroke. Mitral valve prolapse occurs in up to 30% of patients with ADPKD, and tricuspid valve prolapse is less common. Other valvular abnormalities occurring with increased frequency in ADPKD patients include insufficiency of the mitral, aortic, and tricuspid valves. Most patients are asymptomatic but some may progress and require valve replacement. The prevalence of colonic diverticulae and abdominal wall hernias are also increased in ADPKD patients.

Diagnosis Diagnosis is typically made from a positive family history consistent with autosomal dominant inheritance and multiple kidney cysts bilaterally. Renal ultrasonography is often used for pre-symptomatic screening of at-risk subjects and for evaluation of potential living-related kidney donors from ADPKD families. The presence of *at least two renal cysts (unilateral or bilateral)* is sufficient for diagnosis among at-risk subjects between 15 and 29 years of age with a sensitivity value of 96% and specificity value of 100%. The presence of *at least two cysts in each kidney* and *at least four cysts in each kidney*, respectively, are required for the diagnosis among at-risk subjects aged 30–59 years and aged ≥60 years with a sensitivity value of 100% and specificity value of 100%. This is because there is an increased frequency of developing simple renal cysts with age. Conversely, in subjects aged between 30 and 59 years the absence of *at least two cysts in each kidney*, which is associated with a false negative rate of 0%, can be used for disease exclusion. These criteria have a lower sensitivity for patients with a *PKD2* mutation because a late onset of ADPKD2. CT scan and T2-MRI, with and without contrast enhancement, are more sensitive than ultrasonography and can detect cysts of smaller size. However, a CT scan exposes the patient to radiation and radiocontrast, which may cause serious allergic reactions and nephrotoxicity in patients with renal insufficiency. T2-MRI, with gadolinium as a contrast agent, has minimal renal toxicity and can detect cysts of only 2–3 mm in diameter. However, a large majority of cysts may still be below the detection level. Genetic testing by linkage analyses and mutational analyses are available for ambiguous cases. Because of the large size of *PKD1* gene and the presence of multiple highly homologous pseudogenes, mutational analysis of *PKD1* gene is difficult and costly. Application of new technologies such as paired-end next generation sequencing with multiplexing individually bar-coded long range PCR libraries may reduce the costs and improve the sensitivity for clinical genetic testing.

TREATMENT

Autosomal Dominant Polycystic Kidney Disease

No specific treatment to prevent cyst growth or the decline of renal function has been approved by U.S. Food and Drug Administration. Blood pressure control to a target of 140/90 mmHg is recommended according to the guidelines from the eighth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VIII report) for reducing cardiovascular complications in ADPKD and renal disease progression. More rigorous blood pressure control does not equal greater clinical benefits. Maintaining a target systolic blood pressure to 110 mmHg in patients with moderate or advanced disease may increase the risk of renal disease progression by reducing renal blood flow. Lipid-soluble antibiotics against common gram-negative enteric organisms include trimethoprim-sulfamethoxazole, quinolones, and chloramphenicol, and are preferred for cyst infection because most renal cysts are not connected to glomerular filtration and antibiotics that are capable to penetrate the cyst walls are likely to be more effective. Treatment often requires 4–6 weeks. The treatment of kidney stones in ADPKD includes standard measures such as analgesics for pain relief, and hydration to ensure adequate urine flow. Management of chronic flank, back, or abdominal pain due to renal enlargement may include both pharmacologic (non-narcotic and narcotic analgesics) and non-pharmacological (transcutaneous electrical nerve stimulation, acupuncture, and biofeedback). Occasionally surgical decompression of cysts may be necessary. More than half of ADPKD patients eventually require peritoneal dialysis, hemodialysis, or kidney transplantation. Peritoneal dialysis may not be suitable for some patients with massively enlarged polycystic kidneys due to the small intraabdominal space for efficient peritoneal exchange of fluid and solutes and increased chance of abdominal hernia and back pain. Patients with very large polycystic kidneys and recurrent renal cyst infection may require pretransplant nephrectomy or bilateral nephrectomy to accommodate the allograft and reduce the pain.

Specific treatment strategies to ADPKD have focused on slowing renal disease progression and lowering cardiovascular risk. For the latter, the main approach is to control blood pressure by inhibiting the renin-angiotensin-aldosterone system. The HALT PKD trial was set to evaluate the impact of intensive blockade of the renin-angiotensin-aldosterone system, and levels of blood pressure control on progressive renal disease. This trial found that rigorous blood-pressure control could slow cyst growth. Most approaches target the

slowing of renal disease progression by inhibiting cell proliferation and fluid secretion. Several clinical trials have been conducted targeting cell proliferation: sirolimus and everolimus, inhibitors of the mammalian target of rapamycin (mTOR) pathway; OPC31260 and tolvaptan, which inhibits cyclic adenosine monophosphate (cAMP) pathways by antagonizing the activation of vasopressin V2 receptor (V2R) in collecting ducts and reduces cell proliferation by decreasing renal cAMP levels; and somatostatin analogues, which reduces cAMP levels by binding to several G-protein coupled receptors. The TAMPO and ALADIN trials showed that V2R antagonists and somatostatin analogues (octreotide-LAR groups) respectively slowed the decline of renal function. Some side effects, such as liver function impairment, polydipsia, and diarrhea, have been observed for tolvaptan and cholecystitis for octreotide-LAR. A recent report also showed that tolvaptan reduces renal pain. DIPAK, a small multi-center European study, showed that nerve block may be used to relieve pain in ADPKD patients suffering with refractory chronic pain. A combination of different growth inhibitors may enhance efficacy and reduce side effects.

Additional preclinical studies in animal models include the use of inhibitors to nonreceptor tyrosine kinase Src, B-raf, cyclin-dependent kinase (CDK), transcription factors STAT3 and STAT6 (pyrimethamine and leflunomide), purinergic receptors, hepatocyte growth factor receptor, glucosylceramide, and agonists to peroxisome proliferator-activated receptor-gamma (PPARγ) receptors (thiazolidodinediones). Recently, several microRNAs have been identified that mediate disease progression, which may prove to be a new therapeutic target. Food restriction in mouse models of the disease was reported to reduce cyst area, kidney fibrosis, inflammation, and injury. Branched chain amino acids appear to enhance cyst development in a mouse model.

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

Genetic Considerations ARPKD is a significant hereditary renal disease in childhood, with an estimated prevalence of 1 in 20,000 live births. A carrier frequency of up to 1:70 has been reported. Mutations in a single gene, *PKHD1*, are responsible for all the clinical presentations of ARPKD. *PKHD1*, localized on human chromosome region 6p21.1-6p12.2, is one of the largest genes in the genome, occupies ~450 kb of DNA, and contains at least 86 exons. It produces multiple alternatively spliced transcripts. The largest transcript encodes fibrocystin/polyductin (FPC), which is a large receptor-like integral membrane protein of 4074 amino acids. FPC has a single transmembrane, a large N-terminal extracellular region, and a short intracellular cytoplasmic domain. FPC is localized on the primary cilia of epithelia cells of cortical and medullary collecting ducts and cholangiocytes of bile ducts, similar to polycystins and several other ciliopathy proteins. FPC is also expressed on the basal body and plasma membrane. The large extracellular domain of FPC is presumed to bind to an as yet unknown ligand(s), and is involved in cell-cell and cell-matrix interactions. FPC interacts with ADPKD protein PC2, and may also participate in regulation of the mechanosensory function of the primary cilia, calcium signaling, and PCP, suggesting a common mechanism underlying cystogenesis between ADPKD and ARPKD. FPC is also found on the centrosomes and mitotic spindle, and may regulate centrosome duplication and mitotic spindle assembly during cell division. A large number of various mutations have been found throughout *PKHD1*, and are unique to individual families. Most patients are compound heterozygotes for *PKHD1* mutations. Patients with two truncation mutations appear to have an earlier onset of the disease.

Clinical Features Classic ARPKD is generally diagnosed in utero or within the neonatal period, and characterized by greatly enlarged echogenic kidneys in diseased fetuses. Reduced fetal urine production may contribute to oligohydroaminos and pulmonary hypoplasia. About 30% of affected neonates die shortly after birth due to respiratory insufficiency. Close to 60% of mortality occurs within the first month of life. In the classic group, most patients are born with renal insufficiency and ESRD. However, infants often have a transient improvement in their GFR; death from renal insufficiency at this stage is rare. Some patients are diagnosed after the neonatal stage, which form the older group. Morbidity and mortality in this group often involve systemic hypertension, progressive renal insufficiency, and liver manifestations. The hallmarks of ARPKD liver disease are biliary dysgenesis due to a primary ductal plate malformation with associated periportal fibrosis, namely congenital hepatic fibrosis (CHF) and dilatation of intrahepatic bile ducts (Caroli disease). CHF and Caroli disease can then lead to portal hypertension exhibiting hepatosplenomegaly, variceal bleeding, and cholangitis. Some patients with the diagnosis of ARPKD at 1 year of age with nephromegaly exhibit slowly declining renal function over 20 years with only minimally enlarged kidneys at ESRD, and markedly atrophic kidneys following renal transplantation. The slow progression of renal disease is likely due to increasing fibrosis rather than the development of cysts. Systemic hypertension is common in all ARPKD patients, even those with normal renal function.

Diagnosis Ultrasonography, CT, and MRI all can be used for diagnosis. Ultrasonography reveals large, echogenic kidneys with poor corticomedullary differentiation. The diagnosis can be made in utero after 24 weeks of gestation in severe cases. Macrocysts generally are not common at birth in ARPKD patients. The absence of renal cysts in either parent, particularly if they are >40 years of age on ultrasonography helps distinguish ARPKD from ADPKD in older patients. Clinical, laboratory, or radiographic evidence of hepatic fibrosis, hepatic pathology demonstrating characteristic ductal plate abnormalities, family history of affected siblings, or parental consanguinity suggestive of autosomal recessive inheritance is helpful. The lack of mutational hot spots and the large and complex genomic structure of *PKHD1* make molecular diagnosis difficult, however, presymptomatic screen of other at-risk members in a family with already identified ARPKD mutations is straightforward and inexpensive.

TREATMENT

Autosomal Recessive Polycystic Kidney Disease

There is no specific therapy for ARPKD. Appropriate neonatal intensive care, blood pressure control, dialysis, and kidney transplantation increase survival into adulthood. Complications of hepatic fibrosis may necessitate liver transplantation. Patients with severe Caroli disease may need porto-systemic shunting. Upcoming therapies may target abnormal cell signaling mechanisms, as described above for ADPKD.

OTHER DISEASES CHARACTERIZED BY LARGE KIDNEY CYSTS

TUBEROUS SCLEROSIS

Tuberous sclerosis (TS) is a rare autosomal dominant syndrome caused by mutations in one of two genes, *TSC1*, encoding hamartin, or, *TSC2*, encoding tuberin. Published estimates of prevalence vary widely, but it certainly occurs in <1:5,000 births. Kidney cysts are a frequent feature of this condition, as are two other abnormalities of kidney growth, renal cell carcinoma and renal angiomyolipomas. TS is a syndrome affecting multiple organ systems. Other features of TS include benign growths in the nervous system, eyes, heart, lung, liver, and the skin. Essentially all TS patients have such skin lesions, and a large proportion of patients have neurologic and cognitive manifestations. The *TSC2* gene is adjacent to *PKD1* in the human genome. Some patients have deletions in their genomic DNA that inactivate these two genes. Such individuals may have manifestations of both ADPKD and TS.

The most common kidney finding in TS is the presence of angiomyolipomas. These growths tend to be multiple and bilateral. While they are usually benign, they may bleed. Surgical removal is often recommended as a prophylactic measure in people with angiomyolipomas >4 cm in diameter. The cysts in TS are radiographically similar to those

seen in ADPKD. In contrast to ADPKD, there is a clearly increased risk of renal cell carcinoma in TS patients. Regular periodic imaging is recommended in TS patients with kidney involvement to screen for the development of renal cell carcinoma. These cysts may rarely become large and hemorrhagic, occasionally requiring nephrectomy when nephron-sparing surgery is not possible.

Although not common, TS may lead to significant chronic kidney disease (CKD) and progress to end-stage kidney failure. Patients with TS and CKD typically have an unremarkable urine sediment and only minimal to mild amounts of proteinuria.

Mechanistically, the *TSC1* and *TSC2* gene products tuberin and hamartin interact physically. This protein complex is localized to the base of the cilia and inhibits intracellular signaling processes mediated by mTOR (mammalian target of rapamycin), leading to abnormal growth in a number of tissues. Investigation of mTOR inhibitors as therapy for TS is ongoing. There is increasing optimism that this class of drugs will become commonplace for prevention of the renal and non-renal manifestations of TS.

VON HIPPEL-LINDAU DISEASE

Von Hippel-Lindau disease (VHL) is an inherited cancer syndrome with renal manifestations. VHL is an autosomal dominant condition caused by mutations in the VHL tumor-suppressor gene. VHL is localized to the primary cilia and is necessary for the formation of primary cilia. Like many autosomal dominant cancer syndromes, VHL is recessive at the cellular level: a somatic mutation in the second VHL allele leads to loss of VHL in the cell and abnormal growth. Kidney manifestations of VHL include multiple bilateral kidney cysts, and renal cell carcinomas. Kidney cysts and carcinoma affects the majority of VHL patients. Non-renal features of VHL include pheochromocytomas, cerebellar hemangioblastomas, and retinal hemangiomas. While much rarer than ADPKD, it is important for this entity to be considered in the differential diagnosis of an individual with newly recognized kidney cysts.

In these patients, annual screening of the kidneys by imaging with CT or MRI scanning is recommended for early detection of renal cell carcinomas. Increasingly, nephron-sparing surgical approaches are being used for removal of cancerous lesions in order to preserve kidney function.

OTHER INHERITED DISEASES OF TUBULE GROWTH AND DEVELOPMENT

ADPKD is by far the most common adult onset single gene form of adult onset kidney disease. The large cysts that are sometimes seen in VHL and TS are similar in appearance to the cysts seen in ADPKD. A variety of other inherited disorders affecting primarily tubule and renal interstitial function can lead to CKD and eventual end-stage kidney disease in the absence of large tubule-derived cysts.

Inherited diseases affecting the tubulointerstitial compartment of the kidney can lead to secondary glomerular stress and glomerulosclerosis with some degree of concomitant proteinuria. Similarly, disorders of glomerular function will typically lead to secondary interstitial fibrosis and tubule atrophy. From a clinical perspective, therefore, distinguishing between a genetic disease of the renal tubules and a disease of the glomerulus may not be easy, particularly in the absence of a gross phenotype such as large kidney cysts.

AUTOSOMAL DOMINANT INTERSTITIAL KIDNEY DISEASE (MEDULLARY CYSTIC KIDNEY DISEASE)

The medullary cystic kidney diseases (MCKD) are autosomal dominant disorders. The term autosomal dominant tubulointerstitial kidney disease (ADTKD) is replacing MCKD as the preferred designation. Despite the old nosology, kidney cysts are not invariably present. Older literature often grouped MCKD together with the childhood-onset disorders known as the nephronophthises, but these are distinct clinical and genetic entities.

ADTKD-MUC1 Patients with medullary cystic kidney disease type I (MCKD I) have mutations in the mucin 1 gene *MUC1*. In contrast to MCKD II patients, individuals with MCKD I do not have elevated uric acid levels. The disease-causing *MUC1* mutations that have been reported all alter a highly repetitive region within the *MUC1* gene, leading to a large "neoprotein" fragment that may lead to toxic effects on the kidney tubule.

Clinically, patients with MCKD I exhibit slowly progressive CKD in adulthood, with only minimal amounts of increased urine protein and occasional renal cysts seen on ultrasound examination. Kidney histology shows tubulointerstitial fibrosis and tubular atrophy. The mechanisms by which *MUC1* mutations cause human kidney disease are not known. Disease does not recur in transplanted kidneys.

ADTKD-UMOD ADTKD-IUMOD (also called MCKD II) is caused by mutations in the *UMOD* gene, which encodes the protein uromodulin, also known as Tamm-Horsfall protein. Uromodulin is also found on the centrosome, the mitotic spindle, and the primary cilia; it colocalizes with nephrocystin-1 and KIF3A on the cilia. *UMOD* mutations also cause the conditions that have been referred to as familial juvenile hyperuricemic nephropathy (HNFJ1) and glomerulocystic kidney disease (GCKD), although it is not clear that these different names represent clearly distinct disorders. The term *uromodulin-associated kidney disease* (or UAKD) has been suggested as a better name for MCKD II and the various other related *UMOD*-associated diseases. Despite the name, kidney cysts are not a common feature of MCKD II. MCKD II should be suspected clinically in patients with a family history of late onset kidney disease, benign urine sediments, absence of significant proteinuria, and hyperuricemia. Large genome-wide association studies have suggested that certain common non-coding sequence variants in *UMOD* are associated with a moderately increased risk of CKD in the general population. *UMOD*-associated disease is often associated with gout.

Other Forms of Familial Tubulointerstitial Kidney Disease A small number of families have been identified with autosomal dominant tubulointerstitial kidney disease and hyperuricemia who lack *UMOD* mutations. Some of these families carry disease-segregating mutations in the renin gene *REN* (disease designation ADTKD-REN). ADKTKD-REN patients demonstrate hyporeninemia with mild hyperkalemia, and often have hyperuricemia and gout. There are other families who lack mutations in *UMOD, MUC1,* or *REN* mutation. Thus, mutations in other yet-to-be identified genes are able to produce similar interstitial kidney disease, both with and without hyperuricemia.

Kidney biopsies in patients with any of various forms of MCKD typically show interstitial fibrosis. These histologic features are not diagnostic of any particular genetic entity, and the specific diagnosis must be made by other means. Genetic tests for alterations in specific genes are increasingly available in the clinical setting.

Those patients with autosomal dominant interstitial kidney disease, *UMOD* or *REN* mutations, with hyperuricemia and gout should be treated similarly to others with these findings, with uric-acid lowering agents, such as allopurinol or febuxostat.

NEPHRONOPHTHISIS

A large and growing number of genetically distinct but related set of autosomal recessive disorders are referred to as nephronophthisis, or nephronophthisis-related ciliopathies. These entities should not be confused with the adult onset autosomal dominant MCKD discussed above, despite the often confusing nomenclature seen in older medical literature. Each of the individual forms of nephronophthisis is quite rare, but together this category constitutes the most common inherited childhood form of kidney failure requiring kidney replacement therapy.

Like ADPKD and ARPKD, the various genetically heterogeneous entities that fall under the category of nephronophthisis (NPHP) are disorders of ciliary function. Mutations in >90 genes have been identified that lead to NPHP under an autosomal recessive pattern of inheritance. Some of these gene defects cause limited kidney disease, while many cause ciliopathies characterized by multiple organ involvement. The various forms of NPHP share common features, including tubulointerstitial fibrosis, corticomedullary cysts, and progressive CKD,

leading to renal failure. Proteinuria is absent or mild, and the urine sediment is not active.

NPHP is often divided into infantile, juvenile, and adolescent forms. The juvenile form is the most frequent, and usually caused by mutations in the *NPHP2* gene. The infantile form, usually caused by *NPHP2* mutations, is associated with end-stage kidney failure in early childhood. Patients with the adolescent form of NPHP typically develop end–stage kidney failure in early adulthood. Hypertension, if present, tends to be a late finding in the course of the NPHPs. The products of the NPHP genes are referred to as nephrocystins. *NPHP1* through *NPHP20* have been reported; some are referred to by other names, as well.

NPHP can present as an isolated finding, or be part of several multi-organ syndromes. Neurologic abnormalities are present in a significant number of patients. Bone and liver abnormities are seen in some NPHP patients. Senior-Loken syndrome is defined by the presence of NPHP with retinitis pigmentosa. Joubert syndrome is defined by multiple neurologic findings, including hypoplasia of the cerebellar vermis. Some forms of this genetically heterogeneous syndrome include NPHP as a component.

The multisystem disease Bardet-Biedl syndrome (BBS) is defined clinically by a spectrum of features, including truncal obesity, cognitive impairment, retinal dystrophy, polydactyly, developmental urogenital abnormalities, and kidney cysts. The kidney phenotype is NPHP-like, with small cysts deriving from the tubules, tubulointerstitial and often secondary glomerular disease, and urine concentrating defects. There are 19 BBS genes cloned. BBS follows autosomal recessive inheritance. Like ADPKD, ARPKD, and NPHP, BBS is a disease of abnormal ciliary function.

The multiple genes and gene products (nephrocystins) that are responsible for NPHP are expressed in cilia, basal bodies, and the centrosomes of kidney tubules cells. It has been hypothesized that all of the NPHP gene defects lead to a clinical phenotype by interfering with the regulation of PCP.

There are no specific clinical tests that define nephronophthisis. Genetic diagnosis is possible, cumbersome because of the large number of genes that can be responsible, but increasingly feasible due to new DNA sequencing technologies. There are no specific therapies for NPHP. Rather, therapy is aimed at treating signs of these diseases as well as those systemic abnormalities seen with all CKDs. Chronic dialysis or kidney transplantation are eventually required for NPHP-affected individuals.

KARYOMEGALIC TUBULOINTERSTITIAL NEPHRITIS

Karyomegalic tubulointerstitial nephritis is an exceptionally rare form of kidney disease with adult-onset progressive kidney failure. Kidney biopsy shows chronic tubulointerstitial nephritis, as well as interstitial fibrosis. This is a recessive disorder caused by inheritance of two mutant copies of the *FAN1* gene. *FAN1* encodes a component of a DNA repair machinery complex. Individuals with two mutant *FAN1* gene are genetically sensitized to the effect of DNA damage. Kidney histology shows karyomegaly in addition to the non-specific findings of interstitial fibrosis and tubular atrophy.

MEDULLARY SPONGE KIDNEY

Medullary sponge kidney (MSK) is often grouped together with inherited disorders of the kidney affecting tubule growth and development, although it is usually a sporadic finding rather than an inherited phenotype. MSK is caused by developmental malformation and cystic dilatation of the renal collecting ducts. The medullary cysts seen in this entity can be quite variable in size.

MSK is usually a benign entity. The diagnosis of MSK is often made incidentally. In the past, the diagnosis of MSK was often made by intravenous pyelography (IVP). CT urography, which has replaced IVPs for much routine kidney imaging, is not as sensitive in detecting MSK.

MSK is associated with an increased frequency of calcium phosphate and calcium oxalate kidney stones. Altered flow characteristics in the kidney tubules may lead to the development of formation of a nidus for stone formation. Kidney stones in this group are treated the same as are kidney stones in the general population. MSK patients also often exhibit reduced kidney concentrating ability and an increased frequency of urinary tract infections.

CAKUT

The structural abnormalities known as CAKUT (Congenital Abnormalities of the Kidney and Urinary Tract) are a group of etiologically and phenotypically heterogeneous disorders. Some form of CAKUT is estimated to occur in up to 1 in 500 live births. Specific abnormalities classified as part of the CAKUT spectrum include kidney hypoplasia, kidney agenesis, ureteropelvic junction obstruction, and vesicoureteral reflux.

CAKUT can be the cause of clinically significant problems in both adults and children. However, it is a major contributor to kidney failure in children, accounting for more than one-third of end-stage kidney disease in this group.

CAKUT is typically a sporadic finding, but can also cluster in families. Familial forms can be observed as parts of multisystem developmental syndromes. A growing list of specific genes have been identified which when mutated lead to syndromic forms of CAKUT. For example, the branchio-oto-renal syndrome, characterized by developmental abnormalities in the neck, ears, and kidney, can be caused by mutations in the *EYA1* and *SIX1* genes. Mutations in the *PAX2* transcription factor gene can cause the autosomal dominant renal coloboma syndrome, characterized by optic nerve malformations and hypoplastic kidneys. Recent work has demonstrated that a non-trivial fraction of children with CKD have an unsuspected genomic imbalance, often disrupting genes known to relevant to CAKUT and kidney development. It is not uncommon for such genetic lesions that affect both kidney and neurocognitive function.

In many instances, CAKUT is caused by environmental influences rather than genetic alterations. For example, renal tubular dysgenesis, defined by altered tubule development, can be caused by prenatal exposure of angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

MITOCHONDRIAL DISEASE

Inherited disorders of the mitochondrial genome (discussed elsewhere in this text [see also Chap. 472]) commonly affect kidney function. Thirteen of the genes involved in encoding components of the mitochondrial respiratory chain are located on the mitochondrial genome that is inherited maternally. The remainder of these components is encoded by the nuclear genome. These defects of oxidative phosphorylation may affect multiple organs and tissues.

Neuromuscular disease is the best recognized part of this complex phenotype. Kidney disease is now recognized as a common component, as well. Tubulointerstitial disease may be seen on kidney biopsy, and progression to kidney failure may occur. Glomerular involvement, manifest as proteinuria and glomerulosclerosis, can also develop. Changes in proximal tubule activity are the most common renal phenotype. Patients may have several defects in proximal tubule transport, including the Fanconi syndrome. Some patients may also have acidosis, hypophosphatemic rickets, hypercalciuria, glycosuria, and tubular proteinuria. Decreased urine concentrating ability is common.

GLOBAL CONSIDERATIONS

The disorders discussed above are all seen worldwide. In addition, a previously unrecognized epidemic of kidney disease is leading to very high rates of kidney failure in and near the western coast of Central America. This mesoamerican nephropathy is particularly common in Nicaragua and El Salvador. Mesoamerican nephropathy patients do not have significant proteinuria, suggesting that this is a disease of the kidney tubules and interstitium. The cause is unknown, but some have suggested that a combination of toxic environmental factors and heat stress underlie the development of this kidney disease, which has a striking male predominance. However, the fact that in many families, a large fraction of the men are affected with kidney disease has suggested that a strong genetic component is involved, as well.

FURTHER READING

Arts HH, Knoers NV: Current insights into renal ciliopathies: What can genetics teach us? Pediatr Nephrol 28:863, 2013.

Bleyer AJ et al: Autosomal dominant tubulointerstitial kidney disease. Adv Chronic Kidney Dis 24:86, 2017.

Grantham JJ et al: Detected renal cysts are tips of the iceberg in adults with ADPKD. Clin J Am Soc Nephrol 7:1087, 2012.

Henske EP: Tuberous sclerosis and the kidney: From mesenchyme to epithelium, and beyond. Pediatr Nephrol 20:854, 2005.

LaRiviere WB et al: Novel therapeutic approaches to autosomal dominant polycystic kidney disease. Transl Res 165:488, 2015.

Ong AC, Harris PC: A polycystin-centric view of cyst formation and disease: The polycystins revisited. Kidney Int 88:699, 2015.

Porath B et al: Mutations in GANAB, encoding the glucosidase IIalpha subunit, cause autosomal-dominant polycystic kidney and liver disease. Am J Hum Genet 98:1193, 2016.

Reddy BV, Chapman AB: The spectrum of autosomal dominant polycystic kidney disease in children and adolescents. Pediatr Nephrol 32:31, 2017.

Vivante A, Hildebrandt F: Exploring the genetic basis of early-onset chronic kidney disease. Nat Rev Nephrol 12:133, 2016.

Zhou J: Polycystins and primary cilia, primers for cell cycle progression. Ann Rev Physiol 71:83, 2009.

310 Tubulointerstitial Diseases of the Kidney

Laurence H. Beck, Jr., David J. Salant

Inflammation or fibrosis of the renal interstitium and atrophy of the tubular compartment are common consequences of diseases that target the glomeruli or vasculature. Distinct from these secondary phenomena, however, are a group of disorders that primarily affect the tubules and interstitium, with relative sparing of the glomeruli and renal vessels. Such disorders are conveniently divided into acute and chronic tubulointerstitial nephritis (TIN) **(Table 310-1)**.

Acute TIN most often presents with acute renal failure **(Chap. 304)**. The acute nature of this group of disorders may be caused by aggressive inflammatory infiltrates that lead to tissue edema, tubular cell injury, and compromised tubular flow, or by frank obstruction of the tubules with casts, cellular debris, or crystals. There is sometimes flank pain due to distention of the renal capsule. Urinary sediment is often active with leukocytes and cellular casts, but depends on the exact nature of the disorder in question.

The clinical features of chronic TIN are more indolent and may manifest with disorders of tubular function, including polyuria from impaired concentrating ability (nephrogenic diabetes insipidus), defective proximal tubular reabsorption leading to features of Fanconi's syndrome (glycosuria, phosphaturia, aminoaciduria, hypokalemia, and type II renal tubular acidosis [RTA] from bicarbonaturia), or non-anion-gap metabolic acidosis and hyperkalemia (type IV RTA) due to impaired ammoniagenesis, as well as progressive azotemia (rising creatinine and blood urea nitrogen [BUN]). There is often modest proteinuria (rarely >2 g/d) attributable to decreased tubular reabsorption of filtered proteins; however, nephrotic-range albuminuria may occur in some conditions due to the development of secondary focal segmental glomerulosclerosis (FSGS). Renal ultrasonography may reveal changes of "medical renal disease," such as increased echogenicity of the renal parenchyma with loss of corticomedullary differentiation, prominence of the renal pyramids, and cortical scarring in some conditions. The predominant pathology in chronic TIN is interstitial fibrosis with patchy mononuclear cell infiltration and widespread tubular atrophy, luminal dilation, and thickening of tubular basement membranes. Because of the nonspecific nature of the histopathology, biopsy specimens rarely provide a specific diagnosis. Thus, diagnosis relies on careful analysis of history, drug or toxin exposure, associated symptoms, and imaging studies.

TABLE 310-1 Classification of the Causes of Tubulointerstitial Diseases of the Kidney

Acute Tubulointerstitial Disorders

Acute Interstitial Nephritis

Therapeutic agents

- Antibiotics (β-lactams, sulfonamides, quinolones, vancomycin, erythromycin, linezolid, minocycline, rifampin, ethambutol, acyclovir)
- Nonsteroidal anti-inflammatory drugs, COX-2 inhibitors
- Diuretics (rarely thiazides, loop diuretics, triamterene)
- Anticonvulsants (phenytoin, valproate, carbamazepine, phenobarbital)
- Miscellaneous (proton pump inhibitors, H_2 blockers, captopril, mesalazine, indinavir, allopurinol, lenalidomide)

Infection

- Bacteria (*Streptococcus, Staphylococcus, Legionella, Salmonella, Brucella, Yersinia, Corynebacterium diphtheriae*)
- Viruses (EBV, CMV, hantavirus, polyomavirus, HIV)
- Miscellaneous (*Leptospira, Rickettsia, Mycoplasma, Histoplasma*)

Autoimmune

- Tubulointerstitial nephritis with uveitis (TINU)
- Sjögren's syndrome
- Systemic lupus erythematosus
- Granulomatous interstitial nephritis
- IgG4-related systemic disease
- Idiopathic autoimmune interstitial nephritis

Acute obstructive disorders

- Light chain cast nephropathy ("myeloma kidney")
- Acute phosphate nephropathy
- Acute urate nephropathy

Chronic Tubulointerstitial Disorders

- Vesicoureteral reflux/reflux nephropathy
- Sickle cell disease
- Chronic exposure to toxins or therapeutic agents
- Analgesics, especially those containing phenacetin
- Lithium
- Heavy metals (lead, cadmium)
- Aristolochic acid (Chinese herbal and Balkan endemic nephropathies)
- Calcineurin inhibitors (cyclosporine, tacrolimus)

Metabolic Disturbances

- Hypercalcemia and/or nephrocalcinosis
- Hyperuricemia
- Prolonged hypokalemia
- Hyperoxaluria
- Cystinosis **(see Chap. 309)**

Cystic and Hereditary Disorders (see Chap. 309)

- Polycystic kidney disease
- Nephronophthisis
- Adult medullary cystic disease
- Medullary sponge kidney

Miscellaneous

- Aging
- Chronic glomerulonephritis
- Chronic urinary tract obstruction
- Ischemia and vascular disease
- Radiation nephritis (rare)

Abbreviations: CMV, cytomegalovirus; COX, cyclooxygenase; EBV, Epstein-Barr virus.

ACUTE INTERSTITIAL NEPHRITIS

In 1897, Councilman reported on eight cases of acute interstitial nephritis (AIN) in the Medical and Surgical Reports of the Boston City Hospital; three as a postinfectious complication of scarlet fever and two from diphtheria. Later, he described the lesion as "an acute inflammation of the kidney characterized by cellular and fluid exudation in the interstitial tissue, accompanied by, but not dependant on, degeneration of the epithelium; the exudation is not purulent in character, and the lesions may be both diffuse and focal." Today AIN is far more often encountered as an allergic reaction to a drug (Table 310-1). Immune-mediated AIN may also occur as part of a known autoimmune syndrome, but in some cases there is no identifiable cause despite features suggestive of an immunologic etiology (Table 310-1).

ALLERGIC INTERSTITIAL NEPHRITIS

Although biopsy-proven AIN accounts for no more than ~15% of cases of unexplained acute renal failure, this is likely a substantial underestimate of the true incidence. This is because potentially offending medications are more often identified and empirically discontinued in a patient noted to have a rising serum creatinine, without the benefit of a renal biopsy to establish the diagnosis of AIN.

Clinical Features The classic presentation of AIN, namely, fever, rash, peripheral eosinophilia, and oliguric renal failure occurring after 7–10 days of treatment with methicillin or another β-lactam antibiotic, is the exception rather than the rule. More often, patients are found incidentally to have a rising serum creatinine or present with symptoms attributable to acute renal failure (Chap. 304). Atypical reactions can occur, most notably nonsteroidal anti-inflammatory drug (NSAID)-induced AIN, in which fever, rash, and eosinophilia are rare, but acute renal failure with heavy proteinuria is common. A particularly severe and rapid-onset AIN may occur upon reintroduction of rifampin after a drug-free period. More insidious reactions to the agents listed in Table 310-1 may lead to progressive tubulointerstitial damage. Examples include proton pump inhibitors and, rarely, sulfonamide and 5-aminosalicylate (mesalazine and sulfasalazine) derivatives and antiretrovirals. It is not clear if the recent association of proton pump inhibitors with incident chronic kidney disease involves an intermediate step of prolonged, subclinical interstitial nephritis.

Diagnosis Finding otherwise unexplained renal failure with or without oliguria and exposure to a potentially offending agent usually points to the diagnosis. Peripheral blood eosinophilia adds supporting evidence but is present in only a minority of patients. Urinalysis reveals pyuria with white blood cell casts and hematuria. Urinary eosinophils are neither sensitive nor specific for AIN; therefore, testing is not recommended. Renal biopsy is generally not required for diagnosis but reveals extensive interstitial and tubular infiltration of leukocytes, including eosinophils.

TREATMENT

Allergic Interstitial Nephritis

Discontinuation of the offending agent often leads to reversal of the renal injury. However, depending on the duration of exposure and degree of tubular atrophy and interstitial fibrosis that has occurred, the renal damage may not be completely reversible. Glucocorticoid therapy may accelerate renal recovery, but does not appear to impact long-term renal survival. It is best reserved for those cases with severe renal failure in which dialysis is imminent or if renal function continues to deteriorate despite stopping the offending drug (Fig. 310-1 and Table 310-2).

SJÖGREN'S SYNDROME

Sjögren's syndrome is a systemic autoimmune disorder that primarily targets the exocrine glands, especially the lacrimal and salivary glands, and thus results in symptoms, such as dry eyes and mouth, that constitute the "sicca syndrome" (Chap. 354). TIN with a predominant lymphocytic infiltrate is the most common renal manifestation of Sjögren's syndrome and can be associated with distal RTA, nephrogenic diabetes insipidus, and moderate renal failure. Diagnosis is strongly supported by positive serologic testing for anti-Ro (SS-A) and anti-La (SS-B) antibodies. A large proportion of patients with Sjögren's syndrome also have polyclonal hypergammaglobulinemia. Treatment is initially with glucocorticoids, although patients may require maintenance therapy with azathioprine or mycophenolate mofetil to prevent relapse (Fig. 310-1 and Table 310-2).

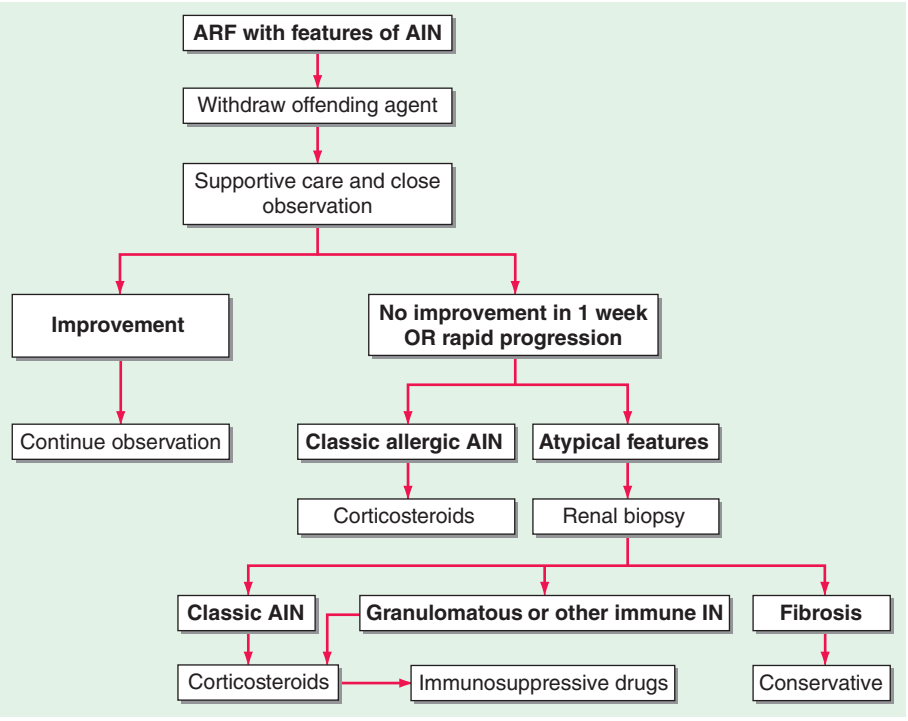


FIGURE 310-1 Algorithm for the treatment of allergic and other immune-mediated acute interstitial nephritis (AIN). ARF, acute renal failure; IN, interstitial nephritis. See text for immunosuppressive drugs used for refractory or relapsing AIN. *(Modified from S Reddy, DJ Salant: Ren Fail 20:829, 1998.)*

TUBULOINTERSTITIAL NEPHRITIS WITH UVEITIS (TINU)

TINU is a systemic autoimmune disease of unknown etiology. It accounts for fewer than 5% of all cases of AIN, affects females three times more often than males, and has a median age of onset of 15 years. Its hallmark feature, in addition to a lymphocyte-predominant interstitial nephritis (Fig. 310-2), is a painful anterior uveitis, often bilateral and accompanied by blurred vision and photophobia. Diagnosis is often confounded by the fact that the ocular symptoms precede or accompany the renal disease in only one-third of cases. Additional extrarenal features include fever, anorexia, weight loss, abdominal pain, and arthralgia. The presence of such symptoms as well as elevated creatinine, sterile pyuria, mild proteinuria, features of Fanconi's syndrome, and elevated erythrocyte sedimentation rate should raise suspicion for this disorder. Serologies suggestive of the more common autoimmune diseases are usually negative, and TINU is often a diagnosis of exclusion after other causes of uveitis and renal disease, such as Sjögren's syndrome, Behçet's disease, sarcoidosis, and systemic lupus erythematosus, have been considered. Clinical symptoms are typically self-limited in children, but are more apt to follow a

TABLE 310-2 Indications for Corticosteroids and Immunosuppressives in Interstitial Nephritis

Absolute Indications
• Sjögren's syndrome
• Sarcoidosis
• SLE interstitial nephritis
• Adults with TINU
• Idiopathic and other granulomatous interstitial nephritis
Relative Indications
• Drug-induced or idiopathic AIN with:
Rapid progression of renal failure
Diffuse infiltrates on biopsy
Impending need for dialysis
Delayed recovery
• Children with TINU
• Postinfectious AIN with delayed recovery (?)

Abbreviations: AIN, acute interstitial nephritis; SLE, systemic lupus erythematosus; TINU, tubulointerstitial nephritis with uveitis.

Source: Modified from S Reddy, DJ Salant: Ren Fail 20:829, 1998.

relapsing course in adults. The renal and ocular manifestations generally respond well to oral glucocorticoids, although maintenance therapy with agents such as methotrexate, azathioprine, or mycophenolate may be necessary to prevent relapses (Fig. 310-1 and Table 310-2).

SYSTEMIC LUPUS ERYTHEMATOSUS

An interstitial mononuclear cell inflammatory reaction often accompanies the glomerular lesion in most cases of class III or IV lupus nephritis **(Chap. 308)**, and deposits of immune complexes can be identified in tubule basement membranes in ~50% of cases. Occasionally, however, the tubulointerstitial inflammation predominates and may manifest with azotemia and type IV RTA rather than features of glomerulonephritis.

GRANULOMATOUS INTERSTITIAL NEPHRITIS

Some patients may present with features of AIN but follow a protracted and relapsing course. Renal biopsy in such patients reveals a more chronic inflammatory infiltrate with granulomas and multinucleated giant cells. Most often, no associated disease or cause is found; however, some of these cases may have or subsequently develop the pulmonary, cutaneous, or other systemic manifestations of *sarcoidosis* such as hypercalcemia. Most patients experience some improvement in renal function if treated early with glucocorticoids before the development of significant interstitial fibrosis and tubular atrophy (Table 310-2). Other immunosuppressive agents may be required for those who relapse frequently upon steroid withdrawal. Other immunosuppressive agents may be required for those who relapse frequently upon steroid withdrawal (Fig. 310-1). Tuberculosis should be ruled out before starting treatment because this too is a rare cause of granulomatous interstitial nephritis.

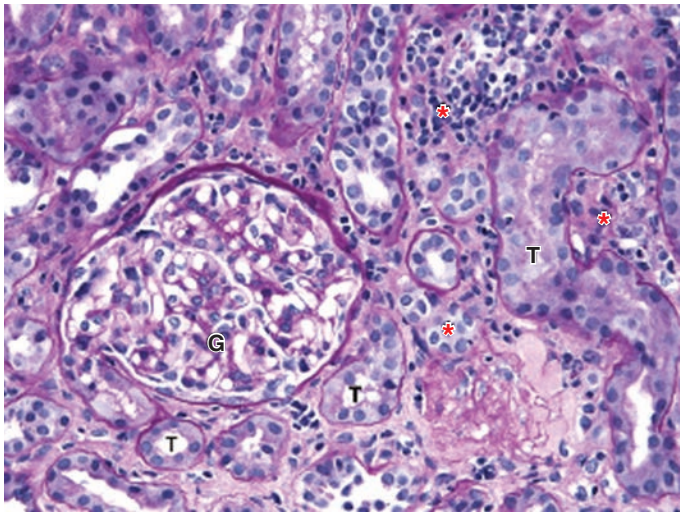


FIGURE 310-2 Acute interstitial nephritis (AIN) in a patient who presented with acute iritis, low-grade fever, erythrocyte sedimentation rate of 103, pyuria and cellular casts on urinalysis, and a newly elevated serum creatinine of 2.4 mg/dL. Both the iritis and AIN improved after intravenous methylprednisolone. This PAS-stained renal biopsy shows a mononuclear cell interstitial infiltrate (*asterisks*) and edema separating the tubules (T) and a normal glomerulus (G). Some of the tubules contain cellular debris and infiltrating inflammatory cells. The findings in this biopsy are indistinguishable from those that would be seen in a case of drug-induced AIN. PAS, Periodic acid–Schiff.

IgG4-RELATED SYSTEMIC DISEASE

A form of AIN characterized by a dense inflammatory infiltrate containing IgG4-expressing plasma cells can occur as a part of a syndrome known as IgG4-related systemic disease. Autoimmune pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, and a chronic sclerosing sialadenitis (mimicking Sjögren's syndrome) may variably be present as well. Fibrotic lesions that form pseudotumors in the affected organs soon replace the initial inflammatory infiltrates and often lead to biopsy or excision for fear of true malignancy. Although the involvement of IgG4 in the pathogenesis is not understood, glucocorticoids have been successfully used as first-line treatment in this group of disorders, once they are correctly diagnosed.

IDIOPATHIC AIN

Some patients present with typical clinical and histologic features of AIN but have no evidence of drug exposure or clinical or serologic features of an autoimmune disease. The presence in some cases of autoantibodies to a tubular antigen, similar to that identified in rats with an induced form of interstitial nephritis, suggests that an autoimmune response may be involved. Like TINU and granulomatous interstitial nephritis, idiopathic AIN is responsive to glucocorticoid therapy but may follow a relapsing course requiring maintenance treatment with another immunosuppressive agent (Fig. 310-1 and Table 310-2). Recently, cases have been identified in which autoantibodies that may be important in disease pathogenesis were seen to target antigens expressed by collecting duct or proximal tubular brush border.

INFECTION-ASSOCIATED AIN

AIN may also occur as a local inflammatory reaction to microbial infection (Table 310-1) and should be distinguished from acute bacterial pyelonephritis **(Chap. 130)**. Acute bacterial pyelonephritis does not generally cause acute renal failure unless it affects both kidneys or causes septic shock. Presently, infection-associated AIN is most often seen in immunocompromised patients, particularly renal transplant recipients with reactivation of polyomavirus BK **(Chaps. 138 and 307).**

CRYSTAL DEPOSITION DISORDERS AND OBSTRUCTIVE TUBULOPATHIES

Acute renal failure may occur when crystals of various types are deposited in tubular cells and interstitium or when they obstruct tubules. Oliguric acute renal failure, often accompanied by flank pain from tubular obstruction, may occur in patients treated with sulfadiazine for toxoplasmosis, indinavir and atazanavir for HIV, and intravenous acyclovir for severe herpesvirus infections. Urinalysis reveals "sheaf of wheat" sulfonamide crystals, individual or parallel clusters of needle-shaped indinavir crystals, or red-green birefringement needle-shaped crystals of acyclovir. This adverse effect is generally precipitated by hypovolemia and is reversible with saline volume repletion and drug withdrawal. Distinct from the obstructive disease, a frank AIN from indinavir crystal deposition has also been reported.

Acute tubular obstruction is also the cause of oliguric renal failure in patients with *acute urate nephropathy*. It typically results from severe hyperuricemia from tumor lysis syndrome in patients with lympho- or myeloproliferative disorders treated with cytotoxic agents, but also may occur spontaneously before the treatment has been initiated **(Chap. 71)**. Uric acid crystallization in the tubules and collecting system leads to partial or complete obstruction of the collecting ducts, renal pelvis, or ureter. A dense precipitate of birefringent uric acid crystals is found in the urine, usually in association with microscopic or gross hematuria.

Prophylactic allopurinol reduces the risk of uric acid nephropathy but is of no benefit once tumor lysis has occurred. Once oliguria has developed, attempts to increase tubular flow and solubility of uric acid with alkaline diuresis may be of some benefit; however, emergent treatment with hemodialysis or rasburicase, a recombinant urate oxidase, is usually required to rapidly lower uric acid levels and restore renal function.

Calcium oxalate crystal deposition in tubular cells and interstitium may lead to permanent renal dysfunction in patients who survive ethylene glycol intoxication, in patients with enteric hyperoxaluria from ileal resection or small-bowel bypass surgery, and in patients with hereditary hyperoxaluria **(Chap. 312)**. *Acute phosphate nephropathy* is an uncommon but serious complication of oral Phosphosoda used as a laxative or for bowel preparation for colonoscopy. It results from calcium phosphate crystal deposition in tubules and interstitium and occurs especially in subjects with underlying renal impairment and hypovolemia. Consequently, Phosphosoda should be avoided in patients with chronic kidney disease.

LIGHT CHAIN CAST NEPHROPATHY

Patients with multiple myeloma may develop acute renal failure in the setting of hypovolemia, infection, or hypercalcemia or after exposure to NSAIDs or radiographic contrast media. The diagnosis of light chain cast nephropathy (LCCN)—commonly known as *myeloma kidney*—should be considered in patients who fail to recover when the precipitating factor is corrected or in any elderly patient with otherwise unexplained acute renal failure.

In this disorder, filtered monoclonal immunoglobulin light chains (Bence-Jones proteins) form intratubular aggregates with secreted Tamm-Horsfall protein in the distal tubule. Casts, in addition to obstructing the tubular flow in affected nephrons, incite a giant cell or foreign body reaction and can lead to tubular rupture, resulting in interstitial fibrosis **(Fig. 310-3)**. Although LCCN generally occurs in patients with known multiple myeloma and a large plasma cell burden, the disorder should also be considered as a possible diagnosis in patients who have known monoclonal gammopathy even in the absence of frank myeloma. Filtered monoclonal light chains may also cause less pronounced renal manifestations in the absence of obstruction, due to direct toxicity to proximal tubular cells and intracellular crystal formation. This may result in isolated tubular disorders such as RTA or full Fanconi's syndrome.

Diagnosis Clinical clues to the diagnosis include anemia, bone pain, hypercalcemia, and an abnormally narrow anion gap due to hypoalbuminemia and hypergammaglobulinemia. Urinary dipsticks detect albumin but not immunoglobulin light chains; however, laboratory detection of increased amounts of protein in a spot urine specimen and a negative dipstick result are highly suggestive that the urine contains Bence-Jones protein. Serum and urine should both be sent for protein electrophoresis and for immunofixation for the detection and identification of a potential monoclonal band. A sensitive method is available to detect urine and serum free light chains.

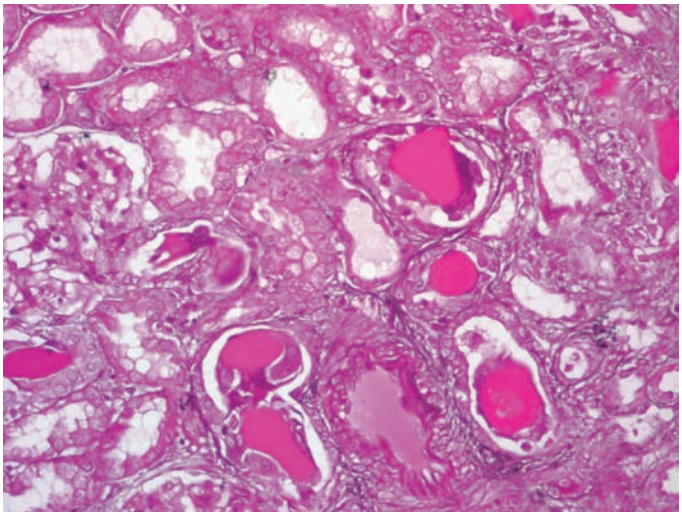


FIGURE 310-3 Histologic appearance of myeloma cast nephropathy. A hematoxylin-eosin–stained kidney biopsy shows many atrophic tubules filled with eosinophilic casts (consisting of Bence-Jones protein), which are surrounded by giant cell reactions. *(Courtesy of Dr. Michael N. Koss, University of Southern California Keck School of Medicine; with permission.)*

TREATMENT

Light Chain Cast Nephropathy

The goals of treatment are to correct precipitating factors such as hypovolemia and hypercalcemia, discontinue potential nephrotoxic agents, and treat the underlying plasma cell dyscrasia **(Chap. 107)**; plasmapheresis to remove light chains is of questionable value for LCCN.

LYMPHOMATOUS INFILTRATION OF THE KIDNEY

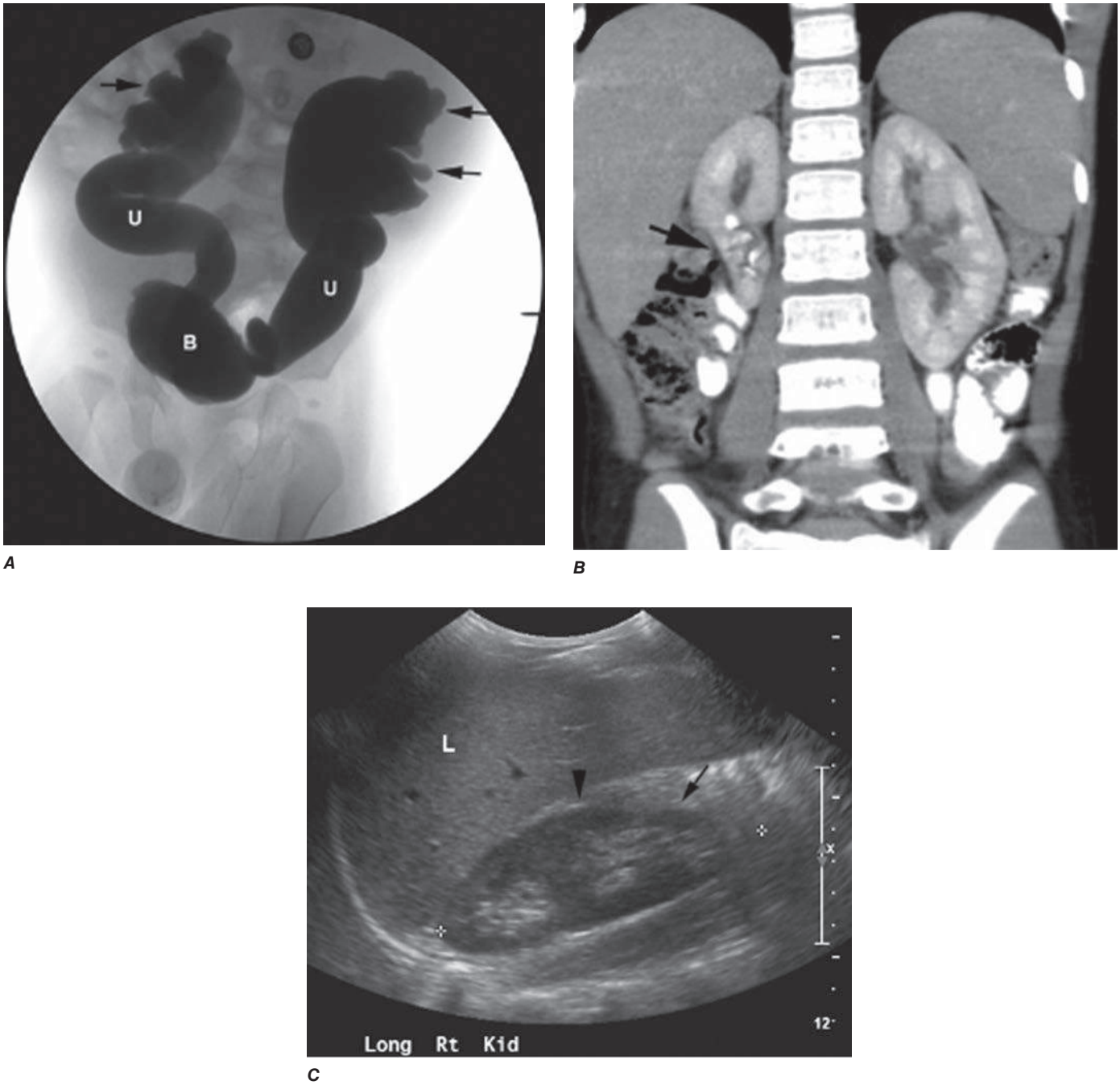
Interstitial infiltration by malignant B lymphocytes is a common autopsy finding in patients dying of chronic lymphocytic leukemia and non-Hodgkin's lymphoma; however, this is usually an incidental finding. Rarely, such infiltrates may cause massive enlargement of the kidneys and oliguric acute renal failure. Although high-dose glucocorticoids and subsequent chemotherapy often result in recovery of renal function, the prognosis in such cases is generally poor.

CHRONIC TUBULOINTERSTITIAL DISEASES

Improved occupational and public health measures, together with the banning of over-the-counter phenacetin-containing analgesics, has led to a dramatic decline in the incidence of chronic interstitial nephritis (CIN) from heavy metal—particularly lead and cadmium—exposure and analgesic nephropathy in North America. Today, CIN is most often the result of renal ischemia or secondary to a primary glomerular disease **(Chap. 308)**. Other important forms of CIN are the result of developmental anomalies or inherited diseases such as reflux nephropathy or sickle cell nephropathy and may not be recognized until adolescence or adulthood. Although it is impossible to reverse damage that has already occurred, further deterioration may be prevented or at least slowed in such cases by treating glomerular hypertension, a common denominator in the development of secondary FSGS and progressive loss of functioning nephrons. Therefore, awareness and early detection of patients at risk may prevent them from developing end-stage renal disease (ESRD).

VESICOURETERAL REFLUX AND REFLUX NEPHROPATHY

Reflux nephropathy is the consequence of vesicoureteral reflux (VUR) or other urologic anomalies in early childhood. It was previously called *chronic pyelonephritis* because it was believed to result from recurrent urinary tract infections (UTIs) in childhood. VUR stems from abnormal retrograde urine flow from the bladder into one or both ureters and kidneys because of mislocated and incompetent ureterovesical valves **(Fig. 310-4)**. Although high-pressure sterile reflux may impair normal growth of the kidneys, when coupled with recurrent UTIs in early childhood, the result is patchy interstitial scarring and tubular atrophy. Loss of functioning nephrons leads to hypertrophy of the remnant glomeruli and eventual secondary FSGS. Reflux nephropathy often goes unnoticed until early adulthood when chronic kidney disease is detected during routine evaluation or during pregnancy. Affected adults are frequently asymptomatic, but may give a history of prolonged bed-wetting or recurrent UTIs during childhood, and exhibit variable renal insufficiency, hypertension, mild to moderate proteinuria, and unremarkable urine sediment. When both kidneys are affected, the disease often progresses inexorably over several years to ESRD, despite the absence of ongoing urinary infections or reflux. A single affected kidney may go undetected, except for the presence of hypertension. Renal ultrasound in adults characteristically shows asymmetric small kidneys with irregular outlines, thinned cortices, and regions of compensatory hypertrophy (Fig. 310-4).



A ***B***

C

FIGURE 310-4 Radiographs of vesicoureteral reflux (VUR) and reflux nephropathy. *A.* Voiding cystourethrogram in a 7-month-old baby with bilateral high-grade VUR evidenced by clubbed calyces (*arrows*) and dilated tortuous ureters (U) entering the bladder (B). ***B.*** Abdominal computed tomography scan (coronal plane reconstruction) in a child showing severe scarring of the lower portion of the right kidney (*arrow*). ***C.*** Sonogram of the right kidney showing loss of parenchyma at the lower pole due to scarring (*arrow*) and hypertrophy of the mid-region (*arrowhead*). *(Courtesy of Dr. George Gross, University of Maryland Medical Center; with permission.)*

TREATMENT

Vesicoureteral Reflux and Reflux Nephropathy

Maintenance of sterile urine in childhood has been shown to limit scarring of the kidneys. Surgical reimplantation of the ureters into the bladder to restore competency is indicated in young children with persistent high-grade reflux, but is ineffective and is not indicated in adolescents or adults after scarring has occurred. Aggressive control of blood pressure with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) and other agents is effective in reducing proteinuria and may significantly forestall further deterioration of renal function.

SICKLE CELL NEPHROPATHY

The pathogenesis and clinical manifestations of sickle cell nephropathy are described in Chap. 311. Evidence of tubular injury may be evident in childhood and early adolescence in the form of polyuria due to decreased concentrating ability or type IV RTA years before there is significant nephron loss and proteinuria from secondary FSGS. Early recognition of these subtle renal abnormalities or development of microalbuminuria in a child with sickle cell disease may warrant consultation with a nephrologist and/or therapy with low-dose ACEIs. Papillary necrosis may result from ischemia due to sickling of red cells in the relatively hypoxemic and hypertonic medullary vasculature and present with gross hematuria and ureteric obstruction by sloughed ischemic papillae (Table 310-3).

TABLE 310-3 Major Causes of Papilary Necrosis
Analgesic nephropathy
Sickle cell nephropathy
Diabetes with urinary tract infection
Prolonged NSAID use (rare)

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

TUBULOINTERSTITIAL ABNORMALITIES ASSOCIATED WITH GLOMERULONEPHRITIS

Primary glomerulopathies are often associated with damage to tubules and interstitium. This may occasionally be due to the same pathologic process affecting the glomerulus and tubulointerstitium, as is the case with immune-complex deposition in lupus nephritis. More often, however, chronic tubulointerstitial changes occur as a secondary consequence of prolonged glomerular dysfunction. Potential mechanisms by which glomerular disease might cause tubulointerstitial injury include proteinuria-mediated damage to the epithelial cells, activation of tubular cells by cytokines and complement, or reduced peritubular blood flow leading to downstream tubulointerstitial ischemia, especially in the case of glomeruli that are globally obsolescent due to severe glomerulonephritis. It is often difficult to discern the initial cause of injury by renal biopsy in a patient who presents with advanced renal disease in this setting.

ANALGESIC NEPHROPATHY

Analgesic nephropathy results from the long-term use of compound analgesic preparations containing phenacetin (banned in the United States since 1983), aspirin, and caffeine. In its classic form, analgesic nephropathy is characterized by renal insufficiency, papillary necrosis (Table 310-3) attributable to the presumed concentration of the drug to toxic levels in the inner medulla, and a radiographic constellation of small, scarred kidneys with papillary calcifications best appreciated by computed tomography **(Fig. 310-5)**. Patients may also have polyuria due to impaired concentrating ability and non-anion-gap metabolic acidosis from tubular damage. Shedding of a sloughed necrotic papilla can cause gross hematuria and ureteric colic due to ureteral obstruction. Individuals with ESRD as a result of analgesic nephropathy are at increased risk of a urothelial malignancy compared to patients with other causes of renal failure. Recent cohort studies in individuals with normal baseline renal function suggest that the moderate chronic use of current analgesic preparations available in the United States, including acetaminophen and NSAIDs, does not seem to cause the constellation of findings known as analgesic nephropathy, although volume-depleted individuals and those with chronic kidney disease are at higher risk of NSAID-related renal toxicity. Nonetheless, it is recommended that heavy users of acetaminophen and NSAIDs be screened for evidence of renal disease.

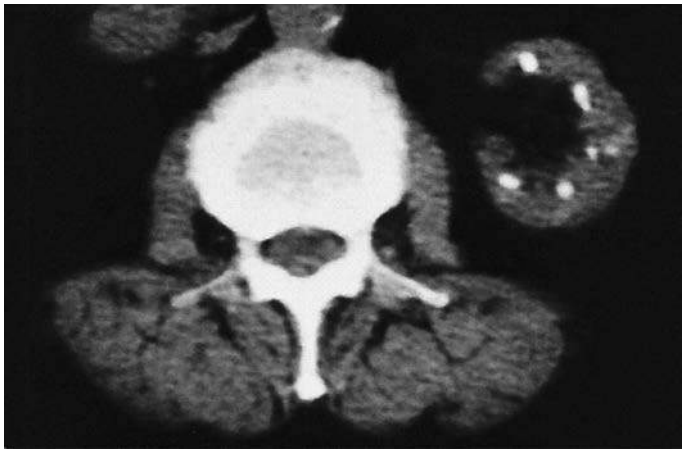


FIGURE 310-5 Radiologic appearance of analgesic nephropathy. A noncontrast computed tomography scan shows an atrophic left kidney with papillary calcifications in a garland pattern. *(Reprinted by permission from Macmillan Publishers, Ltd., MM Elseviers et al: Kidney International 48:1316, 1995.)*

ARISTOLOCHIC ACID NEPHROPATHY

Two seemingly unrelated forms of CIN, Chinese herbal nephropathy and Balkan endemic nephropathy, have recently been linked by the underlying etiologic agent aristolochic acid and are now collectively termed aristolochic acid nephropathy (AAN). In Chinese herbal nephropathy, first described in the early 1990s in young women taking traditional Chinese herbal preparations as part of a weight-loss regimen, one of the offending agents has been identified as aristolochic acid, a known carcinogen from the plant *Aristolochia*. Multiple *Aristolochia* species have been used in traditional herbal remedies for centuries and continue to be available despite official bans on their use in many countries. Molecular evidence has also implicated aristolochic acid in Balkan endemic nephropathy, a chronic TIN found primarily in towns along the tributaries of the Danube River and first described in the 1950s. Although the exact route of exposure is not known with certainty, contamination of local grain preparations with the seeds of *Aristolochia* species seems most likely. Aristolochic acid, after prolonged exposure, produces renal interstitial fibrosis with a relative paucity of cellular infiltrates. The urine sediment is bland, with rare leukocytes and only mild proteinuria. Anemia may be disproportionately severe relative to the level of renal dysfunction. Definitive diagnosis of AAN requires two of the following three features: characteristic histology on kidney biopsy; confirmation of aristolochic acid ingestion; and detection of aristolactam-DNA adducts in kidney or urinary tract tissue. These latter lesions represent a molecular signature of aristolochic acid–derived DNA damage and often consist of characteristic A:T-to-T:A transversions. Due to this mutagenic activity, AAN is associated with a very high incidence of upper urinary tract urothelial cancers, with risk related to cumulative dose. Surveillance with computed tomography, ureteroscopy, and urine cytology is warranted, and consideration should be given to bilateral nephroureterectomy once a patient has reached ESRD.

KARYOMEGALIC INTERSTITIAL NEPHRITIS

Karyomegalic interstitial nephritis is an unusual form of slowly progressive chronic kidney disease with mild proteinuria, interstitial fibrosis, tubular atrophy, and oddly enlarged nuclei of proximal tubular epithelial cells. It has been linked to mutations in *FAN1*, a nuclease involved in DNA repair, which may render carriers of the mutation susceptible to environmental DNA-damaging agents.

LITHIUM-ASSOCIATED NEPHROPATHY

The use of lithium salts for the treatment of manic-depressive illness may have several renal sequelae, the most common of which is nephrogenic diabetes insipidus manifesting as polyuria and polydipsia. Lithium accumulates in principal cells of the collecting duct by entering through the epithelial sodium channel (ENaC), where it inhibits glycogen synthase kinase 3β and downregulates vasopressin-regulated aquaporin water channels. Less frequently, chronic TIN develops after prolonged (>10–20 years) lithium use and is most likely to occur in patients who have experienced repeated episodes of toxic lithium levels. Findings on renal biopsy include interstitial fibrosis and tubular atrophy that are out of proportion to the degree of glomerulosclerosis or vascular disease, a sparse lymphocytic infiltrate, and small cysts or dilation of the distal tubule and collecting duct that are highly characteristic of this disorder. The degree of interstitial fibrosis correlates with both duration and cumulative dose of lithium. Individuals with lithium-associated nephropathy are typically asymptomatic, with minimal proteinuria, few urinary leukocytes, and normal blood pressure. Some patients develop more severe proteinuria due to secondary FSGS, which may contribute to further loss of renal function.

TREATMENT

Lithium-Associated Nephropathy

Renal function should be followed regularly in patients taking lithium, and caution should be exercised in patients with underlying renal disease. The use of amiloride to inhibit lithium entry via ENaC

has been effective to prevent and treat lithium-induced nephrogenic diabetes insipidus, but it is not clear if it will prevent lithium-induced CIN. Once lithium-associated nephropathy is detected, the discontinuation of lithium in attempt to forestall further renal deterioration can be problematic, as lithium is an effective mood stabilizer that is often incompletely substituted by other agents. Furthermore, despite discontinuation of lithium, chronic renal disease in such patients is often irreversible and can slowly progress to ESRD. The most prudent approach is to monitor lithium levels frequently and adjust dosing to avoid toxic levels (preferably <1 meq/L). This is especially important because lithium is cleared less effectively as renal function declines. In patients who develop significant proteinuria, ACEI or ARB treatment should be initiated.

CALCINEURIN-INHIBITOR NEPHROTOXICITY

The calcineurin inhibitor (CNI) immunosuppressive agents cyclosporine and tacrolimus can cause both acute and chronic renal injury. Acute forms can result from vascular causes such as vasoconstriction or the development of thrombotic microangiopathy, or can be due to a toxic tubulopathy. Chronic CNI-induced renal injury is typically seen in solid organ (including heart-lung and liver) transplant recipients and manifests with a slow but irreversible reduction of glomerular filtration rate, with mild proteinuria and arterial hypertension. Hyperkalemia is a relatively common complication and is caused, in part, by tubular resistance to aldosterone. The histologic changes in renal tissue include patchy interstitial fibrosis and tubular atrophy, often in a "striped" pattern. In addition, the intrarenal vasculature often demonstrates hyalinosis, and focal glomerulosclerosis can be present as well. Similar changes may occur in patients receiving CNIs for autoimmune diseases, although the doses are generally lower than those used for organ transplantation. Dose reduction or CNI avoidance appears to mitigate the chronic tubulointerstitial changes, but may increase the risk of rejection and graft loss.

HEAVY METAL (LEAD) NEPHROPATHY

Heavy metals, such as lead or cadmium, can lead to a chronic tubulointerstitial process after prolonged exposure. The disease entity is no longer commonly diagnosed, because such heavy metal exposure has been greatly reduced due to the known health risks from lead and the consequent removal of lead from most commercial products and fuels. Nonetheless, occupational exposure is possible in workers involved in the manufacture or destruction of batteries, removal of lead paint, or manufacture of alloys and electrical equipment (cadmium) in countries where industrial regulation is less stringent. In addition, ingestion of moonshine whiskey distilled in lead-tainted containers has been one of the more frequent sources of lead exposure.

Early signs of chronic lead intoxication are attributable to proximal tubule dysfunction, particularly hyperuricemia as a result of diminished urate secretion. The triad of "saturnine gout," hypertension, and renal insufficiency should prompt a practitioner to ask specifically about lead exposure. Unfortunately, evaluating lead burden is not as straightforward as ordering a blood test; the preferred methods involve measuring urinary lead after infusion of a chelating agent or by radiographic fluoroscopy of bone. Several recent studies have shown an association between chronic low-level lead exposure and decreased renal function, although either of these two factors may have been the primary event. In those patients who have CIN of unclear origin and an elevated total body lead burden, repeated treatments of lead chelation therapy have been shown to slow the decline in renal function.

METABOLIC DISORDERS

Disorders leading to excessively high or low levels of certain electrolytes and products of metabolism can also lead to chronic kidney disease if untreated.

CHRONIC URIC ACID NEPHROPATHY

The constellation of pathologic findings that represent *gouty nephropathy* are very uncommon nowadays and are more of historical interest than clinical importance, as gout is typically well managed with allopurinol and other agents. However, there is emerging evidence that hyperuricemia is an independent risk factor for the development of chronic kidney disease, perhaps through endothelial damage. The complex interactions of hyperuricemia, hypertension, and renal failure are still incompletely understood.

Presently, gouty nephropathy is most likely to be encountered in patients with severe tophaceous gout and prolonged hyperuricemia from a hereditary disorder of purine metabolism **(Chap. 410)**. This should be distinguished from juvenile hyperuricemic nephropathy, a form of medullary cystic kidney disease caused by mutations in uromodulin (UMOD) **(Chap. 309)** and now grouped into the larger category of autosomal dominant tubulointerstitial kidney disease. Histologically, the distinctive feature of gouty nephropathy is the presence of crystalline deposits of uric acid and monosodium urate salts in the kidney parenchyma. These deposits not only cause intrarenal obstruction but also incite an inflammatory response, leading to lymphocytic infiltration, foreign-body giant cell reaction, and eventual fibrosis, especially in the medullary and papillary regions of the kidney. Since patients with gout frequently suffer from hypertension and hyperlipidemia, degenerative changes of the renal arterioles may constitute a striking feature of the histologic abnormality, out of proportion to the other morphologic defects. Clinically, gouty nephropathy is an insidious cause of chronic kidney disease. Early in its course, glomerular filtration rate may be near normal, often despite morphologic changes in medullary and cortical interstitium, proteinuria, and diminished urinary concentrating ability. Treatment with allopurinol and urine alkalinization is generally effective in preventing uric acid nephrolithiasis and the consequences of recurrent kidney stones; however, gouty nephropathy may be intractable to such measures. Furthermore, the use of allopurinol in asymptomatic hyperuricemia has not been consistently shown to improve renal function.

HYPERCALCEMIC NEPHROPATHY

(See also Chap. 403) Chronic hypercalcemia, as occurs in primary hyperparathyroidism, sarcoidosis, multiple myeloma, vitamin D intoxication, or metastatic bone disease, can cause tubulointerstitial disease and progressive renal failure. The earliest lesion is a focal degenerative change in renal epithelia, primarily in collecting ducts, distal tubules, and loops of Henle. Tubular cell necrosis leads to nephron obstruction and stasis of intrarenal urine, favoring local precipitation of calcium salts and infection. Dilation and atrophy of tubules eventually occur, as do interstitial fibrosis, mononuclear leukocyte infiltration, and interstitial calcium deposition (nephrocalcinosis). Calcium deposition may also occur in glomeruli and the walls of renal arterioles.

Clinically, the most striking defect is an inability to maximally concentrate the urine, due to reduced collecting duct responsiveness to arginine vasopressin and defective transport of sodium and chloride in the loop of Henle. Reductions in both glomerular filtration rate and renal blood flow can occur, both in acute and in prolonged hypercalcemia. Eventually, uncontrolled hypercalcemia leads to severe tubulointerstitial damage and overt renal failure. Abdominal x-rays may demonstrate nephrocalcinosis as well as nephrolithiasis, the latter due to the hypercalciuria that often accompanies hypercalcemia.

Treatment consists of reducing the serum calcium concentration toward normal and correcting the primary abnormality of calcium metabolism **(Chap. 403).** Renal dysfunction of acute hypercalcemia may be completely reversible. Gradual progressive renal insufficiency related to chronic hypercalcemia, however, may not improve even with correction of the calcium disorder.

HYPOKALEMIC NEPHROPATHY

Patients with prolonged and severe hypokalemia from chronic laxative or diuretic abuse, surreptitious vomiting, or primary aldosteronism may develop a reversible tubular lesion characterized by vacuolar degeneration of proximal and distal tubular cells. Eventually, tubular atrophy and cystic dilation accompanied by interstitial fibrosis may ensue, leading to irreversible chronic kidney disease. Timely correction of the hypokalemia will prevent further progression, but persistent hypokalemia can cause ESRD.

GLOBAL PERSPECTIVE

The causes of acute and CIN vary widely across the globe. Analgesic nephropathy continues to be seen in countries where phenacetin-containing compound analgesic preparations are readily available. Adulterants in unregulated herbal and traditional medicaments pose a threat of toxic interstitial nephritis, as exemplified by aristolochic acid contamination of herbal slimming preparations. Contamination of food sources with toxins, such as the recent outbreak of nephrolithiasis and acute renal failure from melamine contamination of infant milk formula, poses a continuing risk. Large-scale exposure to aristolochic acid remains prevalent in many Asian countries where traditional herbal medicine use is common. Although industrial exposure to lead and cadmium has largely disappeared as a cause of CIN in developed nations, it remains a risk for nephrotoxicity in countries where such exposure is less well controlled. New endemic forms of chronic kidney disease continue to be described. Most notable is the nephropathy found among Pacific coastal plantation workers in Central America that is estimated to have claimed 20,000 lives thus far due to the development of end-stage kidney disease. This entity has been named Mesoamerican nephropathy, although similar pathophysiologic mechanisms may also be at play in other regional forms of chronic kidney disease in Sri Lanka and southern India. Although a variety of etiologic factors have been proposed, the most likely cause appears to be related to repetitive episodes of heat exposure, dehydration or volume depletion, and consequent metabolic changes leading to uricosuria and elevated levels of vasopressin. Global warming and regional temperature variability have been proposed as contributors to these newly described forms of kidney disease.

FURTHER READING

Bleyer AJ, Kmoch S: Autosomal dominant tubulointerstitial kidney disease: Of names and genes. Kidney Int 86:459, 2014.

Correa-Rotter R et al: CKD of unknown origin in Central America: The case for a Mesoamerican nephropathy. Am J Kidney Dis 63:506, 2014.

Muriithi AK et al: Clinical characteristics, causes and outcomes of acute interstitial nephritis in the elderly. Kidney Int 87:458, 2015.

Praga M et al: Changes in the aetiology, clinical presentation and management of acute interstitial nephritis, an increasingly common cause of acute kidney injury. Nephrol Dial Transplant 30:1472, 2015.

Raissian Y et al: Diagnosis of IgG4-related tubulointerstitial nephritis. J Am Soc Nephrol 22:1343, 2011.

311 Vascular Injury to the Kidney

Ronald S. Go, Nelson Leung

The renal circulation is complex and is characterized by a highly perfused arteriolar network, reaching cortical glomerular structures adjacent to lower-flow vasa recta that descend into medullary segments. Disorders of the larger vessels, including renal artery stenosis and atheroembolic disease, are discussed elsewhere **(Chap. 322)**. This chapter examines primary disorders of the renal microvessels, many of which are associated with thrombosis and hemolysis.

THROMBOTIC MICROANGIOPATHY

Thrombotic microangiopathy (TMA) is a pathologic lesion characterized by endothelial cell injury in the terminal arterioles and capillaries. Platelet and hyaline thrombi causing partial or complete occlusion are integral to the histopathology of TMA. TMA is usually accompanied by microangiopathic hemolytic anemia (MAHA) with its typical features of thrombocytopenia and schistocytes, but not always. In the kidney, TMA is characterized by swollen endocapillary cells (endotheliosis), fibrin thrombi, platelet plugs, arterial intimal fibrosis, and a membranoproliferative pattern in the glomerulus. Fibrin thrombi may extend into the arteriolar vascular pole, producing glomerular collapse and at times cortical necrosis. In kidneys that recover from acute TMA, secondary focal segmental glomerulosclerosis may develop. Diseases associated with this lesion include thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), malignant hypertension, scleroderma renal crisis, antiphospholipid syndrome, preeclampsia/HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, HIV infection, and radiation nephropathy. TMA can also be seen in myeloproliferative neoplasm (MPN)-related glomerulopathy and POEMS (polyneuropathy, endocrinopathy, organomegaly, monoclonal gammopathy and skin changes) syndrome which are not associated with MAHA.

HEMOLYTIC-UREMIC SYNDROME/THROMBOTIC THROMBOCYTOPENIC PURPURA

HUS and TTP are the prototypes for MAHA. Historically, HUS and TTP were distinguished mainly by their clinical and epidemiologic differences. TTP develops more commonly in adults and was thought to have more neurologic complications while HUS occurs more frequently in children, particularly when associated with hemorrhagic diarrhea. However, atypical HUS (aHUS) can have its first appearance in adulthood, and better testing has revealed that neurologic involvement is as common in HUS as in TTP. Currently, HUS and TTP can be differentiated etiologically and treated according to their specific pathophysiologic features.

Hemolytic-Uremic Syndrome HUS is loosely defined by the presence of MAHA and renal impairment. At least four variants are recognized. The most common is Shiga toxin–producing *Escherichia coli* (STEC) HUS, which is also known as D^+ (diarrhea-associated) HUS or enterohemorrhagic *E. coli* (EHEC) HUS. Most cases involve children <5 years of age, but adults also are susceptible, as evidenced by a 2011 outbreak in northern Europe. Diarrhea, often bloody, precedes MAHA within 1 week in >80% of cases. Abdominal pain, cramping, and vomiting are frequent, whereas fever is typically absent. Neurologic symptoms, including dysphasia, hyperreflexia, blurred vision, memory deficits, encephalopathy, perseveration, and agraphia, often develop, especially in adults. Seizures and cerebral infarction can occur in severe cases. STEC HUS is caused by the Shiga toxins (Stx1 and Stx2), which are also referred to as *verotoxins*. These toxins are produced by certain strains of *E. coli* and *Shigella dysenteriae*. In the United States and Europe, the most common STEC strain is O157:H7, but HUS has been reported with other strains ($O157/H^-$, $O111:H^-$, $O26:H11/H^-$, O145:H28, and O104:H4). After entry into the circulation, Shiga toxin binds to the glycolipid surface receptor globotriaosylceramide (Gb3), which is richly expressed on cells of the renal microvasculature. Upon binding, the toxin enters the cells, inducing inflammatory cytokines (interleukin 8 [IL-8], monocyte chemotactic protein 1 [MCP-1], and stromal cell–derived factor 1 [SDF-1]) and chemokine receptors (CXCR4 and CXCR7); this action results in platelet aggregation and the microangiopathic process. *Streptococcus pneumoniae* can also cause HUS. Certain strains produce a neuraminidase that cleaves the N-acetylneuraminic acid moieties normally covering the Thomsen-Friedenreich antigen on platelets and endothelial cells. Exposure of this cryptic antigen to preformed IgM results in severe MAHA.

Atypical HUS or complement medicated HUS is the result of complement dysregulation. The complement dysregulation can be congenital or acquired. The affected patients often have a low C3 and a normal C4 levels characteristic of alternative pathway activation. Factor H deficiency, the most common defect, has been linked to families with aHUS. Factor H competes with factor B to prevent the formation of C3bBb and acts as a cofactor for factor I, which proteolytically degrades C3b. More than 70 mutations of the factor H gene have been identified. Most are missense mutations that produce abnormalities in the

C-terminus region, affecting its binding to C3b but not its concentration. Other mutations result in low levels or the complete absence of the protein. Deficiencies in other complement-regulatory proteins, such as factor I, factor B, membrane cofactor protein (CD46), C3, complement factor H–related protein 1 (CFHR1), CFHR3, CFHR5, and thrombomodulin, have also been reported. Finally, an autoimmune variant of aHUS has been discovered. DEAP (deficiency of CFHR plasma proteins and CFH autoantibody positive) HUS occurs when an autoantibody to factor H is formed. DEAP HUS is often associated with a deletion of an 84-kb fragment of the chromosome that encodes for CFHR1 and CFHR3. The autoantibody blocks the binding of factor H to C3b and surface-bound C3 convertase. Renal injury is often severe resulting in end stage renal disease. The severity of the renal injury and recurrence after kidney transplant depend on the complement regulatory protein.

Thrombotic Thrombocytopenic Purpura Traditionally, TTP is characterized by the pentad: MAHA, thrombocytopenia, neurologic symptoms, fever, and renal failure. The pathophysiology of TTP involves the accumulation of ultra-large multimers of von Willebrand factor as a result of the absence or markedly decreased activity of the plasma protease ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13. TTP is now defined as MAHA associated with ADAMTS13 activity of (<5–10%). These ultra-large multimers form clots and shear erythrocytes, resulting in MAHA; however, the absence of ADAMTS13 alone may not by itself produce TTP. Often, an additional inflammatory trigger (such as infection, surgery, pancreatitis, or pregnancy) is required to initiate clinical TTP. This may be mediated by human neutrophil peptides that inhibit cleavage of von Willebrand factor by ADAMTS13.

Data from the Oklahoma TTP/HUS Registry suggest an incidence rate of 2.9 cases/10^6 patients in the United States. The median age of onset is 40 years. The incidence is more than nine times higher among blacks than among non-blacks. Like that of systemic lupus erythematosus, the incidence of TTP is nearly three times higher among women than among men. If untreated, TTP has a mortality rate exceeding 90%. Even with modern therapy, 20% of patients die within the first month from complications of microvascular thrombosis.

The classic form of TTP is idiopathic TTP, which is the result of a severe deficiency in ADAMTS13. In the past, TTP had traditionally been associated with infection, malignancy, and intense inflammation (e.g., pancreatitis), but ADAMTS13 activity is typically not decreased in these conditions and therefore should be not considered TTP. In idiopathic TTP, the formation of an autoantibody to ADAMTS13 (IgG or IgM) either increases its clearance or inhibits its activity. Upshaw-Schülman syndrome is a hereditary condition characterized by congenital deficiency of ADAMTS13. TTP in these patients can start within the first weeks of life but in some instances may not present until adulthood, especially during pregnancy. Both environmental and genetic factors are thought to influence the development of TTP. Plasma transfusion is an effective strategy for prevention and treatment.

Drug-induced TMA is a recognized complication of treatment with some chemotherapeutic agents, immunosuppressive agents, and quinine. Two different mechanisms are now recognized. Toxic or endothelial damage (pathologically similar to that of HUS) is the main cause of the TMA that develops in association with chemotherapeutic agents (e.g., mitomycin C, gemcitabine) and immunosuppressive agents (cyclosporine, interferon, sirolimus, and tacrolimus). This process is usually dose-dependent. Alternatively, TMA may develop as a result of drug-induced autoantibodies. This form is less likely to be dose-dependent and can, in fact, occur after a single dose in patients with previous exposure. ADAMTS13 deficiency is found in fewer than half of patients with clopidogrel-associated TTP. Quinine appears to induce autoantibodies to granulocytes, lymphocytes, endothelial cells, and platelet glycoprotein Ib/IX or IIb/IIIa complexes, but not to ADAMTS13. Quinine-associated TTP is more common among women. TMA has also been reported with drugs that inhibit vascular endothelial growth factor, such as bevacizumab; the mechanism is not completely understood.

TREATMENT

HUS/TTP

Treatment should be based on pathophysiology. Autoantibody-mediated TTP and DEAP HUS respond to the combination of plasma exchange and prednisone. In addition to removing the autoantibodies, plasma exchange with fresh-frozen plasma replaces ADAMTS13. Twice-daily plasma exchanges with administration of rituximab may be effective in refractory cases. Plasma infusion is usually sufficient to replace the ADAMTS13 in Upshaw-Schülman syndrome. Plasma exchange should be considered if larger volumes are necessary. Drug-induced TMA secondary to endothelial damage typically does not respond to plasma exchange and is treated primarily by discontinuing use of the agent and providing supportive care. Similarly, STEC HUS should be treated with supportive measures as plasma exchange has not been found to be effective. Antimotility agents and antibiotics increase the incidence of HUS among children, but azithromycin was recently found to decrease the duration of bacterial shedding by adults. Plasma infusion/exchange is effective in certain types of aHUS as it replaces complement-regulatory proteins. Eculizumab is a monoclonal antibody to C5 that is approved for use in aHUS which has been shown to abort MAHA and improve renal function. Antibiotics and washed red cells should be given in neuraminidase-associated HUS, and plasmapheresis may be helpful. However, plasma and whole-blood transfusion should be avoided since these products contain IgM, which may exacerbate MAHA. Finally, combined factor H and ADAMTS13 deficiency have been reported. The affected patients are generally less responsive to plasma infusion, a result illustrating the complexity of the management of these cases.

HEMATOPOIETIC STEM CELL TRANSPLANTATION–ASSOCIATED THROMBOTIC MICROANGIOPATHY (HSCT-TMA)

HSCT-TMA develops after HSCT, with an incidence of ~8%. Etiologic factors include conditioning regimens, immunosuppression, infections, and graft-versus-host disease. Other risk factors include female sex and human leukocyte antigen (HLA)–mismatched donor grafts. HSCT-TMA usually occurs within the first 100 days of HSCT. Table 311-1 lists definitions of HSCT-TMA currently used for clinical trials. Diagnosis may be difficult since thrombocytopenia, anemia, and renal insufficiency are common after HSCT. HSCT-TMA carries a high mortality rate (75% within 3 months). The majority of patients have >10% ADAMTS13 activity, and plasma exchange is beneficial in <25% of patients. Discontinuation of calcineurin inhibitors and treatment of infections or sinusoidal obstruction syndrome (if present)

TABLE 311-1 Criteria for Establishing Microangiopathic Kidney Injury Associated with Hematopoietic Stem Cell Transplantation

INTERNATIONAL WORKING GROUP	BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK TOXICITY COMMITTEE
4% schistocytes in the blood	RBC fragmentation and at least 2 schistocytes per high-power field
De novo, prolonged, or progressive thrombocytopenia	Concurrent increase in LDH concentration above baseline
A sudden and persistent increase in LDH concentration	Negative direct and indirect Coombs test
Decrease in hemoglobin level or increased RBC transfusion requirement	Concurrent renal and/or neurologic dysfunction without other explanations
Decrease in haptoglobin concentration	

Note: These features underscore the need to identify pathways of hemolysis and thrombocytopenia that accompany deterioration of kidney function.

Abbreviations: LDH, lactate dehydrogenase; RBC, red blood cell.

are recommended. Treatment with rituximab and defibrotide may also be helpful, but clinical trial data are lacking.

HIV-RELATED TMA

HIV-related TMA is a complication encountered mainly before widespread use of highly active antiretroviral therapy. It is seen in patients with advanced AIDS and low CD4+ T cell counts although it can be the first manifestation of HIV infection. The presence of MAHA, thrombocytopenia, and renal failure are suggestive, but renal biopsy is required for diagnosis since other renal diseases are also associated with HIV infection. Thrombocytopenia may prohibit renal biopsy in some patients. The mechanism of injury is unclear, although HIV can induce apoptosis in endothelial cells. ADAMTS13 activity is not reduced in these patients. Cytomegalovirus co-infection may also be a risk factor. Effective antiviral therapy is key, while plasma exchange should be limited to patients who have evidence of TTP.

RADIATION NEPHROPATHY

Either local or total body irradiation can produce microangiopathic injury. The kidney is one of the most radiosensitive organs, and injury can result with as little as 4–5 Gy. Such injury is characterized by renal insufficiency, proteinuria, and hypertension usually developing ≥6 months after radiation exposure. Renal biopsy reveals classic TMA with damage to glomerular, tubular, and vascular cells, but systemic evidence of MAHA is uncommon. Because of its high incidence after allogeneic HSCT, radiation nephropathy is often referred to as *bone marrow transplant nephropathy*. No specific therapy is available, although observational evidence supports renin-angiotensin system blockade.

SCLERODERMA (PROGRESSIVE SYSTEMIC SCLEROSIS)

Kidney involvement is common (up to 52%) in patients with widespread scleroderma, with 20% of cases resulting directly from scleroderma renal crisis. Other renal manifestations in scleroderma include transient (prerenal) or medication-related forms of acute kidney injury (e.g., associated with *D*-penicillamine, nonsteroidal anti-inflammatory drugs, or cyclosporine). Scleroderma renal crisis occurs in 12% of patients with diffuse systemic sclerosis but in only 2% of those with limited systemic sclerosis. Scleroderma renal crisis is the most severe manifestation of renal involvement, and is characterized by accelerated hypertension, a rapid decline in renal function, nephrotic range proteinuria, and hematuria. Retinopathy and encephalopathy may accompany the hypertension. Salt and water retention with microvascular injury can lead to pulmonary edema. Cardiac manifestations, including myocarditis, pericarditis, and arrhythmias, denote an especially poor prognosis. Although MAHA is present in more than half of patients, coagulopathy is rare.

The renal lesion in scleroderma renal crisis is characterized by arcuate artery intimal and medial proliferation with luminal narrowing. This lesion is described as "onion-skinning" and can be accompanied by glomerular collapse due to reduced blood flow. Histologically, scleroderma renal crisis is indistinguishable from malignant hypertension, with which it can coexist. Fibrinoid necrosis and thrombosis are common. Before the availability of angiotensin-converting enzyme (ACE) inhibitors, the mortality rate for scleroderma renal crisis was >90% at 1 month. Introduction of renin-angiotensin system blockade has lowered the mortality rate to 30% at 3 years. Nearly two-thirds of patients with scleroderma renal crisis may require dialysis support, with recovery of renal function in 50% (median time, 1 year). Glomerulonephritis and vasculitis associated with antineutrophil cytoplasmic antibodies and systemic lupus erythematosus have been described in patients with scleroderma. An association has been found with a speckled pattern of antinuclear antibodies and with antibodies to RNA polymerases I and III. Anti-U3-RNP may identify young patients at risk for scleroderma renal crisis. Anticentromere antibody, in contrast, is a negative predictor of this disorder. Because of the overlap between scleroderma renal crisis and other autoimmune disorders, a renal biopsy is recommended for patients with atypical renal involvement, especially if hypertension is absent.

Treatment with ACE inhibition is the first-line therapy unless contraindicated. The goal of therapy is to reduce systolic and diastolic blood pressure by 20 mmHg and 10 mmHg, respectively, every 24 h until blood pressure is normal. Additional antihypertensive therapy may be given once the dose of drug for ACE inhibition is maximized. Both ACE inhibitors and angiotensin II receptor antagonists are effective, although data suggest that treatment with ACE inhibitors is superior. ACE inhibition alone does not prevent scleroderma renal crisis, but it does reduce the impact of hypertension. Intravenous iloprost has been used in Europe for blood pressure management and improvement of renal perfusion. Kidney transplantation is not recommended for 2 years after the start of dialysis since delayed recovery may occur.

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (Chap. 350) can be either primary or secondary to systemic lupus erythematosus. It is characterized by a predisposition to systemic thrombosis (arterial and venous) and fetal morbidity mediated by antiphospholipid antibodies—mainly anticardiolipin antibodies (IgG, IgM, or IgA), lupus anticoagulant, or anti-β-2 glycoprotein I antibodies (antiβ2GPI). Patients with both anticardiolipin antibodies and antiβ2GPI appear to have the highest risk of thrombosis. The vascular compartment within the kidney is the main site of renal involvement. Arteriosclerosis is commonly present in the arcuate and intralobular arteries. In the intralobular arteries, fibrous intimal hyperplasia characterized by intimal thickening secondary to intense myofibroblastic intimal cellular proliferation with extracellular matrix deposition is frequently seen along with onion-skinning. Arterial and arteriolar fibrous and fibrocellular occlusions are present in more than two-thirds of biopsy samples. Cortical necrosis and focal cortical atrophy may result from vascular occlusion. TMA is commonly present in renal biopsies, although signs of MAHA and platelet consumption are usually absent. TMA is especially common in the catastrophic variant of antiphospholipid syndrome. In patients with secondary antiphospholipid syndrome, other glomerulopathies may be present, including membranous nephropathy, minimal change disease, focal segmental glomerulosclerosis, and pauci-immune crescentic glomerulonephritis.

Large vessels can be involved in antiphospholipid syndrome and may form the proximal nidus near the ostium for thrombosis of the renal artery. Renal vein thrombosis can occur and should be suspected in patients with lupus anticoagulant who develop nephrotic-range proteinuria. Progression to end-stage renal disease can occur, and a thrombosis may form in the vascular access and the renal allografts. Hypertension is common. Treatment entails lifelong anticoagulation. Glucocorticoids may be beneficial in accelerated hypertension. Immunosuppression and plasma exchange may be helpful for catastrophic episodes of antiphospholipid syndrome but by themselves do not reduce recurrent thrombosis.

HELLP SYNDROME

HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome is a dangerous complication of pregnancy associated with microvascular injury. Occurring in 0.2–0.9% of all pregnancies and in 10–20% of women with severe preeclampsia, this syndrome carries a mortality rate of 7.4–34%. Most commonly developing in the third trimester, 10% of cases occur before week 27 and 30% post-partum. Although a strong association exists between HELLP syndrome and preeclampsia, nearly 20% of cases are not preceded by recognized preeclampsia. Risk factors include abnormal placentation, family history, and elevated levels of fetal mRNA for FLT1 (vascular endothelial growth factor receptor 1) and endoglin. Patients with HELLP syndrome have higher levels of inflammatory markers (C-reactive protein, IL-1Ra, and IL-6) and soluble HLA-DR than do those with preeclampsia alone.

Renal failure occurs in half of patients with HELLP syndrome, although the etiology is not well understood. Limited data suggest that renal failure is the result of both preeclampsia and acute tubular necrosis. Renal histologic findings are those of TMA with endothelial cell swelling and occlusion of the capillary lumens, but luminal thrombi are typically absent. However, thrombi become more common in severe eclampsia and HELLP syndrome. Although renal failure is

common, the organ that defines this syndrome is the liver. Subcapsular hepatic hematomas sometimes produce spontaneous rupture of the liver and can be life-threatening. Neurologic complications such as cerebral infarction, cerebral and brainstem hemorrhage, and cerebral edema are other potentially life-threatening complications. Nonfatal complications include placental abruption, permanent vision loss due to Purtscher-like (hemorrhagic and vaso-occlusive vasculopathy) retinopathy, pulmonary edema, bleeding, and fetal demise.

Many features are shared by HELLP syndrome and MAHA. Diagnosis of HELLP syndrome is complicated by the fact that aHUS and TTP also can be triggered by pregnancy and complement mutations are common (30–40%) among patients with HELLP syndrome. Patients with antiphospholipid syndrome also have an elevated risk of HELLP syndrome. A history of MAHA before pregnancy is of diagnostic value. Serum levels of ADAMTS13 activity are reduced (by 30–60%) in HELLP syndrome but not to the levels seen in TTP (<5%). Determination of the ratio of lactate dehydrogenase to aspartate aminotransferase may be helpful. This ratio is 13:1 in patients with HELLP syndrome and preeclampsia as opposed to 29:1 in patients without preeclampsia. Other markers, such as antithrombin III (decreased in HELLP syndrome but not in TTP) and D-dimer (elevated in HELLP syndrome but not in TTP), may also be useful. HELLP syndrome usually resolves spontaneously after delivery, although a small percentage of HELLP cases occur post-partum. Glucocorticoids may decrease inflammatory markers, although two randomized controlled trials failed to show much benefit. Plasma exchange should be considered if hemolysis is refractory to glucocorticoids and/or delivery, especially if TTP has not been ruled out.

Myeloproliferative Neoplasm-Related Glomerulopathy While MAHA is often present in TMA, this is not true for all lesions. Two conditions are now recognized to present with renal TMA but no evidence of systemic MAHA. The first is MPN-related glomerulopathy. MPN represents a group of clonal disorders that includes chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), systemic mastocytosis, chronic eosinophilic leukemia not otherwise specified, chronic neutrophilic leukemia, and unclassifiable MPN. These patients present with renal impairment and nephrotic range proteinuria. MPN-related glomerulopathy usually occurs late in the course of the hematologic condition as median time from diagnosis of MPN to glomerulopathy was 7.2 years. Renal biopsy shows mesangial expansion, hypercellularity, mesangial and segmental sclerosis, luminal hyalinosis, loss of overlying podocytes, and adhesions to Bowman's capsule and duplication of glomerular basement membranes. Foot process effacement ranges from 30 to 95%. Arteriosclerosis is common and ranges from mild to severe. Arteriolar hyalinosis can also be seen. Extremedullary hematopoiesis can sometimes be seen especially in patients with myelofibrosis. MPGN-related glomerulopathy may develop while patients are on treatment with hydroxyurea and JAK2 inhibitors. No standard treatment is available. RAS blockade and corticosteroids have been tried with mixed results.

POEMS Syndrome POEMS syndrome is a systemic disease characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. Peripheral neuropathy with severe motorsensory deficit is the hallmark of the disease. Another characteristic is that >95% of monoclonal light chain is of the lambda isotype. IgA also makes up about 50% of the monoclonal protein. Organomegaly can involve any organ and often presents as lymphadenopathy. In the kidney, the hypertrophy frequently is unilateral. One study suggests the difference in kidney size is due to unilateral contraction; however, a volumemetric study showed that enlargement is responsible for the difference in kidney size in some patients. Glomerulomegaly is not uncommon. Lobular appearance, endothelial cell swelling, hypercellularity, mesangiolysis, microaneurysm, and glomerular enlargement are reminiscent of membranoproliferative glomerulonephritis. Most patients present with mild to moderate renal impairment and low grade proteinuria. Progression to end stage renal disease is rare.

SICKLE CELL NEPHROPATHY

Renal complications in sickle cell disease result from occlusion of the vasa recta in the renal medulla. The low partial pressure of oxygen and high osmolarity predispose to hemoglobin S polymerization and erythrocyte sickling. Sequelae include hyposthenuria, hematuria, and papillary necrosis (which can also occur in sickle trait). The kidney responds by increases in blood flow and glomerular filtration rate mediated by prostaglandins. This dependence on prostaglandins may explain the greater reduction of glomerular filtration rate by nonsteroidal anti-inflammatory drugs in these patients than in others. The glomeruli are typically enlarged. Intracapillary fragmentation and phagocytosis of sickled erythrocytes are thought to be responsible for the membranoproliferative glomerulonephritis–like lesion, and focal segmental glomerulosclerosis is seen in more advanced cases. Proteinuria is present in 20–30%, and nephrotic-range proteinuria is associated with progression to renal failure. ACE inhibitors reduce proteinuria, although data are lacking on prevention of renal failure. Patients with sickle cell disease are also more prone to acute renal failure. The cause is thought to reflect microvascular occlusion associated with nontraumatic rhabdomyolysis, high fever, infection, and generalized sickling. Chronic kidney disease is present in 12–20% of patients. Despite the frequency of renal disease, hypertension is uncommon in patients with sickle cell disease.

RENAL VEIN THROMBOSIS

Renal vein thrombosis either can present with flank pain, tenderness, hematuria, rapid decline in renal function, and proteinuria or can be silent. Occasionally, renal vein thrombosis is identified during a workup for pulmonary embolism. The left renal vein is more commonly involved, and two-thirds of cases are bilateral. Etiologies can be divided into three broad categories: endothelial damage, venous stasis, and hypercoagulability. Homocystinuria, endovascular intervention, and surgery can produce vascular endothelial damage. Dehydration, which is more common among male patients, is a common cause of stasis in the pediatric population. Stasis also can result from compression and kinking of the renal veins from retroperitoneal processes such as retroperitoneal fibrosis and abdominal neoplasms. Thrombosis can occur throughout the renal circulation, including the renal veins, with antiphospholipid syndrome. Renal vein thrombosis can also be secondary to nephrotic syndrome, particularly membranous nephropathy. Other hypercoagulable states less commonly associated with renal vein thrombosis include proteins C and S, antithrombin deficiency, factor V Leiden, disseminated malignancy, and oral contraceptives. Severe nephrotic syndrome may also predispose patients to renal vein thrombosis.

Diagnostic screening can be performed with Doppler ultrasonography, which is more sensitive than ultrasonography alone. Computed tomography angiography is ~100% sensitive. Magnetic resonance angiography is another option but is more expensive. Treatment for renal vein thrombosis consists of anticoagulation and therapy for the underlying cause. Endovascular thrombolysis may be considered in severe cases. Occasionally, nephrectomy may be undertaken for life-threatening complications. Vena caval filters are often used to prevent migration of thrombi.

FURTHER READING

Al-Nouri ZL et al: Drug-induced thrombotic microangiopathy: A systematic review of published reports. Blood 125:616, 2015.

Bose N et al: Scleroderma renal crisis. Sem Arthritis and Rheumatism 44:687, 2015.

Bresin E et al: Combined complement gene mutations in atypical hemolytic uremic syndrome influence clinical phenotype. J Am Soc Nephrol 24:475, 2013.

George JN, Nester CM: Syndromes of thrombotic microangiopathy. N Engl J Med 371:1847, 2014.

Go RS et al: Thrombotic Microangiopathy Care Pathway: A Consensus Statement for the Mayo Clinic Complement Alternative Pathway-Thrombotic Microangiopathy (CAP-TMA) Disease-Oriented Group. Mayo Clin Proc 91:1189, 2016.

312 Nephrolithiasis

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Nephrolithiasis, or kidney stone disease, is a common, painful, and costly condition. Each year, billions of dollars are spent on nephrolithiasis-related activity, with the majority of expenditures on surgical treatment of existing stones. While a stone may form due to crystallization of lithogenic factors in the upper urinary tract, it can subsequently move into the ureter and cause renal colic. Although nephrolithiasis is rarely fatal, patients who have had renal colic report that it is the worst pain they have ever experienced. The evidence on which to base clinical recommendations is not as strong as desired; nonetheless, most experts agree that the recurrence of most, if not all, types of stones can be prevented with careful evaluation and targeted recommendations. Preventive treatment may be lifelong; therefore, an in-depth understanding of this condition must inform the implementation of tailored interventions that are most appropriate for and acceptable to the patient.

There are several types of kidney stones. It is clinically important to identify the stone type, which informs prognosis and selection of the optimal preventive regimen. Calcium oxalate stones are most common (~75%); next, in order, are calcium phosphate (~15%), uric acid (~8%), struvite (~1%), and cystine (<1%) stones. Many stones are a mixture of crystal types (e.g., calcium oxalate and calcium phosphate) and also contain protein in the stone matrix. Rarely, stones are composed of medications, such as acyclovir, atazanavir, and triamterene. Stones that form as a result of an upper tract infection, if not appropriately treated, can have devastating consequences and lead to end-stage renal disease. Consideration should be given to teaching practitioners strategies to prevent recurrence of all stone types and the related morbidity.

EPIDEMIOLOGY

Nephrolithiasis is a global disease. Data suggest an increasing prevalence, likely due to Westernization of lifestyle habits (e.g., dietary changes, increasing body mass index). National Health and Nutrition Examination Survey data for 2007–2010 indicate that up to 19% of men and 9% of women will develop at least one stone during their lifetime. The prevalence is ~50% lower among black individuals than among whites. The incidence of nephrolithiasis (i.e., the rate at which previously unaffected individuals develop their first stone) also varies by age, sex, and race. Among white men, the peak annual incidence is ~3.5 cases/1000 at age 40 and declines to ~2 cases/1000 by age 70. Among white women in their thirties, the annual incidence is ~2.5 cases/1000; the figure decreases to ~1.5/1000 at age 50 and beyond. In addition to the medical costs associated with nephrolithiasis, this condition also has a substantial economic impact, as those affected are often of working age. Once an individual has had a stone, the prevention of a recurrence is essential. Published recurrence rates vary by the definitions and diagnostic methods used. Some reports have relied on symptomatic events, while others have been based on imaging. Most experts agree that radiographic evidence of a second stone should be considered to represent a recurrence, even if the stone has not yet caused symptoms.

ASSOCIATED MEDICAL CONDITIONS

Nephrolithiasis is a systemic disorder. Several conditions predispose to stone formation, including gastrointestinal malabsorption (e.g., Crohn's disease, gastric bypass surgery), primary hyperparathyroidism, obesity, type 2 diabetes mellitus, and distal renal tubular acidosis. A number of other medical conditions are more likely to be present in individuals with a history of nephrolithiasis, including hypertension, gout, cardiovascular disease, cholelithiasis, reduced bone mineral density, and chronic kidney disease.

Although nephrolithiasis does not directly cause upper urinary tract infections (UTIs), a UTI in the setting of an obstructing stone is a urologic emergency ("pus under pressure") and requires urgent intervention to reestablish drainage.

PATHOGENESIS

In the consideration of the processes involved in crystal formation, it is helpful to view urine as a complex solution. A clinically useful concept is *supersaturation* (the point at which the concentration product exceeds the solubility product). However, even though the urine in most individuals is supersaturated with respect to one or more types of crystals, the presence of inhibitors of crystallization prevents the majority of the population from continuously forming stones. The most clinically important inhibitor of calcium-containing stones is urine citrate. While the calculated supersaturation value does not perfectly predict stone formation, it is a useful guide as it integrates the multiple factors that are measured in a 24-h urine collection.

Recent studies have changed the paradigm for the site of initiation of stone formation. Renal biopsies of stone formers have revealed calcium phosphate in the renal interstitium. It is hypothesized that this calcium phosphate deposits at the thin limb of the loop of Henle, and then extends down to the papilla and erodes through the papillary epithelium, where it provides a site for deposition of calcium oxalate and calcium phosphate crystals. The majority of calcium oxalate stones grow on calcium phosphate at the tip of the renal papilla (*Randall's plaque*). Tubular plugs of calcium phosphate may be the initiating event in calcium phosphate stone development. Thus, the process of stone formation may begin years before a clinically detectable stone is identified. The processes involved in interstitial deposition are under active investigation.

RISK FACTORS

Risk factors for nephrolithiasis can be categorized as dietary, nondietary, or urinary. These risk factors vary by stone type and by clinical characteristics.

Dietary Risk Factors Patients who develop stones often change their diet; therefore, studies that retrospectively assess diet may be hampered by recall bias. Some studies have examined the relation between diet and changes in the lithogenic composition of the urine, often using calculated supersaturation. However, the composition of the urine does not perfectly predict risk, and not all components that modify risk are included in the calculation of supersaturation. Thus, dietary associations are best investigated by prospective studies that examine actual stone formation as the outcome. Dietary factors that are associated with an increased risk of nephrolithiasis include animal protein, oxalate, sodium, sucrose, and fructose. Dietary factors associated with a lower risk include calcium, potassium, and phytate.

CALCIUM The role of dietary calcium deserves special attention. Although in the distant past dietary calcium had been suspected of increasing the risk of stone disease, several prospective observational studies and a randomized controlled trial have demonstrated that higher dietary calcium intake is related to a *lower* risk of stone formation. The reduction in risk associated with higher calcium intake may be due to a reduction in intestinal absorption of dietary oxalate that results in lower urine oxalate. Low calcium intake is contraindicated as it increases the risk of stone formation and may contribute to lower bone density in stone formers.

Despite similar bioavailability, supplemental calcium may increase the risk of stone formation. The discrepancy between the risks from dietary calcium and calcium supplements may be due to the timing of supplemental calcium intake or to higher total calcium consumption leading to higher urinary calcium excretion.

OXALATE Urinary oxalate is derived from both endogenous production and absorption of dietary oxalate. Owing to its low and often variable bioavailability, much of the oxalate in food may not be readily absorbed. However, absorption may be higher in stone formers. Although observational studies demonstrate that dietary oxalate is only a weak risk factor for stone formation, urinary oxalate is a strong risk factor for calcium oxalate stone formation, and efforts to avoid high oxalate intake should thus be beneficial.

OTHER NUTRIENTS Several other nutrients have been studied and implicated in stone formation. Higher intake of animal protein may lead to increased excretion of calcium and uric acid as well as to decreased urinary excretion of citrate, all of which increase the risk of stone formation. Higher sodium and sucrose intake increases calcium excretion independent of calcium intake. Higher potassium intake decreases calcium excretion, and many potassium-rich foods increase urinary citrate excretion due to their alkali content. Other dietary factors that have been inconsistently associated with lower stone risk include magnesium and phytate.

Vitamin C supplements are associated with an increased risk of calcium oxalate stone formation in men, possibly because of raised levels of oxalate in urine. Thus, male calcium oxalate stone formers should be advised to avoid vitamin C supplements. Although high doses of supplemental vitamin B_6 may be beneficial in selected patients with type 1 primary hyperoxaluria, the risk is not reduced in other patients.

FLUIDS AND BEVERAGES The risk of stone formation increases as urine volume decreases. When the urine output is <1 L/d, the risk of stone formation more than doubles. Fluid intake is the main determinant of urine volume, and the importance of fluid intake in preventing stone formation has been demonstrated in observational studies and in a randomized controlled trial. Observational studies have found that coffee, tea, beer, wine, and orange juice are associated with a reduced risk of stone formation. Sugar-sweetened beverage consumption may increase risk.

Nondietary Risk Factors Age, race, body size, and environment are important risk factors for nephrolithiasis. The incidence of stone disease is highest in middle-aged white men, but stones can form in infants as well as in the elderly. There is geographic variability, with the highest prevalence in the southeastern United States. Weight gain increases the risk of stone formation, and the increasing prevalence of nephrolithiasis in the United States may be due in part to the increasing prevalence of obesity. Environmental and occupational influences that may lead to lower urine volume, such as working in a hot environment or lack of ready access to water or a bathroom, are important considerations.

Urinary Risk Factors • **URINE VOLUME** As mentioned above, lower urine volume results in higher concentrations of lithogenic factors and is a common and readily modifiable risk factor. A randomized trial has demonstrated the effectiveness of higher fluid intake in increasing urine volume and reducing the risk of stone recurrence.

URINE CALCIUM Higher urine calcium excretion increases the likelihood of formation of calcium oxalate and calcium phosphate stones. While the term *hypercalciuria* is often used, there is no widely accepted cutoff that distinguishes between normal and abnormal urine calcium excretion. In fact, the relation between urine calcium and stone risk appears to be continuous; thus, the use of an arbitrary threshold should be avoided. Levels of urine calcium excretion are higher in individuals with a history of nephrolithiasis; however, the mechanisms remain poorly understood. Greater gastrointestinal calcium absorption is one important contributor, and greater bone turnover (with a resultant reduction in bone mineral density) may be another. Primary renal calcium loss, with lower serum calcium concentrations and elevated serum levels of parathyroid hormone (PTH) (and a normal 25-hydroxy vitamin D level), is rare.

URINE OXALATE Higher urine oxalate excretion increases the likelihood of calcium oxalate stone formation. As for urine calcium, no definition for "abnormal" urine oxalate excretion is widely accepted. Given that the relation between urine oxalate and stone risk is continuous, simple dichotomization of urine oxalate excretion is not helpful in assessing risk. The two sources of urine oxalate are endogenous generation and dietary intake. Dietary oxalate is the major contributor and also the source that can be modified. Notably, higher dietary calcium intake reduces gastrointestinal oxalate absorption and thereby reduces urine oxalate.

URINE CITRATE Urine citrate is a natural inhibitor of calcium-containing stones; thus, lower urine citrate excretion increases the risk of stone formation. Citrate reabsorption is influenced by the intracellular pH of proximal tubular cells. Metabolic acidosis, including that due to higher animal flesh intake, will lead to a reduction in citrate excretion by increasing reabsorption of filtered citrate. However, a notable proportion of patients have lower urine citrate for reasons that remain unclear.

URINE URIC ACID Higher urine levels of uric acid—a risk factor for uric acid stone formation—are found in individuals with excess purine consumption and rare genetic conditions that lead to overproduction of uric acid. This characteristic does not appear to be associated with the risk of calcium oxalate stone formation.

URINE pH Urine pH influences the solubility of some crystal types. Uric acid stones form only when the urine pH is consistently ≤5.5 or lower, whereas calcium phosphate stones are more likely to form when the urine pH is ≥6.5 or higher. Cystine is more soluble at higher urine pH. Calcium oxalate stones are not influenced by urine pH.

Genetic Risk Factors The risk of nephrolithiasis is more than twofold greater in individuals with a family history of stone disease. This association is likely due to a combination of genetic predisposition and similar environmental exposures. While a number of rare monogenic disorders cause nephrolithiasis, the genetic contributors to common forms of stone disease remain to be determined.

The two most common and well-characterized rare monogenic disorders that lead to stone formation are primary hyperoxaluria and cystinuria. *Primary hyperoxaluria* is an autosomal recessive disorder that causes excessive endogenous oxalate generation by the liver, with consequent calcium oxalate stone formation and crystal deposition in organs. Intraparenchymal calcium oxalate deposition in the kidney can eventually lead to renal failure. *Cystinuria* is an autosomal recessive disorder that causes abnormal reabsorption of filtered basic amino acids. The excessive urinary excretion of cystine, which is poorly soluble, leads to cystine stone formation. Cystine stones are visible on plain radiographs and often manifest as staghorn calculi or multiple bilateral stones. Repeat episodes of obstruction and instrumentation can cause a reduction in the glomerular filtration rate (GFR).

APPROACH TO THE PATIENT

Nephrolithiasis

Evidence-based guidelines for the evaluation and treatment of nephrolithiasis have been recently published. Although there is limited evidence for several aspects, there are standard approaches to patients with acute and chronic presentations that can reasonably guide the clinical evaluation.

It typically requires weeks to months (and often much longer) for a kidney stone to grow to a clinically detectable size. Although the passage of a stone is a dramatic event, stone formation and growth are characteristically clinically silent. A stone can remain asymptomatic in the kidney for years or even decades before signs (e.g., hematuria) or symptoms (e.g., pain) become apparent. Thus, it is important to remember that the onset of symptoms, typically attributable to a stone moving into the ureter, does not provide insight into when the stone actually formed. The factors that induce stone movement are unknown.

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

There are two common presentations for individuals with an acute stone event: renal colic and painless gross hematuria. *Renal colic* is a misnomer because pain typically does not subside completely; rather, it varies in intensity. When a stone moves into the ureter, the discomfort often begins with a sudden onset of unilateral flank pain.

The intensity of the pain can increase rapidly, and there are no alleviating factors. This pain, which is accompanied often by nausea and occasionally by vomiting, may radiate, depending on the location of the stone. If the stone lodges in the upper part of the ureter, pain may radiate anteriorly; if the stone is in the lower part of the

ureter, pain can radiate to the ipsilateral testicle in men or the ipsilateral labium in women. Occasionally, a patient has gross hematuria without pain.

Other diagnoses may be confused with acute renal colic. If the stone is lodged at the right ureteral pelvic junction, symptoms may mimic those of acute cholecystitis. If the stone blocks the ureter as it crosses over the right pelvic brim, symptoms may mimic acute appendicitis, whereas blockage at the left pelvic brim may be confused with acute diverticulitis. If the stone lodges in the ureter at the ureterovesical junction, the patient may experience urinary urgency and frequency. In female patients, the latter symptoms may lead to an incorrect diagnosis of bacterial cystitis; the urine will contain red and white blood cells, but the urine culture will be negative. An obstructing stone with proximal infection may present as acute pyelonephritis. A UTI in the setting of ureteral obstruction is a medical emergency that requires immediate restoration of drainage by placement of either a ureteral stent or a percutaneous nephrostomy tube. Other conditions to consider in the differential diagnosis include muscular or skeletal pain, *herpes zoster*, duodenal ulcer, abdominal aortic aneurysm, gynecologic conditions, ureteral stricture, and ureteral obstruction by materials other than a stone, such as a blood clot or sloughed papilla. Extraluminal processes can lead to ureteral compression and obstruction; however, because of the gradual onset, these conditions do not typically present with renal colic.

DIAGNOSIS AND INTERVENTION

Serum chemistry findings are typically normal, but the white blood cell count may be elevated. Examination of the urine sediment will usually reveal red and white blood cells and occasionally crystals **(Fig. 312-1)**. The absence of hematuria does not exclude a stone, particularly when urine flow is completely obstructed by a stone.

The diagnosis is often made on the basis of the history, physical examination, and urinalysis. Thus, it may not be necessary to wait for radiographic confirmation before treating the symptoms. The diagnosis is confirmed by an appropriate imaging study—preferably helical computed tomography (CT), which is highly sensitive, allows visualization of uric acid stones (traditionally considered "radiolucent"), and does not require radiocontrast **(Fig. 312-2)**. Helical CT detects stones as small as 1 mm that may be missed by other imaging modalities.

Typically, helical CT reveals a ureteral stone or evidence of recent passage (e.g., perinephric stranding or hydronephrosis), whereas a plain abdominal radiograph (kidney/ureter/bladder, or KUB) can miss a stone in the ureter or kidney, even if it is radiopaque, and does not provide information on obstruction. Abdominal ultrasound offers the advantage of avoiding radiation and provides information on hydronephrosis, but it is not as sensitive as CT and images only the kidney and possibly the proximal segment of the ureter; thus most ureteral stones are not detectable by ultrasound.

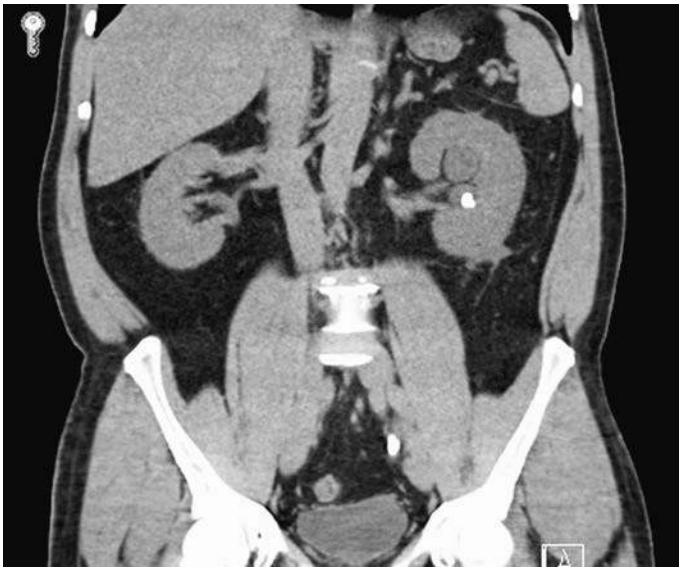

FIGURE 312-2 Coronal noncontrast CT image from a patient who presented with left-sided renal colic. An obstructing calculus, present in the distal left ureter at the level of S1, measures 10 mm in maximal dimension. There is severe left hydroureteronephrosis and associated left perinephric fat stranding. In addition, there is a nonobstructing 6-mm left renal calculus in the interpolar region. *(Image courtesy of Dr. Stuart Silverman, Brigham and Women's Hospital.)*

Many patients who experience their first episode of colic seek emergent medical care. Randomized trials have demonstrated that parenterally administered nonsteroidal anti-inflammatory drugs (such as ketorolac) are just as effective as opioids in relieving symptoms and have fewer side effects. Excessive fluid administration has not been shown to be beneficial; therefore, the goal should be to maintain euvolemia. If the pain can be adequately controlled and the patient is able to take fluids orally, hospitalization can be avoided. Use of an alpha blocker may increase the rate of spontaneous stone passage.

Urologic intervention should be postponed unless there is evidence of UTI, a low probability of spontaneous stone passage (e.g., a stone measuring ≥6 mm or an anatomic abnormality), or intractable pain. A ureteral stent may be placed cystoscopically, but this procedure typically requires general anesthesia, and the stent can be quite

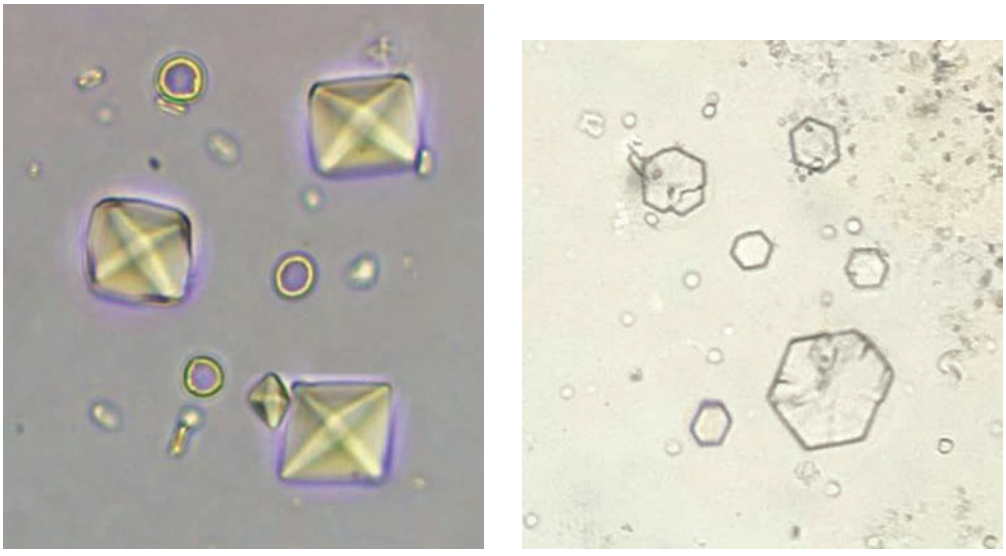

FIGURE 312-1 Urine sediment from a patient with calcium oxalate stones (*left*) and a patient with cystine stones (*right*). Calcium oxalate dihydrate crystals are bipyramidally shaped, and cystine crystals are hexagonal. *(Left panel image courtesy of Dr. John Lieske, Mayo Clinic.)*

uncomfortable, may cause gross hematuria, and may increase the risk of UTI.

If an intervention is indicated, the selection of the most appropriate intervention is determined by the size, location, and composition of the stone; the urinary tract anatomy; and the experience of the urologist. Extracorporeal shockwave lithotripsy (ESWL), the least invasive option, uses shock waves generated outside the body to fragment the stone, but is being used less frequently. An endourologic approach, now more frequently used than ESWL, can remove a stone by basket extraction or laser fragmentation. For large upper-tract stones, percutaneous nephrostolithotomy has the highest likelihood of rendering the patient stone-free. Advances in urologic approaches and instruments have nearly eliminated the need for open surgical procedures such as ureterolithotomy or pyelolithotomy.

EVALUATION FOR STONE PREVENTION

More than half of first-time stone formers will have a recurrence within 10 years. A careful evaluation is indicated to identify predisposing factors, which can then be modified to reduce the risk of new stone formation. It is appropriate to proceed with an evaluation even after the first stone if the patient is interested because recurrences are common and are usually preventable with inexpensive lifestyle modifications or other treatments.

HISTORY

A detailed history, obtained from the patient and from a thorough review of medical records, should include the number and frequency of episodes (distinguishing stone passage from stone formation) and previous imaging studies, interventions, evaluations, and treatments. Inquiries about the patient's medical history should cover UTIs, bariatric surgery, gout, hypertension, and diabetes mellitus. A family history of stone disease may reveal a genetic predisposition. A complete list of current prescription and over-the-counter medications as well as vitamin and mineral supplements is essential. The review of systems should focus on identifying possible etiologic factors related to low urine volume (e.g., high insensible losses) and gastrointestinal malabsorption as well as on ascertaining how frequently the patient voids during the day and overnight.

A large body of compelling evidence has demonstrated the important role of diet in stone disease. Thus, the dietary history should encompass information on usual dietary habits (meals and snacks), calcium intake, consumption of high-oxalate foods (spinach, rhubarb, potatoes), and fluid intake (including amount of specific beverages typically consumed). Amount and frequency of use of vitamin and mineral supplements should be carefully assessed.

PHYSICAL EXAMINATION

The physical examination should assess weight, blood pressure, costovertebral angle tenderness, and lower-extremity edema as well as signs of other systemic conditions such as primary hyperparathyroidism and gout.

LABORATORY EVALUATION

If not recently measured, the following serum levels should be determined: electrolytes (to uncover hypokalemia or renal tubular acidosis), creatinine, calcium, and uric acid. The PTH level should be measured if indicated by high-normal or elevated serum and urine calcium concentrations. Often, 25-hydroxy vitamin D is measured in concert with PTH to investigate the possible role of secondarily elevated PTH levels in the setting of vitamin D insufficiency.

The urinalysis, including examination of the sediment, can provide useful information. In individuals with asymptomatic residual renal stones, red and white blood cells are frequently present in urine. If there is concern about the possibility of an infection, a urine culture should be performed. The sediment may also reveal crystals (Fig. 312-1), which may help identify the stone type and also provide prognostic information, as crystalluria is a strong risk factor for new stone formation.

The results from 24-h urine collections serve as the cornerstone on which therapeutic recommendations are based. Recommendations on lifestyle modification should be deferred until urine collection is complete. As a baseline assessment, patients should collect at least two 24-h urine samples while consuming their usual diet and usual volume of fluid. The following factors should be measured: total volume, calcium, oxalate, citrate, uric acid, sodium, potassium, phosphorus, pH, and creatinine. When available, the calculated supersaturation is also informative. There is substantial day-to-day variability in the 24-h excretion of many relevant factors; therefore, obtaining values from two collections is important before committing a patient to long-term lifestyle changes or medication. The interpretation of the 24-h urine results should take into account that the collections are usually performed on a weekend day when the patient is staying at home; an individual's habits may differ dramatically (beneficially or detrimentally) at work or outside the home. Specialized testing, such as calcium loading or restriction, is not recommended as it does not influence clinical recommendations.

Stone composition analysis is essential if a stone or fragment is available; patients should be encouraged to retrieve passed stones. The stone type cannot be determined with certainty from 24-h urine results, but pure uric acid stones can be identified by low Hounsfield units on CT.

IMAGING

The "gold standard" diagnostic test is helical CT without contrast. If not already performed during an acute episode, a low-dose CT should be considered to definitively establish the baseline stone burden. A suboptimal imaging study may not detect a residual stone that, if subsequently passed, would be mistaken for a new stone. In this instance, the preventive medical regimen might be unnecessarily changed as the result of a preexisting stone.

Recommendations for follow-up imaging should be tailored to the individual patient. While CT provides the best information, the radiation dose is higher than from other modalities; therefore, CT should be performed only if the results will lead to a change in clinical recommendations. Although they are less sensitive, renal ultrasound or a KUB examinaion is typically used to minimize radiation exposure, with recognition of the limitations.

PREVENTION OF NEW STONE FORMATION

Recommendations for preventing stone formation depend on the stone type and the results of metabolic evaluation. After remediable secondary causes of stone formation (e.g., primary hyperparathyroidism) are excluded, the focus should turn to modification of the urine composition to reduce the risk of new stone formation. The urinary constituents are continuous variables, and the associated risk is continuous; thus, there are no definitive thresholds. Dichotomization into "normal" and "abnormal" can be misleading and should be avoided.

For all stone types, consistently diluted urine reduces the likelihood of crystal formation. The urine volume should be at least 2 L/d. Because of differences in insensible fluid losses and fluid intake from food sources, the required total fluid intake will vary from person to person. Rather than specify how much to drink, it is more helpful to educate patients about how much *more* they need to drink in light of their 24-h urine volume. For example, if the daily urine volume is 1.5 L, then the patient should be advised to drink at least 0.5 L more per day in order to increase the urine volume to the goal of 2 L/day.

RECOMMENDATIONS FOR SPECIFIC STONE TYPES

Calcium Oxalate Risk factors for calcium oxalate stones include higher urine calcium, higher urine oxalate, and lower urine citrate. This stone type is insensitive to pH in the physiologic range.

Individuals with higher urine calcium excretion tend to absorb a higher percentage of ingested calcium. Nevertheless, dietary calcium restriction is not beneficial and, in fact, is likely to be harmful (see

"Dietary Risk Factors," above). In a randomized trial in men with high urine calcium and recurrent calcium oxalate stones, a diet containing 1200 mg of calcium and a low intake of sodium and animal protein significantly reduced subsequent stone formation from that with a low-calcium diet (400 mg/d). Excessive calcium intake (>1200 mg/d) should be avoided.

A thiazide diuretic, in doses higher than those used to treat hypertension, can substantially lower urine calcium excretion. Several randomized controlled trials have demonstrated that thiazide diuretics, most commonly chlorthalidone, can reduce calcium oxalate stone recurrence by ~50%. When a thiazide is prescribed, dietary sodium restriction is essential to obtain the desired reduction in urinary calcium excretion and minimize urinary potassium losses. While bisphosphonates may reduce urine calcium excretion in some individuals, there are no data on whether this class of medication can reduce stone formation; therefore, bisphosphonates cannot be recommended solely for stone prevention at present but they can be used to treat those individuals with low bone density.

A reduction in urine oxalate will in turn reduce the supersaturation of calcium oxalate. In patients with the common form of nephrolithiasis, avoiding high-dose vitamin C supplements is the only known strategy that reduces endogenous oxalate production.

Oxalate is a metabolic end product; therefore, any dietary oxalate that is absorbed will be excreted in the urine. Reducing absorption of exogenous oxalate involves two approaches. First, the avoidance of foods that contain high amounts of oxalate, such as spinach, rhubarb, almonds, and potatoes, is prudent. However, extreme oxalate restriction has not been demonstrated to reduce stone recurrence and could be harmful to overall health, given other health benefits of many foods that are erroneously considered to be high in oxalate. Controversy exists regarding the most clinically relevant measure of the oxalate content of foods (e.g., bioavailability). Notably, the absorption of oxalate is reduced by higher calcium intake; therefore, individuals with higher-than-desired urinary oxalate should be counseled to consume adequate calcium. Oxalate absorption can be influenced by the intestinal microbiota, depending on the presence of oxalate-degrading bacteria. Currently, however, there are no available therapies to alter the microbiota that beneficially affect urinary oxalate excretion over the long term.

Citrate is a natural inhibitor of calcium oxalate and calcium phosphate stones. Higher-level consumption of foods rich in alkali (i.e., fruits and vegetables) can increase urine citrate. For patients with lower urine citrate in whom dietary modification does not adequately increase urine citrate, the addition of supplemental alkali (typically potassium citrate or bicarbonate) will lead to an increase in urinary citrate excretion. Sodium salts, such as sodium bicarbonate, while successful in raising urine citrate, are typically avoided due to the adverse effects of sodium on urine calcium excretion. Urine pH in the physiologic range does not influence calcium oxalate stone formation.

Past reports suggested that higher levels of urine uric acid may increase the risk of calcium oxalate stones, but more recent studies do not support this association. However, allopurinol reduced stone recurrence in one randomized controlled trial in patients with calcium oxalate stones and high urine uric acid levels. The lack of association between urine uric acid level and calcium oxalate stones suggests that a different mechanism underlies the observed beneficial effect of allopurinol.

Additional dietary modifications may be beneficial in reducing stone recurrence. Restriction of nondairy animal protein (e.g., meat, chicken, seafood) is a reasonable approach and may result in higher excretion of citrate and lower excretion of calcium. In addition, reducing sodium intake to <2.5 g/d may decrease urinary excretion of calcium. Sucrose and fructose intake should be minimized.

For adherence to a dietary pattern that is more manageable for patients than manipulating individual nutrients, the DASH (Dietary Approaches to Stop Hypertension) diet provides an appropriate and readily available option. Randomized trials have conclusively shown the DASH diet to reduce blood pressure. At present, only data from observational studies are available, but these demonstrate a strong and consistent inverse association between the DASH diet and risk of stone formation.

Calcium Phosphate Calcium phosphate stones share risk factors with calcium oxalate stones, including higher concentrations of urine calcium and lower concentrations of urine citrate, but additional factors deserve attention. Higher urine phosphate levels and higher urine pH (typically ≥6.5) are associated with an increased likelihood of calcium phosphate stone formation. Calcium phosphate stones are more common in patients with distal renal tubular acidosis and primary hyperparathyroidism.

There are no randomized trials on which to base preventive recommendations for calcium phosphate stone formers, so the interventions are focused on modification of the recognized risk factors. Thiazide diuretics (with sodium restriction) may be used to reduce urine calcium, as described above for calcium oxalate stones. In patients with low urine citrate levels, alkali supplements (e.g., potassium citrate or bicarbonate) may be used to increase these concentrations. However, the urine pH of these patients should be monitored initially because supplemental alkali can raise urine pH, thereby potentially increasing the risk of stone formation. Because these patients tend to have a urinary acidification defect, reducing the urine pH is not an option. Reduction of dietary phosphate may be beneficial by reducing urine phosphate excretion.

Uric Acid The two main risk factors for uric acid stones are persistently low urine pH and higher uric acid excretion. Urine pH is the predominant influence on uric acid solubility; therefore, the mainstay of prevention of uric acid stone formation entails increasing urine pH. Alkalinizing the urine can be readily achieved by increasing the intake of foods rich in alkali (e.g., fruits and vegetables) and reducing the intake of foods that produce acid (e.g., animal flesh). If necessary, supplementation with bicarbonate or citrate salts (preferably potassium-based) can be used to reach the recommended pH goal of 6.5 throughout the day and night.

Urine uric acid excretion is determined by uric acid generation. Uric acid is the end product of purine metabolism; thus, reduced consumption of purine-containing foods can lower urine uric acid excretion. It is noteworthy that the serum uric acid level is dependent on the fractional excretion of uric acid and therefore does not provide information on urine uric acid excretion. For example, an individual with high uric acid generation and concurrent high fractional excretion of uric acid will have high urine uric acid excretion with a normal (or even low) serum uric acid level. If alkalinization of the urine alone is not successful and if dietary modifications do not reduce urine uric acid sufficiently, then the use of a xanthine oxidase inhibitor, such as allopurinol or febuxostat, can reduce urine uric acid excretion by 40–50%.

Cystine Cystine excretion is not easily modified. Long-term dietary cystine restriction is not feasible and is unlikely to be successful; thus the focus for cystine stone prevention is on increasing cystine solubility. This goal may be achieved by treatment with medication that covalently binds to cystine (tiopronin or penicillamine) and a medication that raises urine pH. Tiopronin is the preferred choice due to its better adverse event profile. The preferred alkalinizing agent to achieve a urine pH of 7.5 is potassium citrate or bicarbonate as sodium salts may increase cystine excretion. As with all stone types, and especially in patients with cystinuria, maintaining a high urine volume is an essential component of the preventive regimen.

Struvite Struvite stones, also known as *infection stones* or *triple-phosphate stones*, form only when the upper urinary tract is infected with urease-producing bacteria such as *Proteus mirabilis, Klebsiella pneumoniae*, or *Providencia* species. Urease produced by these bacteria hydrolyzes urea and may elevate the urine pH to a supraphysiologic level (>8.0). Struvite stones may grow quickly and fill the renal pelvis (*staghorn calculi*).

Struvite stones require complete removal by a urologist. New stone formation can be avoided by the prevention of UTIs. In patients with recurrent upper UTIs (e.g., some individuals with surgically altered

urinary drainage or spinal cord injury), the urease inhibitor acetohydroxamic acid can be considered; however, this agent should be used with caution because of potential side effects.

LONG-TERM FOLLOW-UP

In general, the preventive regimens described above do not cure the underlying pathophysiologic process. Thus these recommendations typically need to be followed for the patient's lifetime, and it is essential to tailor recommendations in a way that is acceptable to the patient. Because the memory of the acute stone event fades and patients often return to old habits (e.g., insufficient fluid intake), long-term follow-up, including repeat 24-h urine collections, is important to ensure that the preventive regimen has been implemented and has resulted in the desired reduction in the risk of new stone formation.

Follow-up imaging should be planned thoughtfully. Many patients with recurrent episodes of renal colic that lead to emergency room visits often undergo repeat CT studies. While CT does provide the best information, the radiation dose is substantially higher than that with plain abdominal radiography (KUB). Small stones may be missed by KUB, and ultrasound has a limited ability to determine size and number of stones. Minimizing radiation exposure should be a goal of the long-term follow-up plan and must be balanced against the gain in diagnostic information.

FURTHER READING

PEARLE MS et al: Medical management of kidney stones: AUA guideline. J Urol 192:316, 2014.

PROCHASKA ML et al: Insights into nephrolithiasis from the Nurses' Health Studies. Am J Public Health 106:1638, 2016.

TABLE 313-1 Common Mechanical Causes of Urinary Tract Obstruction

URETER	BLADDER OUTLET	URETHRA
Congenital		
Ureteropelvic junction narrowing or obstruction	Bladder neck obstruction	Posterior urethral valves
Ureterovesical junction narrowing or obstruction and reflux	Ureterocele	Anterior urethral valves
Ureterocele		Stricture
Retrocaval ureter		Meatal stenosis
		Phimosis
Acquired Intrinsic Defects		
Calculi	Benign prostatic hyperplasia	Stricture
Inflammation	Cancer of prostate	Tumor
Infection	Cancer of bladder	Calculi
Trauma	Calculi	Trauma
Sloughed papillae	Diabetic neuropathy	Phimosis
Tumor	Spinal cord disease	
Blood clots	Anticholinergic drugs and α-adrenergic antagonists	
Acquired Extrinsic Defects		
Pregnant uterus	Carcinoma of cervix, colon	Trauma
Retroperitoneal fibrosis		
Aortic aneurysm	Trauma	
Uterine leiomyomata		
Carcinoma of uterus, prostate, bladder, colon, rectum		
Lymphoma		
Pelvic inflammatory disease, endometriosis		
Accidental surgical ligation		

313 Urinary Tract Obstruction

Julian L. Seifter

Obstruction to the flow of urine, with attendant stasis and elevation in urinary tract pressure, impairs renal and urinary conduit functions and is a common cause of acute and chronic kidney disease (obstructive nephropathy). Early recognition and prompt treatment of urinary tract obstruction (UTO) can prevent or reverse devastating effects on kidney structure and function, and decrease susceptibility to hypertension, infection, and stone formation. Chronic obstruction may lead to permanent loss of renal mass (renal atrophy) and excretory capability. Since obstructive disease may be secondary to serious underlying inflammatory, vascular, or malignant disease, familiarity with clinical findings, appropriate diagnostic testing, and therapeutic approach is of great importance to the clinician.

ETIOLOGY

Obstruction to urine flow can result from *intrinsic* or *extrinsic mechanical blockade* as well as from *functional defects* not associated with fixed occlusion of the urinary drainage system. Mechanical obstruction can occur at any level of the urinary tract, from within the renal tubules, or the renal calyces to the external urethral meatus (obstructive uropathy). Normal points of narrowing, such as the ureteropelvic and ureterovesical junctions, bladder neck, and urethral meatus, are common sites of obstruction. When lower UTO is above the level of the bladder, unilateral dilatation of the ureter (*hydroureter*) and renal pyelocalyceal system (*hydronephrosis*) occurs; lesions at or below the level of the bladder cause bilateral involvement.

Common forms of obstruction are listed in Table 313-1. Childhood causes include *congenital malformations*, such as narrowing of the ureteropelvic junction (UPJ) and abnormal insertion of the ureter into the bladder, the most common cause. Vesicoureteral reflux in the absence of urinary tract infection or bladder neck obstruction often resolves with age. Reinsertion of the ureter into the bladder is indicated if reflux is severe and unlikely to improve spontaneously, if renal function deteriorates, or if urinary tract infections recur despite chronic antimicrobial therapy. Vesicoureteral reflux may cause prenatal hydronephrosis and, if severe, can lead to recurrent urinary infections, hypertension and renal scarring in childhood. Posterior urethral valves are the most common cause of bilateral hydronephrosis in boys. In adults, UTO is due mainly to *acquired defects*. Pelvic tumors, calculi, and urethral stricture predominate. Ligation of, or injury to, the ureter during pelvic or colonic surgery can lead to hydronephrosis which, if unilateral, may remain undetected. Obstructive uropathy may also result from extrinsic neoplastic (carcinoma of cervix or colon) or inflammatory disorders. Lymphomas and pelvic or colonic neoplasms with retroperitoneal involvement are causes of ureteral obstruction. As many as 50% of men aged >40 years may have lower urinary tract symptoms associated with benign prostatic hypertrophy, but these symptoms may occur without bladder outlet obstruction.

Functional impairment of urine flow occurs when voiding is altered by abnormal pontine or sacral centers of micturition control. It may be asymptomatic or associated with lower urinary tract symptoms such as frequency, urgency, and postmicturition incontinence, nocturia, straining to void, slow stream, hesitancy, or a feeling of incomplete emptying. A history should be sought for trauma, back injury, surgery, diabetes, neurologic or psychiatric conditions, and medications. Causes include neurogenic bladder, often with adynamic ureter, and vesicoureteral reflux. Reflux in children may result in severe unilateral or bilateral hydroureter and hydronephrosis. Overflow urinary incontinence combined with fecal incontinence may require an urgent evaluation for cauda equina syndrome. Urinary retention may be the consequence of α-adrenergic and anticholinergic agents, as well as opiates. Hydronephrosis in pregnancy is due to relaxational effects of progesterone on smooth muscle of the renal pelvis, as well as ureteral compression by the enlarged uterus, more often on the right side.

Diagnostic tools to identify anatomic obstruction include urinary flow measurements and a postvoid residual. Bladder volume may be readily assessed by bedside ultrasound. Cystourethroscopy and urodynamic studies may be reserved for the symptomatic patient to assess the filling phase (cystometry), pressure-volume relationship of the bladder, bladder compliance, and capacity. Pressure-flow analysis evaluates bladder contractility and bladder outlet resistance during voiding. Bladder obstruction is characterized by high pressures in women, whereas in men, a diagnosis of bladder outlet obstruction is based on flow rate and voiding pressures. A voiding cystourethrogram may be useful in evaluating incomplete emptying and bladder neck and urethral pathology.

CLINICAL FEATURES AND PATHOPHYSIOLOGY

The pathophysiology and clinical features of UTO are summarized in **Table 313-2**. Flank *pain*, the symptom that most commonly leads to medical attention, is due to distention of the collecting system or renal capsule. Pain severity is influenced more by the rate at which distention develops than by the degree of distention. Acute supravesical obstruction, as from a stone lodged in a ureter **(Chap. 312)**, is associated with excruciating, sometimes intermittent, pain, known as *renal colic*. This pain often radiates to the lower abdomen, testes, or labia. By contrast, more insidious causes of obstruction, such as chronic narrowing of the UPJ, may produce little or no pain and yet result in total destruction of the affected kidney. Flank pain that occurs only with micturition is pathognomonic of vesicoureteral reflux.

Obstruction of urine flow results in an increase in hydrostatic pressures proximal to the site of obstruction. It is this buildup of pressure that leads to the accompanying pain, the distention of the collecting system in the kidney, and elevated intratubular pressures that initiate tubular dysfunction. In the first days of obstruction, the dilatation of the poorly compliant collecting system may be minimal. As the increased hydrostatic pressure is expressed in the urinary space of the glomeruli, further filtration decreases or stops completely.

Azotemia develops when overall excretory function is impaired, often in the setting of bladder outlet obstruction, bilateral renal pelvic or ureteric obstruction, or unilateral disease in a patient with a solitary functioning kidney. Complete bilateral obstruction should be suspected when acute renal failure is accompanied by anuria. Any patient with renal failure otherwise unexplained, or with a history of nephrolithiasis, hematuria, diabetes mellitus, prostatic enlargement, pelvic surgery, trauma, or tumor should be evaluated for UTO.

In the acute setting, partial, bilateral obstruction may mimic prerenal azotemia with a high blood urea nitrogen-to-creatinine ratio, concentrated urine and sodium retention. Renal vascular resistance may be increased. However, with more prolonged obstruction, symptoms of *polyuria* and *nocturia* commonly accompany partial UTO and result from loss of medullary hypertonicity with diminished renal concentrating ability. Failure to produce urine free of salt (natriuresis) is due to downregulation of salt reabsorption in the proximal tubule and of transport proteins including the Na^+, K^+ adenosine triphosphatase (ATPase), NaK_2Cl cotransporter (NaK_2Cl) in the thick ascending limb, and the epithelial Na^+ channel (ENaC) in collecting duct cells. In addition to direct effects on renal transport mechanisms, increased prostaglandin E_2 (PGE_2) (due to induction of cyclooxygenase-2 [COX-2]), angiotensin II (with its downregulation of Na^+ transporters), and atrial or B-type natriuretic peptides (ANP or BNP) (due to volume expansion in the azotemic patient) contribute to decreased salt reabsorption along the nephron.

Dysregulation of aquaporin-2 water channels in the collecting duct contributes to the polyuria. The defect usually does not improve with administration of vasopressin and is therefore a form of acquired nephrogenic diabetes insipidus.

Wide fluctuations in urine output in a patient with azotemia should always raise the possibility of intermittent or partial UTO. If fluid intake is inadequate, severe dehydration and hypernatremia may develop. However, as with other causes of poor renal function, excesses of salt and water intake may result in edema and hyponatremia.

Partial bilateral UTO often results in *acquired distal renal tubular acidosis, hyperkalemia*, and *renal salt wasting*. The H^+-ATPase, situated on the apical membrane of the intercalated cells of the collecting duct, is critical for distal H^+ secretion. The trafficking of intracellular H^+ pumps from the cytoplasm to the cell membrane is disrupted in UTO. The decreased function of the ENaC, in the apical membrane of neighboring collecting duct principal cells, contributes to decreased Na^+ reabsorption (salt-wasting), and, therefore, decreased K^+ secretion via K^+ channels. Ammonium (NH_4^+) excretion important to the elimination of H^+ is impaired. These defects in tubule function are often accompanied by renal tubulointerstitial damage. Azotemia with hyperkalemia and metabolic acidosis should prompt consideration of UTO.

The renal interstitium becomes edematous and infiltrated with mononuclear inflammatory cells early in UTO. Later, interstitial fibrosis and atrophy of the papillae and medulla occur and precede these processes in the cortex. The increase in angiotensin II noted in UTO contributes to the inflammatory response and fibroblast accumulation through mechanisms involving profibrotic cytokines. With time, this process leads to chronic kidney damage.

UTO must always be considered in patients with urinary tract infections or urolithiasis. Urinary stasis encourages the growth of organisms. Urea-splitting bacteria are associated with magnesium ammonium phosphate (struvite) calculi that may take on a staghorn appearance. *Hypertension* is frequent in acute and subacute unilateral obstruction and is usually a consequence of increased release of renin by the involved kidney. Chronic kidney disease from bilateral UTO, often associated with extracellular volume expansion, may result in significant hypertension. *Erythrocytosis*, an infrequent complication of obstructive uropathy, is secondary to increased erythropoietin production.

TABLE 313-2 Pathophysiology of Bilateral Ureteral Obstruction

HEMODYNAMIC EFFECTS	TUBULE EFFECTS	CLINICAL FEATURES
Acute		
↑ Renal blood flow ↓ GFR ↓ Medullary blood flow ↑ Vasodilator prostaglandins, nitric oxide	↑ Ureteral and tubule pressures ↑ Reabsorption of Na^+, urea, water	Pain (capsule distention) Azotemia Oliguria or anuria
Chronic		
↓ Renal blood flow ↓↓ GFR ↑ Vasoconstrictor prostaglandins ↑ Renin-angiotensin production	↓ Medullary osmolarity ↓ Concentrating ability Structural damage; parenchymal atrophy ↓ Transport functions for Na^+, K^+, H^+	Azotemia Hypertension AVP-insensitive polyuria Natriuresis Hyperkalemic, hyperchloremic acidosis
Release of Obstruction		
Slow ↑ in GFR (variable)	↓ Tubule pressure ↑ Solute load per nephron (urea, NaCl) Natriuretic factors present	Postobstructive diuresis Potential for volume depletion and electrolyte imbalance due to losses of Na^+, K^+, PO_4^{2-}, Mg^{2+}, and water

Abbreviations: AVP, arginine vasopressin; GFR, glomerular filtration rate.

DIAGNOSIS

A history of difficulty in voiding, pain, infection, or change in urinary volume is common. Evidence for distention of the kidney or urinary bladder can often be obtained by palpation and percussion of the abdomen. A careful rectal and genital examination may reveal enlargement or nodularity of the prostate, abnormal rectal sphincter tone, or a rectal or pelvic mass.

Urinalysis may reveal hematuria, pyuria, and bacteriuria. The urine sediment is often normal, even when obstruction leads to marked

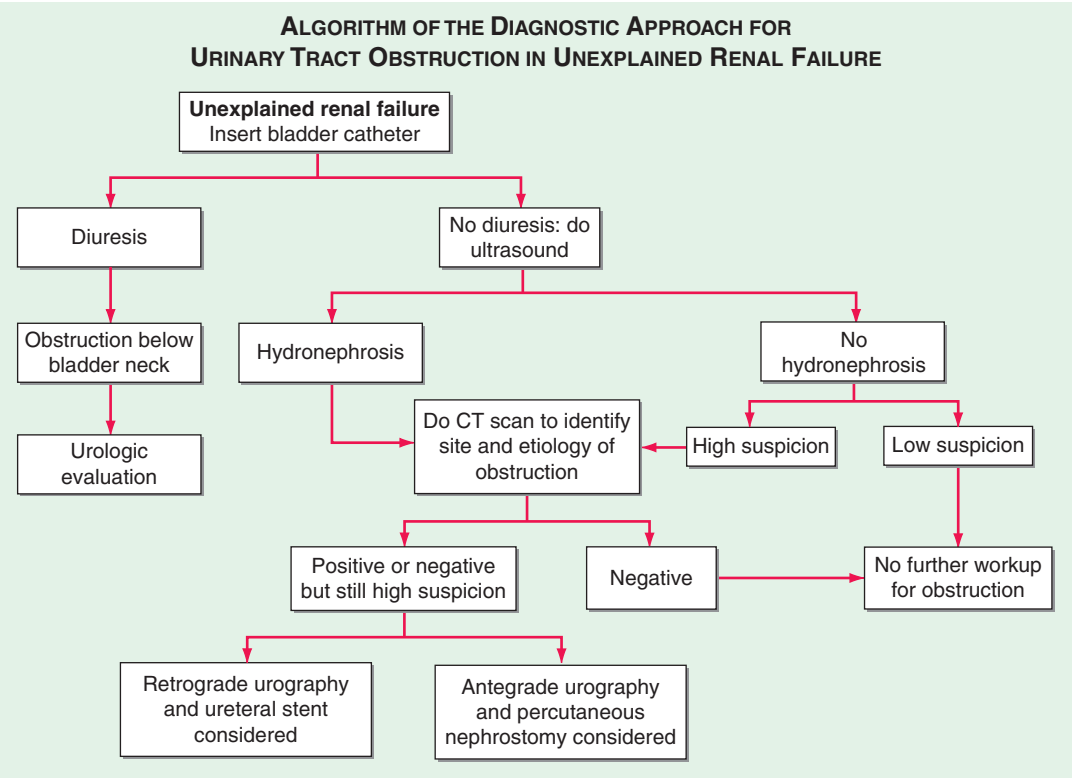

FIGURE 313-1 Diagnostic approach for urinary tract obstruction in unexplained renal failure. CT, computed tomography.

azotemia and extensive structural damage. An abdominal scout film, although insensitive, may detect nephrocalcinosis or a radiopaque stone. As indicated in Fig. 313-1, if UTO is suspected, a bladder catheter should be inserted. Abdominal ultrasonography should be performed to evaluate renal and bladder size, as well as pyelocalyceal contour. Ultrasonography is ~90% specific and sensitive for detection of hydronephrosis. False-positive results are associated with diuresis, renal cysts, or the presence of an extrarenal pelvis, a normal congenital variant. Congenital UPJ obstruction may be mistaken for renal cystic disease. Hydronephrosis may be absent on ultrasound when obstruction is less than 48 h in duration or associated with volume contraction, staghorn calculi, retroperitoneal fibrosis, or infiltrative renal disease. Duplex Doppler ultrasonography may detect an increased resistive index in urinary obstruction.

Recent advances in technology have led to alternatives and have largely replaced the once standard intravenous urogram in the further evaluation of UTO. The high-resolution multidetector row computed tomography (CT) scan in particular has advantages of visualizing the retroperitoneum, as well as identifying both intrinsic and extrinsic sites of obstruction. Noncontrast CT scans improve visualization of the urinary tract in the patient with renal impairment and are safer for patients at risk for contrast nephropathy. Magnetic resonance urography is a promising technique but, at this time, not superior to the CT scan and carries the risk of certain gadolinium agents in patients with renal insufficiency. CT scanning may define the site of obstruction, identify and characterize kidney stones, and demonstrate dilatation of the calyces, renal pelvis, and ureter above the obstruction. The ureter may be tortuous in chronic obstruction. Radionuclide scans are able to give differential renal function but give less anatomic detail than CT scans. Furosemide is sometimes given to increase detection with imaging, and to distinguish functional from anatomic obstruction. The increase in urinary flow may bring out the pain of an acute obstructive process.

To facilitate visualization of a suspected lesion in a ureter or renal pelvis, *retrograde* or *antegrade urography* should be attempted. These procedures do not carry risk of contrast-induced acute kidney injury in patients with renal insufficiency. The retrograde approach involves catheterization of the involved ureter under cystoscopic control, whereas the antegrade technique necessitates percutaneous placement of a catheter into the renal pelvis. Although the antegrade approach may provide immediate decompression of a unilateral obstructing lesion, many urologists initially attempt the retrograde approach unless the catheterization is unsuccessful.

Voiding cystourethrography is of value in the diagnosis of vesicoureteral reflux and bladder neck and urethral obstructions. Postvoiding films reveal residual urine. Endoscopic visualization by the urologist often permits precise identification of lesions involving the urethra, prostate, bladder, and ureteral orifices.

TREATMENT

Urinary Tract Obstruction

UTO complicated by infection requires immediate relief of obstruction to prevent development of generalized sepsis and progressive renal damage. Sepsis necessitates prompt urologic intervention. Drainage may be achieved by nephrostomy, ureterostomy, or ureteral, urethral, or suprapubic catheterization. Prolonged antibiotic treatment may be necessary. Chronic or recurrent infections in a poorly functioning obstructed kidney may necessitate nephrectomy. When infection is not present, surgery is often delayed until acid-base, fluid, and electrolyte status is restored. Nevertheless, the site of obstruction should be ascertained as soon as feasible. Elective relief of obstruction is usually recommended in patients with urinary retention, recurrent urinary tract infections, persistent pain, or progressive loss of renal function. Benign prostatic hypertrophy may be treated medically with α-adrenergic blockers and 5α-reductase inhibitors. Renal colic may be treated with anti-inflammatory medication as edema often contributes to an obstructing ureteral stone, and α-adrenergic blockers may also be of benefit. Use of opiates in patients with decreased renal function may be dangerous and should be used with caution. Functional obstruction secondary to neurogenic bladder may be decreased with the combination of frequent voiding and cholinergic drugs.

PROGNOSIS

With relief of obstruction, the prognosis regarding return of renal function depends largely on whether irreversible renal damage has occurred. When obstruction is not relieved, the course will depend mainly on whether the obstruction is complete or incomplete and bilateral or unilateral, as well as whether or not urinary tract infection is also present. Complete obstruction with infection can lead to total destruction of the kidney within days. Partial return of glomerular filtration rate may follow relief of complete obstruction of 1 and 2 weeks' duration, but after 8 weeks of obstruction, recovery is unlikely. In the absence of definitive evidence of irreversibility, every effort should be made to decompress the obstruction in the hope of restoring renal function at least partially. A renal radionuclide scan, performed after a prolonged period of decompression, may be used to predict the reversibility of renal dysfunction.

POSTOBSTRUCTIVE DIURESIS

Relief of bilateral, but not unilateral, complete obstruction commonly results in polyuria, which may be massive. The urine is usually hypotonic and may contain large amounts of sodium chloride, potassium, phosphate, and magnesium. The natriuresis is due in part to the correction of extracellular volume expansion, the increase in natriuretic factors accumulated during the period of renal failure, and depressed salt and water reabsorption when urine flow is reestablished. The retained urea is excreted with improved GFR, resulting in an osmotic diuresis which increases the urine volume of electrolyte-free water. The urinary concentrations of sodium and potassium that when added are less than the serum sodium is evidence of electrolyte free-water excretion. In the majority of patients, this diuresis results in the *appropriate* excretion of the excesses of retained salt and water. When extracellular volume and composition return to normal, the diuresis usually abates spontaneously. Occasionally, iatrogenic expansion of extracellular volume is responsible for, or sustains, the diuresis observed in the postobstructive period. Replacement with intravenous fluids in amounts less than urinary losses usually prevents this complication. More aggressive fluid management is required in the setting of hypovolemia, hypotension, or disturbances in serum electrolyte concentrations.

The loss of electrolyte-free water with urea may result in hypernatremia. Measured urinary output and serum and urine sodium, potassium and osmolal concentrations should guide the use of appropriate intravenous replacement. Often replacement with 0.45% saline is required. Relief of obstruction may be followed by urinary salt and water losses severe enough to provoke profound dehydration and vascular collapse. In these patients, decreased tubule reabsorptive capacity is probably responsible for the marked diuresis. Appropriate therapy in such patients includes intravenous administration of salt-containing solutions to replace sodium and volume deficits.

FURTHER READING

Frokiaer J, Zeidel ML: Urinary tract obstruction, in *Brenner and Rector's The Kidney*, 10th ed, BM Brenner (ed). Philadelphia, Saunders, 2015, pp 1257–1282.

Meldrum KK: Pathophysiology of urinary tract obstruction, in *Campbell-Walsh Urology*, 11th ed, AJ Wein et al (eds). Philadelphia, Elsevier; 2016, pp 1089–1103.

Smith-Bindman R et al: Ultrasonography versus computed tomography for suspected nephrolithiasis. N Engl J Med 371:1100, 2014.

Stoller ML: Urinary obstruction & stasis, in *Smith and Tanagho's General Urology*, 18th ed, JW McAninch, TF Lue (eds). New York, McGraw-Hill, 2013, pp. 170–182.

Tanagho EA, Nguyen HT: Vesicoureteral reflux, in Smith and Tanagho's *General Urology*, 18th ed, WJ McAninch, TF Lue (eds). New York, McGraw-Hill, 2013, pp. 182–197.