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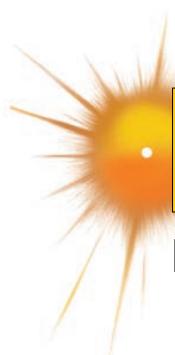
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Approach to the Patient with Renal Disease or Urinary Tract Disease

Julian L. Seifter



The upper urinary tract consists of the kidneys, their vasculature, and the renal parenchyma and its collecting system. The lower urinary tract is composed of the peristaltic ureters from each kidney, the bladder which receives and stores urine from each ureter, and the urethra which, upon bladder contraction, excretes the final urine. The excretory system as a whole begins with a plasma ultrafiltrate from renal cortical glomeruli, modified by the renal tubules of the nephron, and ends with the excretion of urinary water and solutes.

Disease can occur at any level of these functional structures with either no symptoms or signs (such as an incidental renal mass picked up on ultrasound); with nonspecific findings (such as fatigue); with signs highly specific for a syndrome of dysfunction referable to a structure, but not diagnostic of a particular disease (such as proteinuria); or with a finding highly characteristic of a specific diagnosis (such as polycystic kidney disease). Disorders of the kidney presenting without symptoms (such as invisible microhematuria or a stone) are often discovered by laboratory testing or imaging.

It is important to perform renal testing in patients with systemic disease (for example, routine screening for albuminuria in diabetes mellitus [DM]). Likewise, one should look at renal function when a patient's history includes known risk for renal or urinary tract complications (for example lithium for psychiatric treatment, occupational use of lead, or, in the case of bladder cancer, exposure to aniline dyes). This chapter will address an approach to patients with and without known history of kidney disease, as well as those who have one of a wide variety of systemic illnesses that involve the kidney or the lower urinary tract.

To begin with the evaluation of renal disorders, note that it is time-consuming and wasteful to do random testing prematurely, which would generate a very long list of potential diagnoses. A better approach is to look at the evidence from the history, physical examination, and basic laboratory studies to arrive at a logical basis for targeted tests that would identify a particular disease process (**Table 308-1**). The findings

are influenced by the regions of the kidney that are involved and by factors such as family history, toxic exposures, the patient's birth weight and age, and time course of the findings. As a rule, kidney diseases that begin primarily with glomerular dysfunction have albuminuria as the hallmark, whereas those kidney diseases that begin in the tubular structures may present primarily with electrolyte disorders or disorders of dilution and concentration of the urine. In both glomerular and tubular disorders, upon progressing to chronic disease, the distinction is more difficult because glomerular diseases eventually affect the tubular interstitium and tubular diseases progress to glomerular dysfunction and scarring.

One example of the progression from a tubular disorder to chronic kidney disease with late glomerular damage is the lysosomal storage disease cystinosis, one of the childhood Fanconi's syndromes. Within the first year of life, the affected child may become easily dehydrated from salt-wasting; feed and grow poorly; develop polyuria, hypotension, and muscle weakness; and show the features of proximal tubular dysfunction. Electrolyte losses result in hypokalemic renal tubular acidosis (RTA), renal glycosuria, phosphaturia causing growth delay from renal rickets, and acidemia. The accumulation of lysosomal cystine leads to destruction of the proximal tubule and adjacent interstitium, while glomerular filtration remains near normal and urine contains little albumin.

Even with treatment, progressive scarring of the capillaries within the interstitial space eventually, over a decade or more, leads to albuminuria and progressive decrease in GFR. Electrolytes like K^+ and HPO_4^{2-} are retained at this stage and metabolic acidosis results from failure of the kidney to produce NH_4^+ rather than losses of HCO_3^- . Hypertension and edema from salt and water retention replace the low blood pressure associated with the loss of fluid at the earlier stage of tubular dysfunction. Anemia results from loss of erythropoietin production in chronic kidney disease. The symptoms of weakness and fatigue are nonspecific in that they might correlate with anemia, hypo- or hyperkalemia, hypophosphatemia, acidosis, l-carnitine deficiency from proximal tubule reabsorptive failure in Fanconi's syndrome, or azotemia. Hepatomegaly on a newborn examination, typical of but not specific to cystinosis, might raise suspicion of other inborn errors of metabolism such as glycogen storage diseases. However, the finding of photosensitivity related to highly refractile cystine crystals deposited in the cornea is very specific for cystinosis.

In the following discussion, the focus is on symptoms and signs that constitute the major syndromes seen in the patient with kidney or lower urinary tract disease. These syndromes are the foundation for the diagnosis of particular diseases.

TABLE 308-1 Acute Kidney Injury

FEATURES	PRERENAL	RENAL	POSTRENAL
CONTEXT	Heart failure, hepatic failure, burns, shock, post-op, dehydration, renovascular disease, vascular drugs	ATN, bilateral cortical necrosis, AIN, crush injuries, myoglobinuria, hemoglobinuria, ischemia, sepsis, recent contrast drugs	Bladder outlet obstruction, obstruction of solitary kidney, abdominal mass, bilateral stones, drugs
URINE OUTPUT	Oliguria (usually <500 mL/day) Anuria	Oliguria Normal Polyuria	Anuria Polyuria Both
CLINICAL HISTORY AND EXAM	Trauma, shock, hypotension, burns, GI, sweat, or renal losses	Rhabdomyolysis, hemolysis, thrombotic microangiopathy, AIN, atheroemboli	Extrinsic ureteral obstruction, retroperitoneal disease, bladder outlet or urethral obstruction by prostate or cervical cancer
URINALYSIS	Concentrated acid urine, hyaline casts, crystalluria	"Muddy brown" granular casts, hematuria, dysmorphic RBCs, RBC casts in GN, WBC casts in AIN, eosinophils in atheroemboli	Intrarenal obstruction by uric acid or calcium phosphate in tumor lysis syndrome, blood clots in lower urinary tract bleeding, CaOx after ethylene glycol ingestion
URINE CHEMISTRY	Low FENa 1%, U/P Cr 40, UNa 10, U/P Osm 1	FENa 1–3%, U/P Cr 40, UOsm –Isomotic	Early looks like prerenal, late looks like renal
LABORATORY STUDIES	High BUN/Cr ratio, usually hypercatabolic with increased uric acid; may have hyper- or hyponatremia	May have eosinophilia in allergic AIN, high phosphate, low Ca, high PTH, metabolic acidosis	Hydronephrosis on ultrasound, extrinsic or intrinsic diseases on CT scan, tumors on MRI

Nephritis literally means an inflammatory condition of the kidney. Nephritic inflammation may occur in association with infection, allergic response to medications, systemic autoimmune disorders, or toxic exposures. The kidneys may be one of many organs, or the only organ, involved in the inflammatory disorder. Inflammation with enlargement of the kidneys is often associated with point tenderness over the flank and sometimes exquisite costovertebral angle tenderness, requiring gentle palpation for diagnosis.

The nephritic syndromes may be further subdivided depending on the inflamed structures within the kidney, including vascular, glomerular, and tubulointerstitial; and also, on the time course of progression of the inflammatory process, which may be acute, subacute, or chronic.

GLOMERULONEPHRITIS

Glomerulonephritis (GN) is associated with hypertension, volume expansion, and an abnormal urinalysis. In most cases, the volume expansion manifests as edema and hypertension; in the child, ascites may develop; and in the elderly, restlessness and anxiety may be the first signs of incipient acute pulmonary edema. There may be orthopnea at night or dyspnea on exertion, with or without significant peripheral edema. Acute GN is usually associated with low urine output (oliguria or at times complete anuria), low urine sodium content, and concentrated urine, resulting in the retention of salt and water. It is an absolute necessity to observe the urine, including a spun urinary sediment, to diagnose active GN.

The disease presentation may be acute or subacute (postinfectious GN and rapidly progressive GN), occurring over days or weeks; or it may be chronic, occurring over many months to years. The pathologic correlate of these presentations—the relative amount of acute inflammatory, proliferative, or necrotizing lesions in renal tissue versus chronic sclerotic and atrophic findings on renal biopsy—reflects the acuity versus chronicity of disease. Therefore, in these progressive destructive conditions, early diagnosis is critical and treatment for acute reversible disease should be instituted as quickly as possible.

The evaluation of the findings on history, physical examination, and urinalysis in narrowing diagnostic possibilities for a specific etiology of the glomerular syndromes is demonstrated in Fig. 308-1. The nephritic urinalysis shows hematuria, proteinuria, cells or clumps of cells, and cellular casts in the spun urinary sediment. The cells in the urine are usually a mixture of red blood cells and inflammatory cells, including polymorphonuclear (PMN) leukocytes. Microscopic hematuria is invisible to the naked eye, as opposed to macroscopic hematuria, identifiable as cola or “tea-colored” urine, caused by hemoglobin entering an acid urine. The red cells enter the renal tubules through breaks in the basement membrane of glomeruli. The process of moving across the membrane causes erythrocytes to become misshapen or dysmorphic. It is unusual in these nephritic syndromes to see blood clots or gross hematuria, a term used for overtly blood-red urine that characterizes other syndromes or lower urinary tract bleeding. However, in episodes of IgA nephropathy, glomerular hematuria is often “gross” as RBCs traverse rents in the glomerular basement membrane (GBM).

Postinfectious Glomerulonephritis Postinfectious glomerulonephritis (PIGN) is the classic example of acute GN, a complement-mediated immune complex response, to a bacterial antigen occurring 10 days to 3 weeks after a specific nephritogenic strain of group A streptococcal pharyngitis, or after skin infection such as impetigo. Because the sore throat or skin infection may have already resolved, antibiotic treatment may not be necessary at this stage of renal complication, but it is important for the clinician to inquire about these possible prior events. Subacute bacterial endocarditis, if present by history, may also result in a circulating immune complex disorder, even while the patient remains on antibiotic treatment. These glomerulonephritic and other immune complex conditions are recognized by low-C3 complement levels in the blood. However, the postinfectious cases should be distinguished from cases of infection-associated glomerulonephritis that occur during an ongoing infection, such as a staphylococcal (often MRSA) abscess or empyema, which are treated with antibiotics and purulent drainage and are characteristically associated with IgA and complement deposition in the glomeruli.

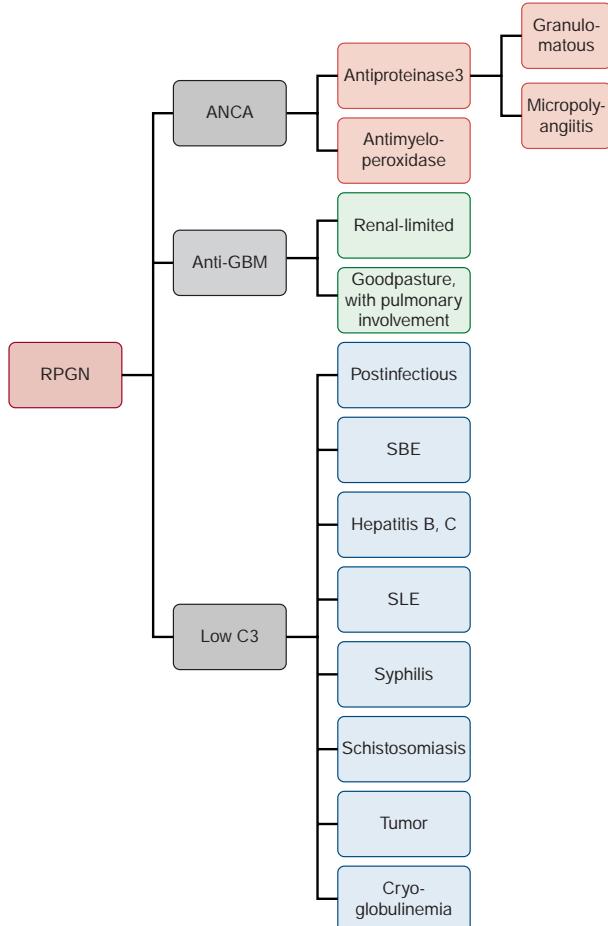


FIGURE 308-1 Rapidly progressive glomerulonephritis. The syndrome of RPGN is diagnosed clinically. The three major categories are the antineutrophilic cytoplasmic antibodies (ANCA-positive vasculitides); antiglomerular basement membrane antibody-positive (anti-GBM); and immune complex disorders with low C3 complement. C3 is synthesized in the liver, bound to circulating infectious or neoplastic antigens with their antibody complexes, and deposited in the glomerular subendothelium is associated with non-renal manifestations. Syphilis is usually accompanied by vasculitis, and cryoglobulins may be in setting of hepatitis C or myeloma and often lowers C4 as well. SBE, subacute bacterial endocarditis; SLE, systemic lupus erythematosus.

Postinfectious GN is to be distinguished from synpharyngitic hematuria, another glomerular syndrome that frequently produces gross hematuria, a heavier excretion of red blood, which may appear to the patient as a frightening hemorrhage. The patient may present with this concern so it is important for the clinician to recognize that as little as 10–20 mL of blood will turn a liter of urine red. Synpharyngitic hematuria, usually with a viral pharyngitis, is most often related to IgA nephropathy rather than postinfectious GN. Another feature that distinguishes IgA nephropathy from postinfectious GN is that the former usually demonstrates normal circulating C3 complement as opposed to low complement in PIGN. IgA nephropathy can cause chronic microhematuria or bouts of gross hematuria or can occur in association with other immunologic conditions including celiac disease, rheumatoid arthritis, reactive arthritis, and ankylosing spondylitis. IgA nephropathy and staphylococcal-associated GN are more common in Asian populations.

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (RPGN) Rapidly progressive glomerulonephritis (RPGN) is a syndrome arising from a variety of causes (Fig. 308-1). Pathologically it is associated with a proliferation of glomerular parietal epithelial cells and inflammatory cells called *cellular crescents* surrounding the capillary that, over time, becomes fibrotic and atrophic with global loss of the glomerular tuft.

When >50% of glomeruli are affected (diffuse), this highly destructive process usually leads to glomerular sclerosis. Recognition of RPGN and choice of appropriate therapy are extremely important because, if left unchecked, the syndrome can lead to complete and irreversible loss of kidney function, as well as fatal pulmonary hemorrhage when associated with lung vasculitis.

In the case of RPGN, one sees the typical signs of the nephritic syndrome, though other clues to diagnosis may be present in the pulmonary-renal syndromes, where the patient may present with hemoptysis, interstitial lung disease, epistaxis, or upper airway symptoms of sinusitis or nasal congestion. Blood testing helps narrow the differential diagnosis. The antineutrophil cytoplasmic antibody (ANCA) test, particularly those made up of antimyeloperoxidase (pANCA) or anti-proteinase-3 antibodies (cANCA), is diagnostic for the pauci-immune disorders of systemic vasculitis. Granulomatous vasculitis (formerly known as Wegener's granulomatosis) and microscopic polyangiitis are conditions particularly associated with pulmonary and upper respiratory disease. By contrast, a positive test for antiglomerular basement membrane (anti-GBM) antibodies would be consistent with either renal-limited anti-GBM disease or, when associated with pulmonary hemorrhage, with Goodpasture disease. The latter is more often seen in young males who smoke or have a history of inhaling hydrocarbon solvents.

The immune complex diseases that manifest as RPGN have low C3 levels secondary to high clearance of circulating complement with immune complex deposits in the glomerular subendothelial space. Certain of these disorders, such as systemic lupus erythematosus (SLE) and cryoglobulinemia, can present with pulmonary hemorrhage. Patients with cryoglobulinemia often have low C4 complement and a high rheumatoid factor, and the syndrome may be caused by paraproteinemias or hepatitis C. Another cause of crescentic RPGN but with normal C3 complement is a form of IgA vasculitis (Henoch-Schonlein purpura), a syndrome of skin vasculitis characterized by palpable purpura, gastrointestinal bleeding, and arthralgias, and in the vasculitic form, pulmonary hemorrhage. The C3 complement (an acute phase reactant) is detected in the kidney biopsy but not associated with low serum levels. The diagnostic tests and distinct diseases associated with these immune complex disorders are shown in Fig. 308-1.

Tubulointerstitial Nephritis Tubulointerstitial nephritis (TIN) comprises inflammatory disorders of the renal tubules and interstitium, which may be caused by infection, autoimmune disease, allergic immunologic responses to certain drugs (Fig. 308-2) and have a time course ranging from days to weeks and months.

ACUTE ALLERGIC AND IMMUNE INTERSTITIAL NEPHRITIS Acute allergic or immune interstitial nephritis (AIN) usually occurs 1 day to 2 weeks following exposure to an offending drug and may be associated with a rapid and potentially reversible loss of kidney function, which may occur in the setting of a change in dose or the restarting of a previously used medication. Associated glomerular proteinuria sometimes occurs with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or ampicillin. Clinically, there may be fever, rash, and eosinophilia; the last is typical for certain penicillins, fluoroquinolones, and some biologic cancer drugs that act as checkpoint inhibitors (CPIs) but is atypical for NSAIDs. Patients who recover from CPI-induced acute kidney injury (AKI) may be restarted on the inhibitor.

The urinalysis usually shows pyuria and at times eosinophiluria, but the most characteristic cell types are activated T lymphocytes and plasma cells, along with some white blood cell casts. A cyto-centrifuged specimen containing the sediment within a small tube mounted perpendicular to the slide, then stained with Giemsa, best demonstrates these cell types.

The patient may experience symptoms of polyuria and tender kidneys, and signs of tubular dysfunction including nephrogenic diabetes insipidus, hypo- or hyperkalemia and hyperchlormic metabolic acidosis. Common drugs that cause AIN include the proton pump inhibitors (PPIs) and sulfa drugs, especially sulfamethoxazole, but also extending to sulfa-containing diuretics such as acetazolamide, thiazides, and

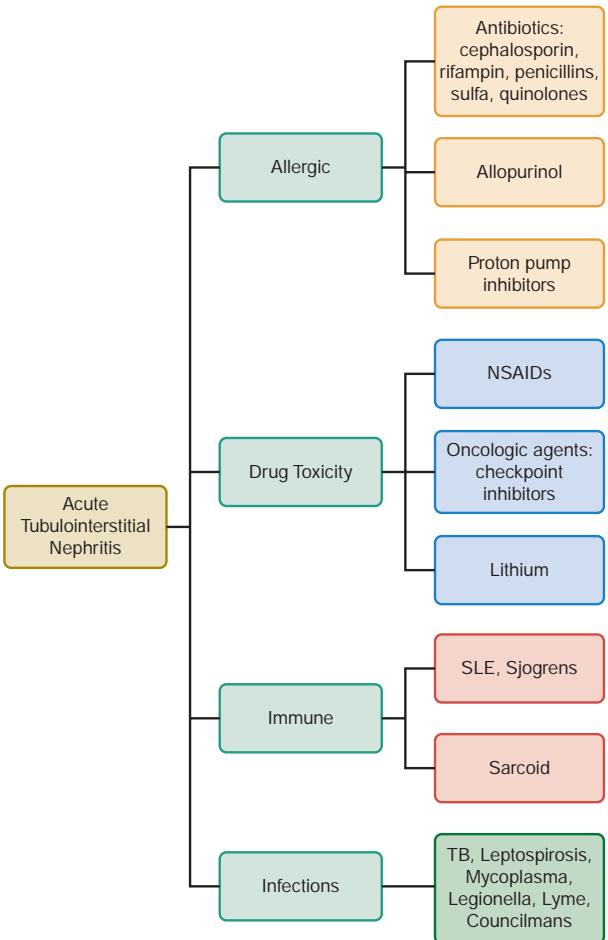


FIGURE 308-2 Acute tubulointerstitial nephritis. Diseases resulting from injury to the tubular and interstitial components of the renal cortex and medulla.

furosemide, and less frequently, bumetanide. PPI's may increase risk for AIN in patients on check point inhibitors. Frequently, rifampin and a few other drugs cause a noncaseating granulomatous interstitial nephritis; in caseating granulomas resulting from hematogenous spread of mycobacterium tuberculosis, the first granulomas appear connected to the glomeruli in the cortex where oxygen tension is at its highest. Granulomatous TIN may occur in sarcoidosis.

Systemic infections including bacterial, viral, fungal, and parasitic may induce tubulointerstitial nephritis, first described pathologically in the preantibiotic era as Councilman's nephritis in the course of scarlet fever.

Autoimmune interstitial nephritis is seen in diseases such as lupus nephritis, ANCA-positive vasculitis, and other rheumatic disorders including Sjogren's syndrome, which may present with dry eyes as part of the sicca syndrome. In a patient with photophobia and red painful eye, the clinician should look at renal function and the urinalysis for evidence of tubulointerstitial nephritis uveitis (TINU) syndrome.

Noninflammatory Interstitial Diseases Noninflammatory interstitial diseases are often caused by toxic exposures that damage the tubular interstitial structures. For example, a cancer patient on ifosfamide may develop Fanconi's syndrome, indicating proximal tubule damage. Heavy-metal exposures such as cadmium, lead, and mercury from old dental fillings may lead to proximal tubule injury and, again, Fanconi's syndrome. A patient with hypomagnesemia and acute kidney injury (AKI) may have had past exposure to platinum-containing chemotherapeutic agents and a patient with nephrogenic diabetes insipidus, unresponsive to antidiuretic hormone, may have

2282 had treatment with lithium, analgesics, or chemotherapy. Hypokalemia and interstitial disease are consistent with a past history of exposure to aminoglycosides or amphotericin-B. The patient with the former may complain of hearing loss and the patient with the latter may present with hypokalemia and RTA.

Chronic interstitial diseases should be suspected in cases of paraproteinemia (light-chain nephropathy or amyloidosis) and in patients who ingest herbal remedies containing aristolochic acid, as occurs commonly in China and has been determined to be the cause of Balkan nephropathy. Perhaps the most common cause of chronic interstitial nephritis is prolonged analgesic use to treat chronic pain (not only NSAIDs but acetaminophen or combinations of phenacetin, aspirin, and caffeine) as part of the analgesic syndrome. The clinician should ask about a prior history of pain and also gastrointestinal symptoms that may precede the kidney disease; the analgesic drugs often go unreported by the patient. It is important to recognize this syndrome because, if the drugs are not discontinued, a later development may be urothelial cancers of the distal ureter and urinary bladder. Lithium after prolonged use can also cause chronic interstitial nephritis along with nephrogenic diabetes insipidus and slowly progressive kidney failure.

Patients who have hypercalcemia or hyperoxaluria may develop nephrocalcinosis, a form of interstitial nephritis characterized by calcifications within the renal parenchyma, often at the cortical medullary boundary. When nephrocalcinosis and nephrolithiasis are concurrent, the most common etiologies include hypercalcemic disorders, particularly primary hyperparathyroidism, and congenital medullary sponge disease (tubular ectasia), as well as hereditary distal RTA. In patients with DM, chronic analgesic use, or sickle-cell diseases, the phenomenon of papillary necrosis is associated with chronic interstitial damage characterized by nephrogenic diabetes insipidus. For example, phenacetin toxicity is a result of the drug's concentrating in the medulla due to the normal urinary concentrating mechanism; ironically, the first function lost because of medullary toxicity is the ability to concentrate the urine. In the ensuing papillary necrosis, the patient may observe solids in the urine, which are sloughed tissue from the ischemic medulla. When a patient with inflammatory bowel disease or one who has had gastric bypass procedures such as the Roux-en-Y develops kidney injury, with or without calcium oxalate kidney stones, a 24-h urine oxalate measurement must be determined to diagnose intestinal hyperoxaluria, which otherwise may lead to nephrocalcinosis. Chronic bacterial pyelonephritis is not a common cause of chronic renal failure because it rarely affects both kidneys. Acute pyelonephritis in a solitary kidney or transplanted kidney may cause AKI.

PROTEINURIC STATES AND NEPHROTIC SYNDROME

Proteinuric States Some patients notice generalized edema and foamy urine, manifestations of proteinuria. Proteinuria is not synonymous with nephrotic syndrome (NS). In DM the urinary loss of microalbuminuria (MALB) defines glomerular proteinuria, which typically occurs after years of small-vessel disease (explaining the likelihood of coincident small-vessel retinopathy) and predicts future development of progressive renal failure and NS. The rate of renal progression is greater with hypertension, obesity, and poor glucose control. Further risks are nephrectomy, hepatitis C, and, as in focal segmental glomerular sclerosis (FSGS), in patients of African ancestry is likely due to the prevalence of the APOL1 gene mutations. Because treatment of patients with MALB is indicated, the clinician caring for diabetic patients should screen regularly for the presence of small amounts of albumin in the urine, which can be detected as microalbuminuria (30–300 mg/day of albumin excretion) by radioimmunoassay. Subnephrotic albuminuria is characteristic of focal diseases of the kidney with <50% of glomeruli involved, whereas NS is likely diffuse, involving most glomeruli. Lower levels of albuminuria are characteristic of glomerulonephritis, as discussed above.

Microalbuminuria is beneath detection by urinary dipstick protein analysis. Any detectable albuminuria on dipstick is called *overt proteinuria* and when detected at the highest level on the strip is

consistent with nephrotic proteinuria. The dipstick measurement picks up only the most acidic proteins like albumin but not proteins with a higher isoelectric point, most notably kappa and lambda light chains found in multiple myeloma. Additionally, the filtration of light chains may cause glomerular damage and albuminuria (kappa light-chain nephropathy or lambda AL amyloid) but does not require an abnormal glomerulus because their charge and molecular weight allow them to freely cross the glomerular barrier. Such filtration is considered overflow proteinuria.

A laboratory measurement of albumin or total protein should be normalized to urine creatinine concentration as a ratio in order to discount the effects of urinary dilution or concentration. It is also important to note that the ratio of total protein concentration to creatinine concentration is not specific for albumin excretion and may indicate the presence of light chains. The detection of light chains requires a urine protein electrophoresis.

Another type of proteinuria known as tubular proteinuria, which is mostly -2 microglobulin, is secreted by proximal tubular cells and is common in interstitial nephritis.

Nephrotic Syndrome Nephrotic syndrome (NS) has three defining features: edema, hypoalbuminemia (<3.5 g/dL), and proteinuria >3.5 g/day. The syndrome is often associated with lipid abnormalities such as a high LDL, low HDL, and lipiduria. The urine may contain large tubular epithelial cells that are engulfed with the lipid in a recognizable shape under polarized light. These oval fat bodies may also contain cholesterol monohydrate crystals, which appear as Maltese crosses. Under low light, the refractile lipid may be seen as fatty casts.

Clinically, patients present with generalized edema and, in contrast to heart failure with orthopnea, facial, eyelid and periorbital swelling is observed in NS. Penile and scrotal edema can be severe enough to obstruct urethral urine flow in men. In some cases, edema may form large bullae that may rupture, predisposing to ulceration and cellulitis. The skin becomes smooth and may appear to "weep." Patients may have hoarseness caused by vocal cord edema. On occasion, nephrotic range proteinuria is not associated with edema, for example in the case of human immunodeficiency virus-associated nephropathy (HIVAN), which is more common in blacks with HIV. In these cases, rapid loss of renal function may occur due to implosion of the glomerular capillary by proliferation of visceral epithelial cells that crush the glomerular loops, decreasing capillary flow and filtering surface area (collapsing glomerulopathy). This glomerulopathy is a severe, treatment-resistant form of FSGS. Other secondary forms of FSGS, more often not associated with NS, include remnant kidney after partial surgical removal, adaptive injury, chronic hypoxemia, sickle cell diseases, recurrent vasculitis with healing of some glomeruli, obesity, and congenital urogenital anomalies. Very heavy proteinuria is often noted in this syndrome. Secondary forms of FSGS are shown in Fig. 308-3. Other secondary forms of FSGS, more often not associated with NS, include remnant kidney after partial surgical removal, adaptive injury, chronic hypoxemia from chronic lung or congenital heart disease, sickle cell diseases, recurrent vasculitis with healing of some glomeruli, obesity, and congenital urogenital anomalies.

NS is a hypercatabolic state with negative nitrogen balance due to proximal tubule absorption and lysosomal catabolism exceeding hepatic albumin synthesis. A characteristic finding of rapid-onset hypoalbuminemia in NS is horizontal linear white lines in the nail bed, known as Muehrcke's lines. When NS in the adult occurs abruptly, with severe elevation of cholesterol, one must consider glomerular epithelial injury (podocytopathy), which may be idiopathic minimal change disease (MCD), a name historically based on the appearance of renal tissue on light microscopy and often preceded by an upper respiratory infection, allergies, or immunization. Secondary causes of MCD are Hodgkin's lymphoma or other lymphoproliferative disorders. MCD can occur at any age and in the adult may present with AKI as well, primarily because of the underlying vascular disease and hypoalbuminemia.

Age is important in the onset of NS, in that young children <6 years of age frequently have MCD. Several gene mutations encoding for proteins of the podocyte, such as nephrin (*NPHS1*) and podocin (*NPHS2*)

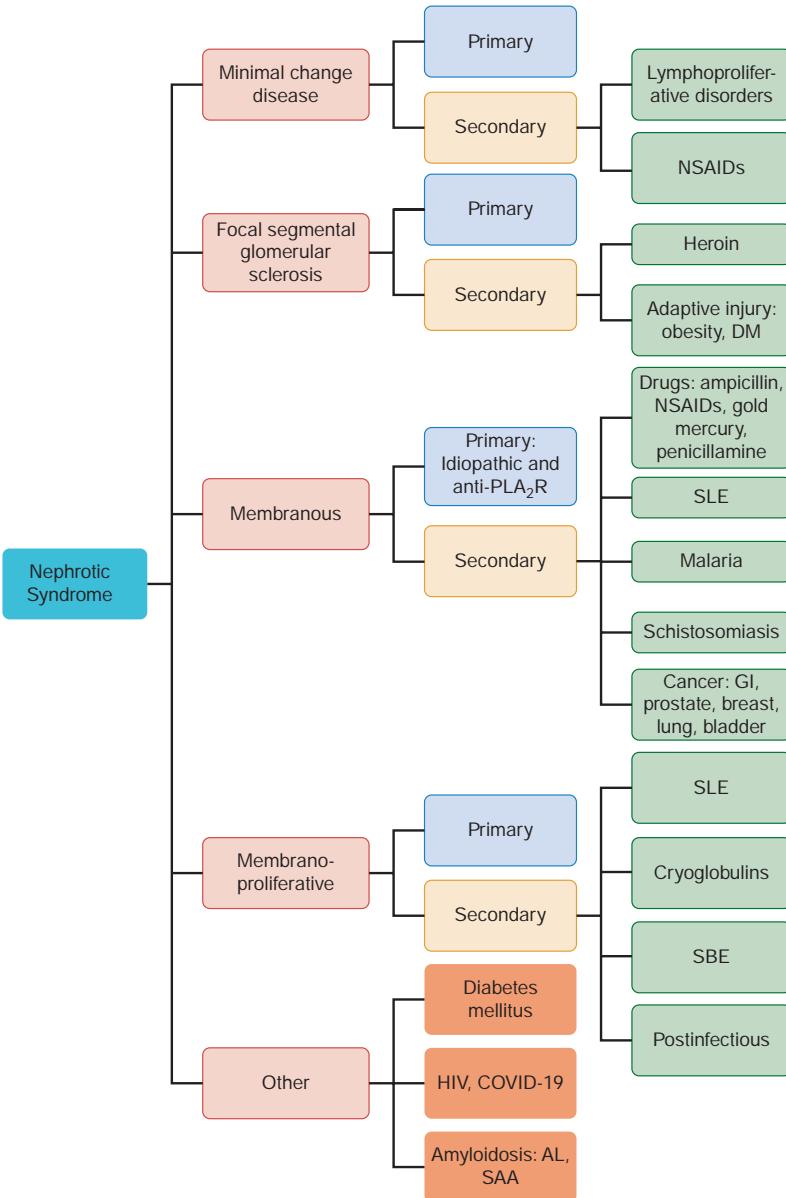


FIGURE 308-3 Nephrotic syndrome. Different pathologic syndromes broken down into the idiopathic and secondary causes. 70% of primary membranous nephropathy (MN) is associated with antibodies to the integral subepithelial basement membrane antigen phospholipase A₂ receptor (PLA₂R). The former term for primary membrano-proliferative GN has been replaced by pathologic syndromes involving complement deposition (C3 glomerulopathy and dense-deposit disease in children). AL amyloid is the form of amyloidosis secondary to lambda light-chain deposition and SAA is the protein (serum amyloid A) associated with chronic inflammatory diseases such as rheumatoid arthritis, familial Mediterranean fever, and tuberculosis.

in the slit diaphragm, have been shown to be responsible for most cases of hereditary nephrotic syndrome (see Table 308-2).

In children who have a serum albumin concentration <2 g/dL, tissue ischemia may develop, causing a “nephrotic crisis,” in which severe abdominal pain may be mistaken for a surgical abdomen. A 20-year-old presenting with NS may have MCD, FSGS, or membranous nephropathy (MN).

Like MCD, MN exists as primary or secondary etiology. Whereas NS is a cause of a hypercoagulable state, particularly when it is accompanied by severe hypoalbuminemia (<2 g/dL), MN is the NS most often associated with renal vein thrombosis (RVT) for a number of reasons, among them the urinary loss of antithrombin-3 and plasminogen, as

well as hyperfibrinogenemia. RVT may present with back pain or pulmonary emboli.

NS with heavy proteinuria or large kidneys on ultrasound in advanced stages of chronic kidney disease (CKD) is often noted in diabetic nephropathy, amyloid, HIVAN, and MN with RVT. MN may be the presenting finding in cases of SLE, whereas diffuse proliferative GN with low C3, when associated with SLE, occurs in patients who also have signs and symptoms of joint, skin, or systemic organ involvement. A cause of very early MN is an idiosyncratic reaction to NSAIDs, even when taken in small amounts. Many other drugs including penicillamine, mercury, and gold can cause MN. Proteinuria from any cause may present earlier, or increase, when DM, obesity, partial nephrectomy, or increased renal venous pressure exists.

Solid tumors, particularly lung, gastric, intestinal, bladder, breast, and prostate, may underlie a paraneoplastic syndrome of MN. While it is important to take a history and examine the patient carefully for signs of cancer, it is not the rule to work up every patient with MN exhaustively for cancer. But the neoplastic nephropathy may be a sign of recurrent disease and may even be recognized by tumor antigens. MN also occurs in the context of many infectious diseases, including syphilis, malaria, schistosomiasis, and hepatitis B. Recently, 70% of patients with primary MN have been found to have circulating levels of an autoantibody to the phospholipase A₂ receptor (anti-PLA₂R) in the subepithelial region of the glomerular basement membrane.

Patients who have a nephrotic and nephritic sediment in childhood may have membranoproliferative glomerular nephritis (MPGN) with low C3 as a primary disease (C3 glomerulopathy or dense-deposit disease). The adult presenting with a nephrotic and nephritic picture should be considered to have an immune complex disorder unless proven otherwise. In amyloidosis there may be a simultaneous and severe tubular syndrome in addition to the albuminuria, consisting of nephrogenic diabetes insipidus and a hyperkalemic RTA. When NS is associated with Fanconi's syndrome (glycosuria, phosphaturia, uricosuria, and aminoaciduria), one must consider multiple myeloma in the adult.

HEMATURIA AND LOWER URINARY TRACT SYNDROMES

Because blood could enter the urinary tract from any structure, identifying the source is a necessary first step. As a rule, hematuria associated with flank pain or ureteral colic is more characteristic of a lower urinary tract source, such as a stone or

an obstructing lesion. However, when flank pain without colic is noted, one has to consider swelling of the kidney and stretching of the renal capsule, as might be seen in acute urinary obstruction, kidney infection, interstitial nephritis, and, on occasion, acute glomerular nephritis. Heavy bleeding with clots is more characteristic of lower tract bleeding but could result from trauma to the kidney. In patients who have acute flank pain and hypertension, assuming the pain is due to a kidney stone may miss an occlusive vascular event from an embolus or in situ clot within the arterial blood supply. Patients who engage in strenuous exercise may develop hematuria that can be ruled out by retesting the urine after a week or two of rest. True hematuria can be distinguished from hemoglobinuria and myoglobinuria by urinalysis.

TABLE 308-2 Hereditary and Congenital Diseases

HEREDITARY GLOMERULAR DISEASES: NEPHROTIC SYNDROME OR RENAL FAILURE	HEREDITARY TUBULAR DISEASES	APOL1	CILIOPATHIES	CHANNELOPATHIES	CONGENITAL ANOMALIES
Podocyte mutations: basement membrane mutations; hereditary nephritis; X-linked and somatic mutations; <i>COL4A5</i> ; Alport's syndrome with hematuria neurosensory hearing loss, conus latus; Fabry's disease (X-linked alpha-galactosidase deficiency)	Fanconi's syndrome with renal glycosuria, proximal tubule RTA, hypophosphatemia, hypouricemia; distal RTA with hearing loss, renal calcification; nephrogenic diabetes insipidus; hyper- or hypotensive disorders with hypo- or hyperkalemia; metabolic alkalosis or acidosis	Mutant allele in African-American population, leading to susceptibility to further injury in many other disorders including diabetes mellitus	Autosomal dominant and recessive polycystic kidney disease; medullary cystic kidneys (metabolic acidosis and salt-wasting); other phenotypes	Gitelman's and Bartter's syndromes; disorders of eNaC and proton pumps	Unilateral agenesis; dysgenetic disease; medullary sponge kidney (hematuria, stones, or infection); horseshoe kidney (proteinuria); malposition; ureteropelvic obstruction; cystoureteral reflux (proteinuria)

Symptoms of lower urinary tract disorders are dysuria, urinary frequency, urgency, incomplete emptying, hematuria that is most pronounced at the beginning of the stream, as well as a poor urinary stream. Among these disorders are urinary tract infection and prostatic hypertrophy. Hematuria of recent onset noted in the fourth decade of life or beyond should undergo a urologic evaluation and most likely cystoscopic examination of the bladder. However, chronic hematuric conditions may be associated with chronic glomerular disease such as thin basement membrane, hereditary nephritis, or IgA nephropathy. That is why it is so important to search for previous examinations such as insurance, military, or employment exams done in the past to determine if hematuria was present in order to establish chronicity.

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is defined by the retention of nitrogenous solutes such as urea, uric acid, and creatinine. The creatinine concentration goes up primarily related to the amount of water absorbed along the nephron. Because the urea but not creatinine has a reabsorptive component, the clearance of urea is less than the clearance of creatinine. With a constant catabolic rate, a decrease in glomerular filtration alone will affect the BUN and creatinine proportionately. In contrast, a disorder associated with enhanced urinary concentration (high ADH), in which urea as well as water has increased reabsorption in the process of concentrating the urine, the retention of urea nitrogen exceeds that of creatinine, accounting for an elevated BUN-to-creatinine ratio. Oliguric or oligoanuric states are often characterized as *prerenal*, meaning preglomerular vascular disease or low perfusion states; *renal*, indicating intrinsic renal disease; or *postrenal*, indicating obstructive nephropathy or uropathy (see Table 308-1).

Prerenal states are often related to a decreased perfusion pressure to the glomerular capillaries or some other interference with filtration. The differential diagnosis includes proliferative GN (the bloodless capillary); a preglomerular vascular disease such as scleroderma or thrombotic microangiopathy; the use of pressors for the maintenance of blood pressure; vasoconstrictive substances including cocaine, iodinated IV contrast media, hemoglobin or myoglobin, and certain antibiotics like vancomycin, cyclosporine, and tacrolimus (calcineurin inhibitors); other vasoconstrictive drugs like nonsteriodals; and renal nerve stimulation. Hypercalcemia and hypoxia are also vasoconstrictive. Correcting hypoxemia has a diuretic effect.

Intrinsic Renal Disease All of these will decrease perfusion pressure and decrease GFR while stimulating sodium and water reabsorption. Therefore, the characteristic urinary findings are low urinary sodium excretion and concentrated urine. The urine sodium concentration is usually low and the urine to plasma creatinine concentration is usually >40 . The same result could occur in bilateral renal artery stenosis, heart failure, and other circulatory collapse. If damage is done to the renal tubules, so-called **intrinsic renal disease**, there may or may not be oliguria and in fact there could be polyuria (unresponsiveness to ADH), sodium-wasting, potassium-wasting, and acid-base disorders, each of which may predominate. One of the most frequent causes of oliguric acute renal failure is

acute tubular necrosis (ATN), caused by gram-negative sepsis, hemodynamic collapse, hemoglobinuria or myoglobinuria, and medication or toxin ingestion. Examples are crush injury, heroin and alcohol stupor, and compartment syndrome. Drug causes include NSAIDs, aminoglycosides, and chemotherapeutic drugs like cisplatin and methotrexate.

Postrenal States Postrenal states accompanied by anuria suggest complete obstruction to the flow of urine, while polyuria and bland urinary sediment suggest incomplete obstruction combined with ADH unresponsiveness. The fractional excretion of sodium is usually $>1\text{--}2\%$, whereas in oliguric prerenal syndromes the fractional excretion of sodium is usually $<1\%$. Exception to the low sodium excretion would be in the case of hyperchloremic metabolic alkalosis, where chloride is being conserved and sodium excreted with bicarbonate.

Urinary tract obstruction is usually characterized by hydronephrosis visualized on ultrasound images or large volumes of urine removed by bladder catheterization, indicating bladder outlet obstruction. Exceptions to finding hydronephrosis on an imaging study include the extrinsic obstructive compression of the kidney or ureter in retroperitoneal disease; cases in which imaging was done too soon, for example <4 days after obstruction; or when the patient was simultaneously obstructed and volume depleted.

As mentioned earlier, acute tubular diseases that are not primarily due to inflammation can be caused by intratubular obstruction, from hyperoxaluric states, or by uric acid or phosphates in tumor lysis syndrome following chemotherapy for lymphoproliferative disorders. Other drug therapies that cause tubular injury include cisplatin, ifosfamide, methotrexate, aminoglycosides, and amphotericin B, and toxicity through exposure to heavy metals.

Kidney injury in the setting of systemic disease with dysfunction in other organs includes the cardiorenal, pulmonary renal, and hepatorenal syndromes. Other syndromes that typically involve the kidney include febrile illness, systemic infection with septic shock, hemodynamic collapse due to cytokines, or capillary leak syndrome. These syndromes as well as the endothelial origins of thrombotic microangiopathies and hemolytic uremic syndrome are shown in Fig. 308-4. Obstetric patients with abruptio placenta may develop bilateral cortical necrosis and as a consequence, anuria, and often irreversible renal failure. In addition, patients with atheroembolic syndrome can present with AKI or chronic progressive damage following an aortic catheterization. If the blood vessels catheterized involve the aortic arch, an encephalopathic syndrome that can mimic uremic encephalopathy may follow. As many as 70% of patients with COVID-19 who required ventilators during the early phase of the pandemic developed multiorgan failure, including AKI. AKI may also be a risk for chronic kidney disease following a COVID-19 infection.

CHRONIC KIDNEY DISEASE AND THE UREMIC SYNDROME

Chronic kidney disease (CKD), progressing over months to years, can be the long-term result of any of the previously mentioned diseases. If the time course is unknown, other ways to diagnose CKD versus

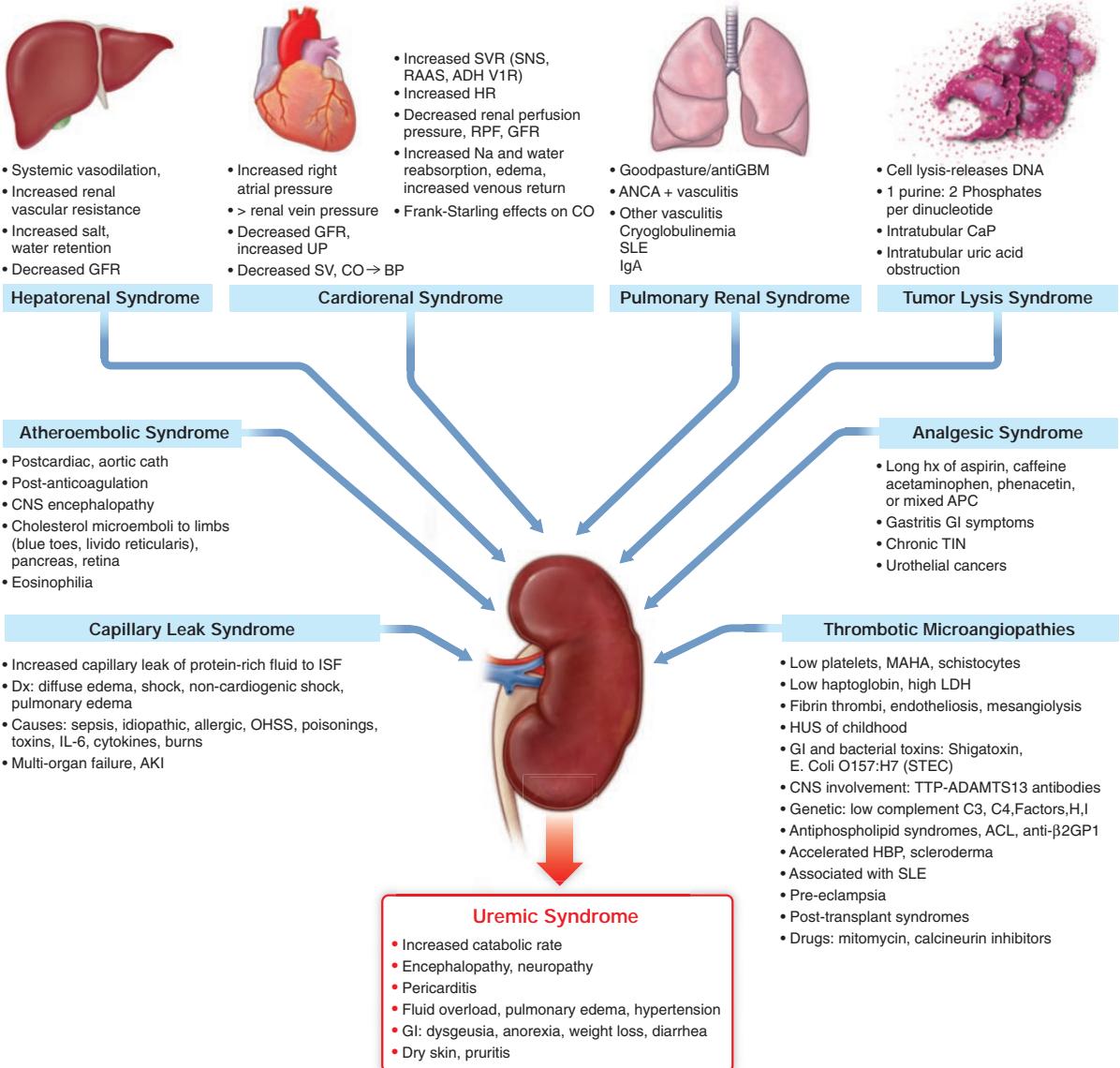


FIGURE 308-4 Categories of systemic or non-renal-based syndromes that involve the kidney and in advanced cases can cause the uremic syndrome requiring renal replacement therapy. ACL, anticardiolipin antibodies; ADH V1R, antidiuretic hormone V1 receptor; anti-β2GP1, anti-beta-2-glycoprotein-1; APC, aspirin, acetaminophen, caffeine; BP, blood pressure; CaP, calcium phosphate crystals; CO, cardiac output; HUS, hemolytic-uremic syndrome; IgA, immunoglobulin A; ISF, interstitial fluid; LDH, lactic dehydrogenase; MAHA, microangiopathic hemolytic anemia; OHSS, ovarian hyperstimulation syndrome; RAAS, renin angiotensin aldosterone system; RPF, renal plasma flow; SV, stroke volume; SNS, sympathetic nervous system; SVR, systemic vascular resistance; TIN, tubulointerstitial nephritis; TTP, thrombotic thrombocytopenic purpura; UP, urine protein.

a more recent kidney disorder are useful, for example, the finding of bilaterally small kidneys on a renal ultrasound. Kidneys by this method are normally 10–12 cm in length. Small kidneys, <8 cm, are likely atrophic with irreversibly low function; but in some cases of CKD, such as diabetes, the kidneys may be large despite kidney failure. Remarkably, even atrophic kidneys may still produce renin to sustain blood pressure and erythropoietin to minimize anemia; however, due to low calcitriol in CKD, patients develop secondary hyperparathyroidism. The normal parathyroid gland weighing 25 mg would be limited in raising PTH, such that very elevated PTH likely is in favor of CKD. Thinning of the renal cortex is also a sign of chronicity.

DM accounts for approximately 50% of CKD patients that progress to end-stage renal disease (ESRD). Other important causes leading to ESRD are IgA nephropathy, ischemic nephropathy without proteinuria manifesting after age 50 years with hypertension, and signs of other

large-vessel disease, such as intermittent claudication from peripheral vascular disease, stroke, and coronary artery disease. In contrast, renal arterial disease due to fibromuscular dysplasia, seen predominantly in white women in the fourth decade of life, does not progress to renal failure and is a treatable form of hypertension. Other arterial diseases include polyarteritis nodosum (PAN) and, in medium-sized vessels, a Kawasaki-like illness affecting children, which has had a thirtyfold increase since the onset of COVID-19 as part of the multisystem inflammatory syndrome.

Heredity and congenital diseases of the kidney are shown in Table 308-2. Autosomal dominant PKD occurs in all ethnic populations. The patient may first show signs of cysts in late teenage years with hypertension, urinary or cyst infection, or pain and bleeding. Kidney stones may be seen. By the age of 30 years, individuals with the disorder will have ultrasound-detectable cysts. The clinician should know that

TABLE 308-3 Stages of Chronic Kidney Disease

STAGES OF CKD, ABNORMALITY > 3 MONTHS	RANGE OF eGFR	CLINICAL FEATURES	IMPORTANCE
1	>60 mL/min/1.73 m ²	Abnormal urinalysis, abnormal renal imaging	Risk of progression to later stages increases with increased proteinuria and dependent on cause of disease
2	>60 mL/min/1.73 m ²	Abnormal urinalysis, abnormal renal imaging	Mild risk of progression to later stages increases with increased proteinuria and dependent on cause of disease
3a	45–60 mL/min/1.73 m ²	Cardiovascular disease or other organ damage	Moderate risk of progression of disease. Pay attention to other vascular risk factors, high BP, lipids, smoking, weight
3b	30–45 mL/min/1.73 m ²	Proteinuria	High risk of progression
4	15–30 mL/min/1.73 m ²		High likelihood of progression to ESRD, need preparation and education regarding choices for RRT including transplant and dialysis
5	<15 mL/min/1.73 m ²		Highest risk of requiring RRT

a diagnosis of PCKD requires multiple cysts in both kidneys. Cysts are also found in the liver. The first manifestation of PCKD may be a cerebral hemorrhage, since berry aneurysms are present in a small subset of patients with this disease, most commonly in the circle of Willis.

Hereditary nephritis with many variations includes the Alport syndrome, involving a gene mutation (*COL4A5*, accounting for the majority of cases) effecting the alpha 3 region of the noncollagenous domain of type IV collagen in GBM. There is an X-linked pattern of genetic transmission, where males may be most severely affected by renal failure in middle age. The syndrome involves hematuria, neurosensory hearing loss, and ocular deformities of the lens. A predominant symptom in hereditary nephritis is microscopic hematuria and the pathologic correlate to this is thin basement membranes. It must be distinguished from the less severe and more common related condition known as thin basement membrane disease as a cause of hematuria.

Certain congenital abnormalities of the kidney, such as horseshoe and ectopic kidneys, also shown in Table 308-2, consist of low nephron numbers that may result in secondary FSGS. The condition known as ureteral reflux is an abnormality involving the functional insertion of the ureter into the muscular bladder, which normally closes off the ureter upon bladder contraction. In reflux disease the ureter cannot prevent retrograde flux of urine during micturition. In children this may cause hypertension and, in some cases, secondary FSGS. Surgical correction of the abnormality may be curative, but the child may outgrow it in adulthood in any case.

The stages of CKD are listed in Table 308-3 and are important in terms of planning for renal replacement therapy (dialysis and transplantation), and for assessing and slowing the rate of progression, defined as the decline in GFR over time. In CKD, the estimated GFR (eGFR) is determined by the current stable serum creatinine, entered into one of several equations derived from clinical trial data that compared the subject's value to actual measurements of GFR. For example, the Modification of Diet in Renal Disease (MDRD) study used a radioisotope (I^{125} -iothalamate) clearance to measure true GFR. The equation contains additional factors such as age and sex to derive the current eGFR, corrected for 1.73 m² body-surface area. This value of eGFR is *not* a creatinine clearance, nor a measurement of GFR.

There has been debate about the inclusion of corrective factors that would alter the result from that equation, based on the patient's ethnicity and race. For example, it has been recommended in some centers to multiply the eGFR value by a factor of 1.2 in black patients in order to correct for the perceived underestimate of GFR using the MDRD equation. There is considerable objection to making this correction, which may have the effect of introducing bias based on race. Because the corrected eGFR will give a higher value to the GFR, there could be delays in discussion of renal replacement therapy and in initiation of treatment. Consequently, the correction has fallen out of favor. Recently an alternative, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), has been used that excludes race as a parameter. Another method of calculating GFR uses cystatin-C.

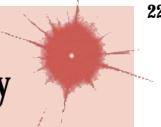
In the course of CKD, the clinician must evaluate the patient for symptoms and signs of worsening renal function. When the eGFR is <15–20 mL/min, the patient should already have had conversations

about choices of eventual treatment and, if indicated, surgical preparation for peritoneal or hemodialysis. Attention should be given to the sensitive topic of transition to a lifesaving but mechanical procedure. It is also important to discuss transplantation and issues of timing. The ethical standard is for separate clinicians to evaluate the recipient and donor of a kidney transplant. Confidentiality and privacy are essential. Very importantly, access to transplantation has not been equally offered to minority populations and it is incumbent on the clinician to avoid bias by discussing the option with every patient.

Symptoms of CKD are often nonspecific and include fatigue, weakness, loss of appetite and taste, weight loss, mood changes, and metabolic encephalopathy that may involve cognitive changes such as decline in executive function and the ability to calculate and remember. Other symptoms are peripheral and autonomic neuropathies and sleep and movement disorders such as restless legs and asterixis or myoclonus. Patients with AKD lose their ability to concentrate the urine, and therefore have an obligate urine output of approximately 2 L. This results in nocturia, since the bladder fills during the night. Ironically, the loss of nocturia may be sensed by the patient as an improvement of symptoms but actually indicates worsening oliguria. Pruritis commonly occurs. Clinical issues include changes in medications and doses. The full uremic syndrome is characterized by severe hypertension, the above-mentioned encephalopathic manifestations, GI bleeding, pericarditis, severe electrolyte disturbances, particularly hyperkalemia, and secondary hyperparathyroidism. Anemia is frequently present and though it may be due to iron deficiency or decreased erythropoietin, other causes of anemia should be investigated. Patients respond well to erythropoietic stimulating agents, with the goal of therapy >10 g/dL but <12 g/dL. Notably, not all patients are anemic. For example, some patients with urinary tract obstruction, polycystic kidney disease, renal vascular disease, and renal cell carcinoma may in fact have erythrocytosis.

In nephrotic syndrome, heavy proteinuria may persist throughout the course of CKD and carries a worse prognosis. In all kidney diseases, including the nephritic processes, renal disease may progress to late stages even when the acute inflammation has subsided. However, the underlying mechanisms of progressive renal failure involve inflammatory pathways (reflected in elevated levels of C-reactive protein and erythrocyte sedimentation rate in CKD), emphasizing the importance of managing risk factors for cardiovascular disease, such as hypertension, smoking, hyperlipidemias, diabetes, and obesity early in the course of CKD.

Some chronic renal syndromes may present with predominant tubular dysfunction, including genetic diseases known as channelopathies. Examples are the depletion of electrolytes such as phosphorus and potassium and proximal RTA due to Fanconi's syndrome, mentioned above; hypokalemic alkalosis and volume depletion in Bartter's syndrome (mutations resulting in abnormal loop of Henle function); and electrolyte losses in Gitelman's, a defect in the thiazide-sensitive sodium-chloride transporter. Gitelman's also causes hypochloremic hypokalemic metabolic alkalosis. Bartter's and Gitelman's can be distinguished by examining the urine for the usual solutes regulated by these transporters. Thus, Bartter's is associated with hypercalcioria



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and the inability to put out a concentrated urine, whereas Gitelman's is associated with hypocalciuria and preserved ability to concentrate the urine. Fanconi's syndrome results in hypokalemic acidosis and can be distinguished from distal RTA, which does not associate with the loss of glucose, amino acids, and phosphate in the urine.

Disorders involving the collecting duct and its transporters of sodium, potassium, and acid base can result in syndromes that also suggest certain diagnoses. For example, polyuria due to inappropriate free water losses and insensitive to ADH is characteristic of nephrogenic diabetes insipidus and it is common to see simultaneous defects in potassium secretion and hydrogen ion secretion, with hypertension suggesting blockade of one of the sodium regulators of ENaC. These disorders are usually associated with hyporenin and/or hypoaldosterone states, which include UTO, type 4 RTAs in DM, amyloidosis, or Addison's disease. In contrast, hypokalemic metabolic alkalosis with volume expansion may suggest an adrenal adenoma, unilateral renal artery stenosis, ACTH-secreting tumors, licorice abuse, or potassium-sparing diuretics.

Renal Masses Patients with renal cell carcinoma may have been diagnosed via an incidental finding in an abdominal imaging study, or sometimes by a palpable mass best felt with the patient supine, usually a thin patient but occasionally a very large protruding mass. Very large masses or multiple masses that are easily palpable may represent cystic diseases of the kidney, including polycystic kidney disease (PKD) or even a single cyst, versus a congenital ureteral pelvic obstruction. Other times, a renal cell carcinoma can present as anemia, possibly caused by hematuria, or as back pain associated with metastatic lytic vertebral lesions. Metastases may involve the lungs and the bone marrow as well.

Imaging and Renal Biopsy Indications For hematuric syndromes, imaging may add valuable information, particularly in the patient who has heavy bleeding or blood clots in the urine. Renal pathology may be detected as an abdominal mass, as in the case of renal cell carcinoma, chronic urinary tract obstruction, or cystic diseases of the kidney including polycystic kidney disease (PKD) and simple cyst. If the patient has a known history of tubular sclerosis or the finding of skin fibroadenoma, one might identify a renal mass found on CT imaging as an angiomyolipoma.

The renal ultrasound is efficacious in determining the size and symmetry of the kidneys and in excluding urinary obstruction. It is helpful in detecting renal cysts or mass, but less useful in kidney stone disease. Ultrasound is not as accurate a tool for angiomyolipomas. The renal-limited noncontrast CT scan is the standard test for nephrolithiasis but carries the risk of accumulative radiation. MRI is often useful in evaluating and following renal masses, including renal cell carcinoma. The patient with renal disease may develop the complication of systemic sclerosis after receiving gadolinium; new contrast media to replace it are emerging. CT iodinated contrast media remain a problem, particularly in the patient with vascular disease of the kidney. Radioisotope scanning is useful in demonstrating the percentage of renal function coming from each kidney. Finally, in many of the diseases discussed above, diagnosis ultimately depends on renal biopsy and pathologic evaluation.

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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. 309-1. 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 produces 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

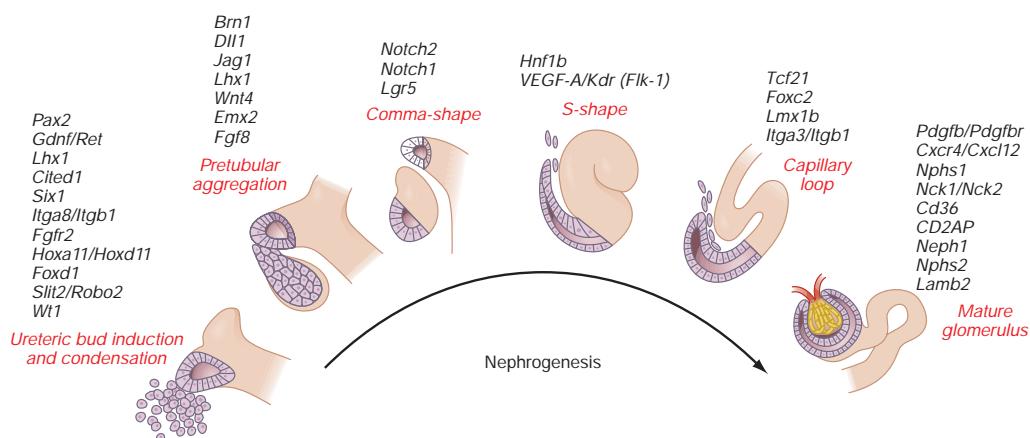


FIGURE 309-1 Genes controlling renal nephrogenesis. A growing number of genes have been identified at various stages of glomerulotubular development in the mammalian kidney. The genes listed have been tested in various genetically modified mice, and their location corresponds to the classical stages of kidney development postulated by Saxen in 1987.

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 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 ultrafiltration forms 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. 309-2A). 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 rising or falling 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, greater solute delivery to the macula densa (Fig. 309-2B) 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, a lower rate of 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 TGF, whereas nitric oxide (NO) blunts TGF. A distinct feedback mechanism may exist between the connecting tubule and GFR in which high Na⁺ delivery evokes afferent arteriolar dilation possibly mediated by prostaglandins.

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. 309-2B). 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. 309-2C). Angiotensin II evokes vasoconstriction of the efferent arteriole, and the resulting increased glomerular hydrostatic pressure elevates GFR to normal levels.

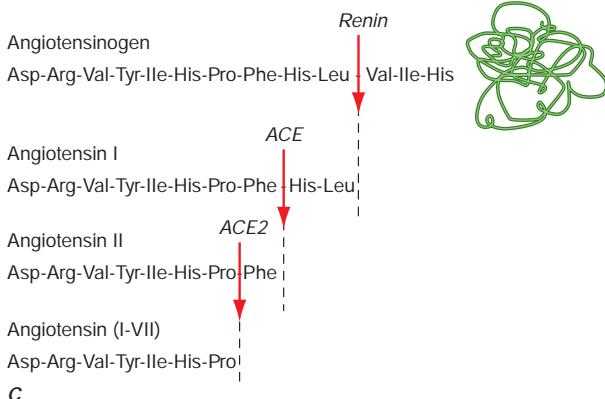
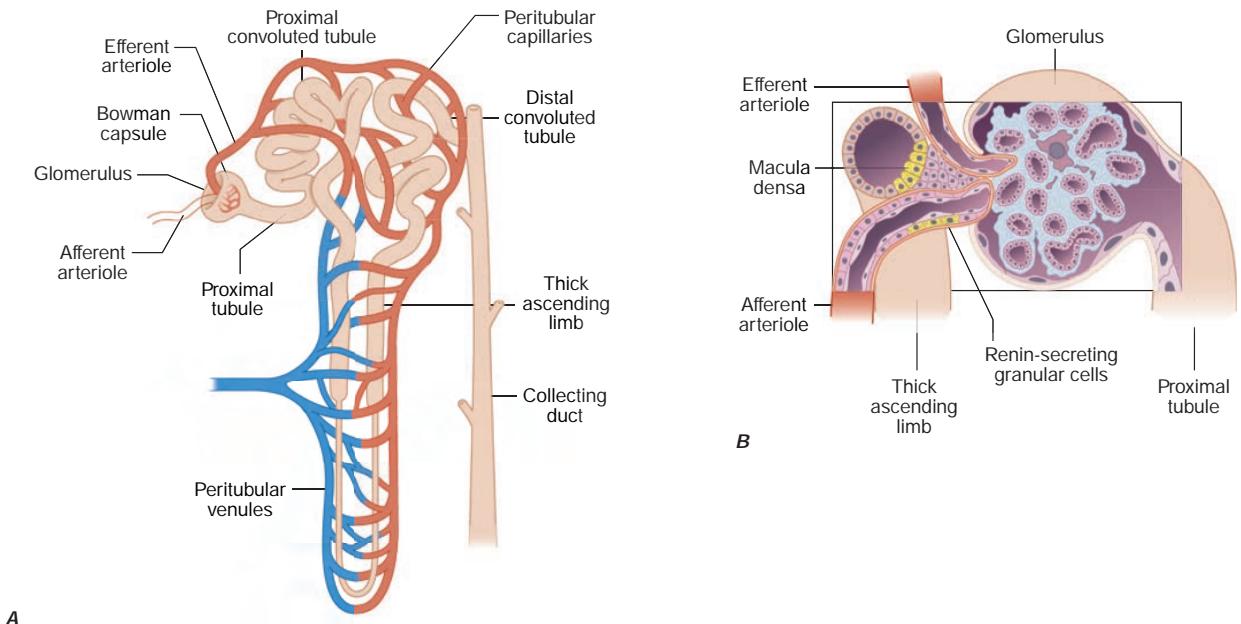


FIGURE 309-2 Renal microcirculation and the renin-angiotensin system. **A**, Diagram illustrating relationships of the nephron with glomerular and peritubular capillaries. **B**, Expanded view of the glomerulus with its juxtaglomerular apparatus including the macula densa and adjacent afferent arteriole. **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 in morphology and function along the nephron (Fig. 309-3). 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

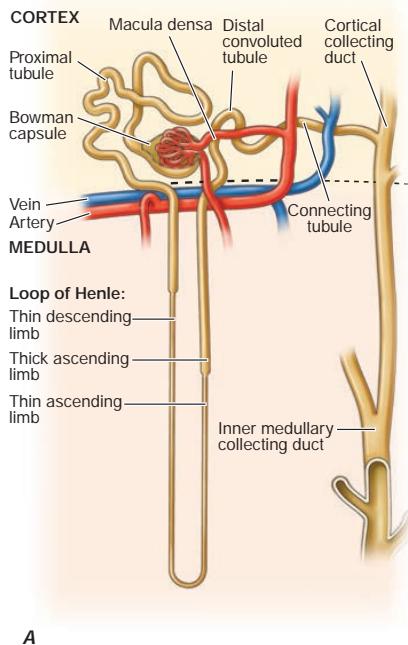
There are two types of epithelial transport. Movement of fluid and solutes sequentially across the apical and basolateral cell membranes (or vice versa) mediated by transporters, channels, or pumps is called

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

MEMBRANE TRANSPORT

Cell membranes are composed of hydrophobic lipids that repel water and aqueous solutes. The movement of solutes and water across cell membranes is made possible by discrete classes of integral membrane proteins, including channels, pumps, and transporters. These different mechanisms mediate specific types of transport activities, including

active transport (pumps), passive transport (channels), facilitated diffusion (transporters), and secondary active transport (cotransporters). Active transport requires metabolic energy generated by the hydrolysis of ATP. Active transport pumps are ion-translocating ATPases, including the ubiquitous Na^+/K^+ -ATPase, the H^+ -ATPases, and Ca^{2+} -ATPases. Active transport creates asymmetric ion concentrations across a cell membrane and can move ions against a chemical gradient. The potential energy stored in a concentration gradient of an ion such as Na^+ can be used to drive transport through other mechanisms (secondary active transport). 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 309-1).



A

SEGMENTAL NEPHRON FUNCTIONS

Each anatomic segment of the nephron has unique characteristics and specialized functions enabling selective transport of solutes and water (Fig. 309-3A). 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 reabsorption 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. 309-3B). 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

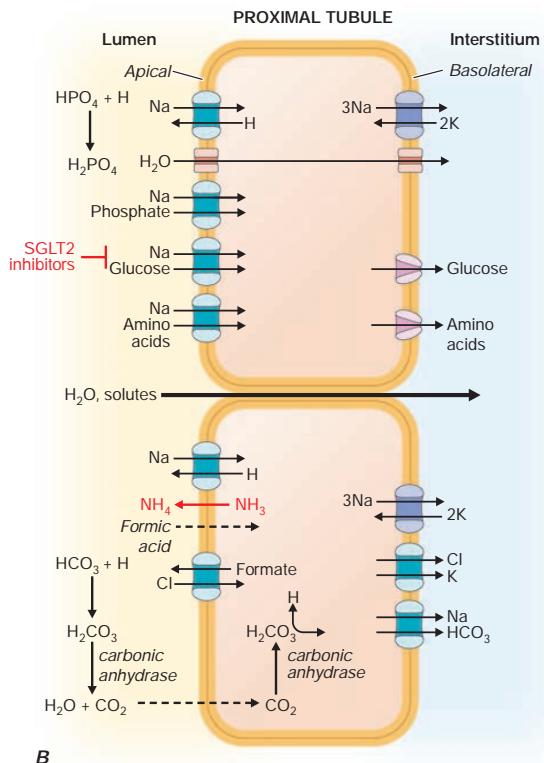


FIGURE 309-3 Transport activities of the major nephron segments. Representative cells from five major tubular segments are illustrated with the lumen side (apical membrane) facing left and interstitial side (basolateral membrane) facing right. **A.** Overview of entire nephron. **B.** Proximal tubular cells. **C.** Typical cell in the thick ascending limb of the loop of Henle. **D.** Distal convoluted tubular cell. **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.

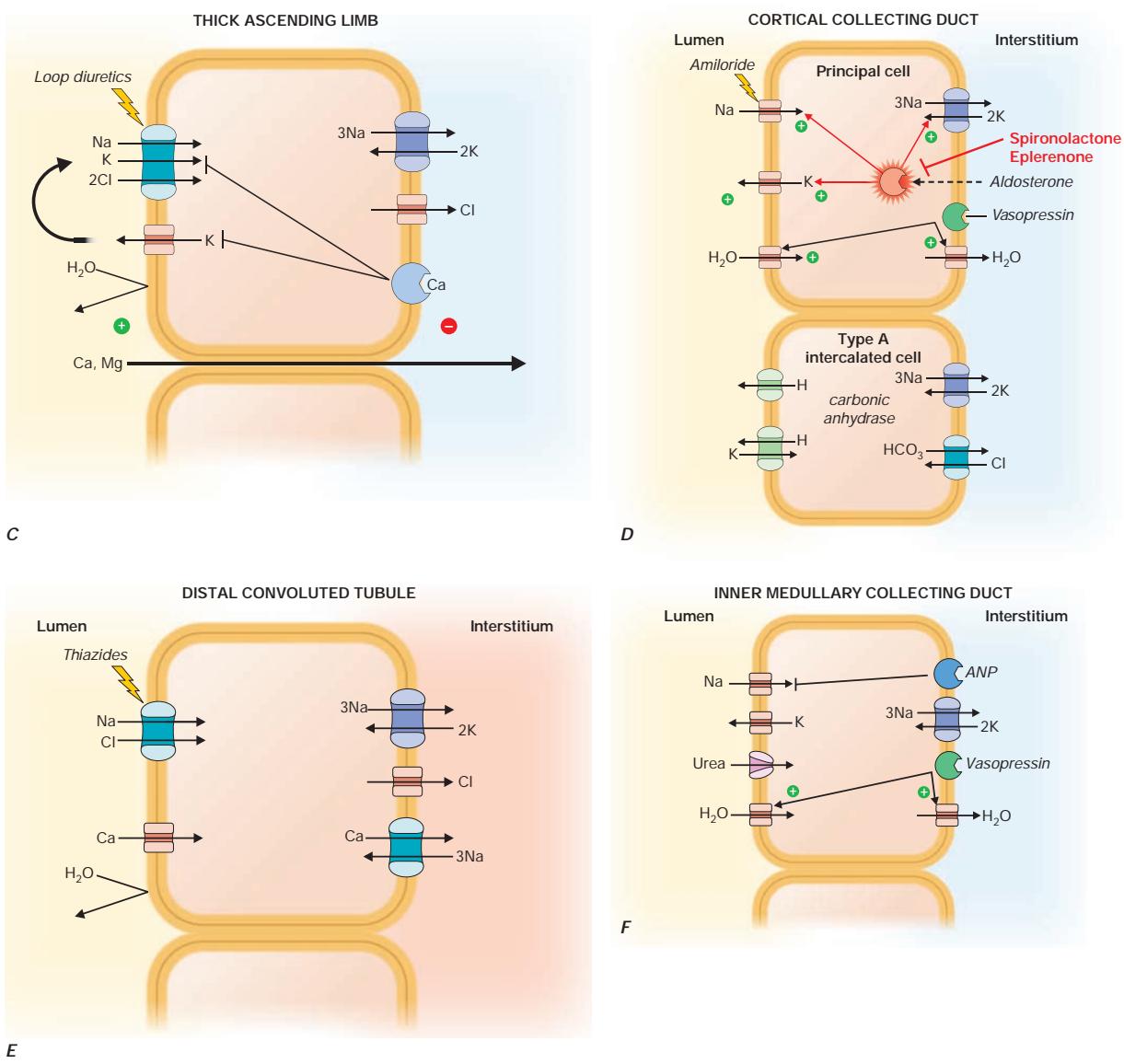


FIGURE 309-3 (Continued)

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 (H₂CO₃) 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⁺/HCO₃⁻ cotransporter. This process is saturable, which can result in renal 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 (NH₃) and phosphate. Renal NH₃ is produced by glutamine metabolism in the proximal tubule. Subsequent diffusion of NH₃ out of the proximal tubular cell enables trapping of H⁺, which is secreted by Na⁺/H⁺ exchange, in the lumen as ammonium ion (NH₄⁺). 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 (HPO₄²⁻) is also titrated in the proximal tubule by secreted H⁺ to form H₂PO₄⁻, 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⁻.

TABLE 309-1 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 (<i>SLC4A4</i> , 4q21)	604278
Fanconi-Bickel syndrome	Glucose transporter, GLUT2 (<i>SLC2A2</i> , 3q26.2)	227810
Isolated renal glycosuria	Sodium glucose cotransporter (<i>SLC5A2</i> , 16p11.2)	233100
Cystinuria		
Type I	Cystine, dibasic and neutral amino acid transporter (<i>SLC3A1</i> , 2p16.3)	220100
Non-type I	Amino acid transporter, light subunit (<i>SLC7A9</i> , 19q13.1)	600918
Lysinuric protein intolerance	Amino acid transporter (<i>SLC7A7</i> , 4q11.2)	222700
Hartnup disorder	Neutral amino acid transporter (<i>SLC6A19</i> , 5p15.33)	34500
Hereditary hypophosphatemic rickets with hypercalcemia	Sodium phosphate cotransporter (<i>SLC34A3</i> , 9q34)	241530
Renal hypouricemia		
Type 1	Urate-anion exchanger (<i>SLC22A12</i> , 11q13)	220150
Type 2	Urate transporter, GLUT9 (<i>SLC2A9</i> , 4p16.1)	612076
Dent's disease	Chloride channel, CIC-5 (<i>CLCN5</i> , Xp11.22)	300009
X-linked recessive nephrolithiasis with renal failure	Chloride channel, CIC-5 (<i>CLCN5</i> , Xp11.22)	310468
X-linked recessive hypophosphatemic rickets	Chloride channel, CIC-5 (<i>CLCN5</i> , Xp11.22)	307800
Disorders Involving the Loop of Henle		
Bartter's syndrome		
Type 1	Sodium, potassium chloride cotransporter (<i>SLC12A1</i> , 15q21.1)	241200
Type 2	Potassium channel, ROMK (<i>KCNJ1</i> , 11q24)	601678
Type 3	Chloride channel, CIC-Kb (<i>CLCNKB</i> , 1p36)	602023
with sensorineural deafness	Chloride channel accessory subunit, Barttin (<i>BSND</i> , 1p31)	602522
Autosomal dominant hypocalcemia with Bartter-like syndrome	Calcium-sensing receptor (<i>CASR</i> , 3q13.33)	601199
Familial hypocalciuric hypercalcemia	Calcium-sensing receptor (<i>CASR</i> , 3q13.33)	145980
Primary hypomagnesemia	Claudin-16 or paracellin-1 (<i>CLDN16</i> or <i>PCLN1</i> , 3q27)	248250
Isolated renal magnesium loss	Sodium potassium ATPase, γ_1 -subunit (<i>ATP1G1</i> , 11q23)	154020
Disorders Involving the Distal Tubule and Collecting Duct		
Gitelman syndrome	Sodium chloride cotransporter (<i>SLC12A3</i> , 16q13)	263800
Primary hypomagnesemia with secondary hypocalcemia	Melastatin-related transient receptor potential cation channel 6 (<i>TRPM6</i> , 9q22)	602014
Pseudoaldosteronism (Liddle's syndrome)	Epithelial sodium channel β and γ subunits (<i>SCNN1B</i> , <i>SCNN1G</i> , 16p12.1)	177200
Recessive pseudohypoaldosteronism type 1	Epithelial sodium channel, α , β , and γ subunits (<i>SCNN1A</i> , 12p13; <i>SCNN1B</i> , <i>SCNN1G</i> , 16pp12.1)	264350
Pseudohypoaldosteronism type 2 (Gordon's hyperkalemia-hypertension syndrome)	Kinases WNK-1, WNK-4 (<i>WNK1</i> , 12p13; <i>WNK4</i> , 17q21.31)	145260
X-linked nephrogenic diabetes insipidus	Vasopressin V2 receptor (<i>AVPR2</i> , Xq28)	304800
Nephrogenic diabetes insipidus (autosomal)	Water channel, aquaporin-2 (<i>AQP2</i> , 12q13)	125800
Distal renal tubular acidosis		
autosomal dominant	Anion exchanger-1 (<i>SLC4A1</i> , 17q21.31)	179800
autosomal recessive	Anion exchanger-1 (<i>SLC4A1</i> , 17q21.31)	602722
with neural deafness	Proton ATPase, $\beta 1$ subunit (<i>ATP6V1B1</i> , 2p13.3)	192132
with normal hearing	Proton ATPase, 116-kD subunit (<i>ATP6V0A4</i> , 7q3)	602722

^aOnline Mendelian Inheritance in Man database (<https://www.ncbi.nlm.nih.gov/omim>).

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. Inhibitors of the Na⁺-glucose cotransporter SLGT2 in proximal tubules block glucose reabsorption and lower blood glucose, which has therapeutic benefits in diabetes mellitus and chronic diabetic kidney disease.

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 several protein-bound drugs not filtered at the glomerulus (penicillins, cephalosporins, and salicylates). Probenecid inhibits renal organic anion secretion and was historically used to elevate plasma concentrations of certain drugs such as 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 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 on 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 1'-hydroxylase to produce 1,25-di-hydroxy vitamin D (calcitriol), the most active form of the hormone, which 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 1'-hydroxylation of vitamin D, whereas 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, α_2 -microglobulin, and other small proteins, are taken up by the proximal tubule through a process of absorptive endocytosis and are degraded in acidified endocytic lysosomes. Acidification of these vesicles depends on a vacuolar H^+/ATPase and Cl^- channel. Impaired acidification of endocytic vesicles because of mutations in a Cl^- channel gene (*CLCN5*) causes low-molecular-weight proteinuria in Dent's disease.

LOOP OF HENLE

The loop of Henle consists of three major segments: descending thin limb, ascending thin limb, and ascending thick limb. 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 $\text{Na}^+/\text{K}^+/2\text{Cl}^-$ cotransporter on the apical membrane in series with basolateral Cl^- channels and Na^+/K^+ -ATPase (Fig. 309-3C). The $\text{Na}^+/\text{K}^+/2\text{Cl}^-$ 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, ~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, is 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 $\text{Na}^+/\text{K}^+/2\text{Cl}^-$ 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 hypercalcioria 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. 309-3D). Apical Ca^{2+} -selective channels (TRPV5) and basolateral $\text{Na}^+/\text{Ca}^{2+}$ 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 $\text{Na}^+/\text{Ca}^{2+}$ 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 *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, which raises intracellular levels of cyclic AMP. This signaling cascade stimulates the insertion of water channels into the apical membrane of collecting duct cells to promote water permeability, 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-reabsorbing, 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

2294 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. 309-3E). 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, which potentiates 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, resulting in lower 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 potentiate 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 promote 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 in response to vasopressin.

Intercalated cells do not participate in Na^+ reabsorption but instead mediate acid-base balance. These cells perform two types of transport: active H^+ transport mediated by H^+ -ATPase (proton pump) and $\text{Cl}^-/\text{HCO}_3^-$ 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 $\text{Cl}^-/\text{HCO}_3^-$ anion exchanger for bicarbonate reabsorption (Fig. 309-3E). 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 $\text{Cl}^-/\text{HCO}_3^-$ exchanger on the apical membrane to mediate bicarbonate secretion while the proton pump resides on the basolateral membrane to enable H^+ 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. 309-3F). 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 raise 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. 309-4A), and *extracellular blood volume* is regulated by Na^+ balance (Fig. 309-4B). 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. 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 impair cell function (Fig. 309-4A).

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 lower plasma Na^+ concentration triggers more 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 regulate blood volume and osmolality). Changing the intake or excretion of water provides a means for adjusting plasma tonicity; thus, osmoregulation governs water balance.

The kidneys contribute to 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,

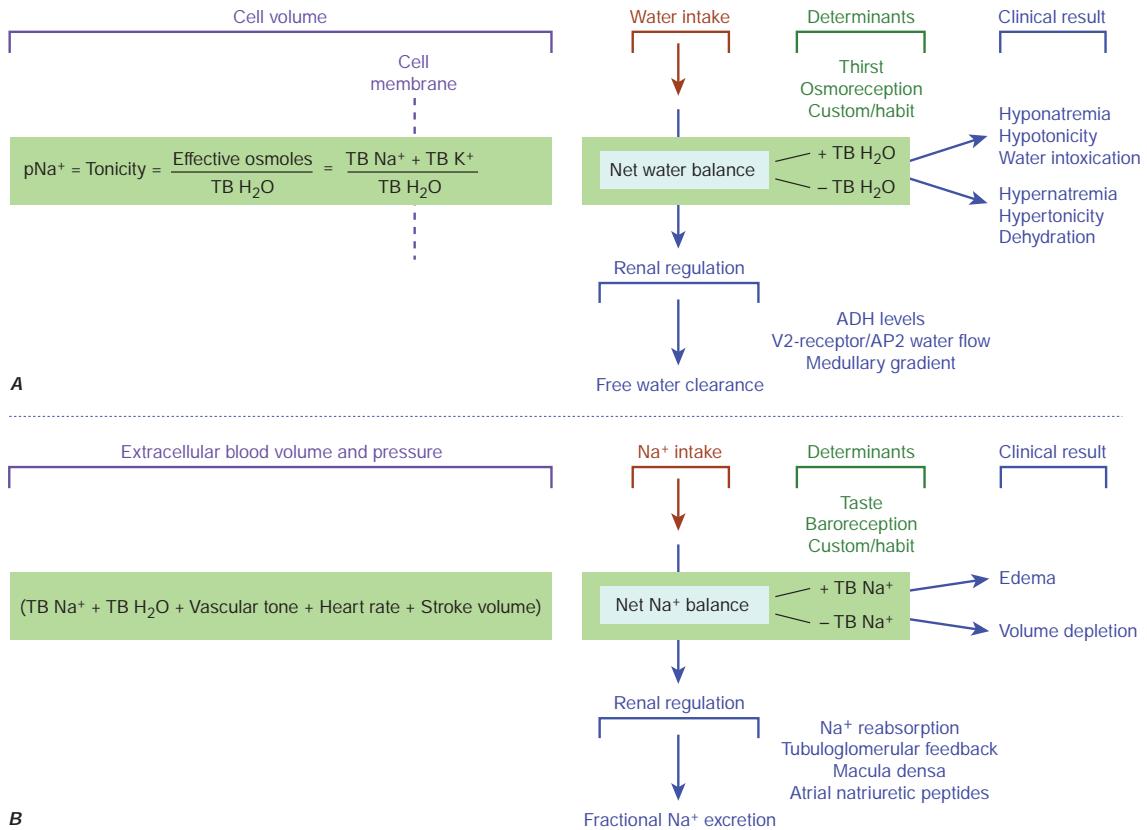


FIGURE 309-4 Determinants of sodium and water balance. **A.** Plasma Na⁺ concentration is a surrogate marker for plasma tonicity. Tonicity is determined by the number of effective osmoles in the body divided by the total body H₂O (TB H₂O), which translates simply into the total body Na⁺ (TB Na⁺) and anions outside the cell separated from the total body K⁺ (TB K⁺) inside the cell by the cell membrane.⁶ Net wafer 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 (~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 H₂O (TB H₂O), 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.

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. 309-4B), 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, Ca²⁺ signaling, adenosine, vasopressin, and the neural adrenergic axis. If Na⁺ intake exceeds Na⁺ excretion (positive Na⁺ balance), then a rising 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 fall 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 α_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 boosts 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. 309-2C).

Aldosterone is synthesized and secreted by granulosa cells in the adrenal cortex. It binds to cytoplasmic mineralocorticoid receptors in the collecting duct principal cells and boosts the 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 higher channel density at the plasma membrane and greater capacity for Na⁺ reabsorption by the collecting duct.

Chronic exposure to aldosterone is associated with lower urinary Na^+ excretion lasting only a few days, after which Na^+ excretion returns to previous levels. This phenomenon, called *aldosterone escape*, is explained by lower 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.

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310

Acute Kidney Injury

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Acute kidney injury (AKI) is defined by the impairment of kidney filtration and excretory function over days to weeks (generally known or expected to have occurred within 7 days), 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 the ability of the kidney to maintain effective circulating volume regulation, excrete nitrogenous wastes and metabolic toxins, and maintain 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 (ICU). AKI severity is staged based on the magnitude of the rise in Scr and severity and duration of oliguria (**Table 310-1**). 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. Large studies have shown that increases in Scr as low as 0.3 mg/dL in hospitalized patients are independently associated with an approximately fourfold increase in hospital mortality, with higher changes in creatine, and longer duration of elevation associated with greater increased risk of morbidity and mortality. Morbidity of AKI in those admitted to the ICU exceeds 50% in many studies. AKI also has longer term implications even if the patient survives the hospitalization. AKI increases the risk for the development or worsening of chronic kidney disease (CKD) and development of dialysis-requiring end-stage kidney disease (ESKD). AKI may also occur in the community. Common causes of community-acquired AKI include volume depletion, heart failure, adverse effects of medications, obstruction of

TABLE 310-1 Staging of Acute Kidney Injury Severity

STAGE	SERUM CREATININE	URINE OUTPUT
1	1.5–1.9 times baseline OR 0.3 mg/dL (26.5 $\mu\text{mol/L}$) increase	<0.5 mL/kg per h for 6–12 h
2	2.0–2.9 times baseline	<0.5 mL/kg per h for 12 h
3	3.0 times baseline OR increase in serum creatinine to 4.0 mg/dL (353.6 $\mu\text{mol/L}$) OR initiation of renal replacement therapy OR, in patients <18 years of age, decrease in eGFR to <35 mL/min per 1.73 m^2	<0.3 mL/kg per h for 24 h OR Anuria for 12 h

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 developed and developing countries—particularly because 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. In developing countries, resources to diagnose and manage AKI are often limited.

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. 310-1**).

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 vascular responses such as nonsteroidal anti-inflammatory drugs (NSAIDs) and inhibitors of angiotensin II (**Fig. 310-2**). By definition, prerenal azotemia involves no parenchymal damage to the kidney and is rapidly reversible once parenchymal blood flow and intraglomerular hemodynamics are restored. In many cases, however, 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 to the tubular cells with necrosis, hence termed acute tubular necrosis (ATN).

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 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

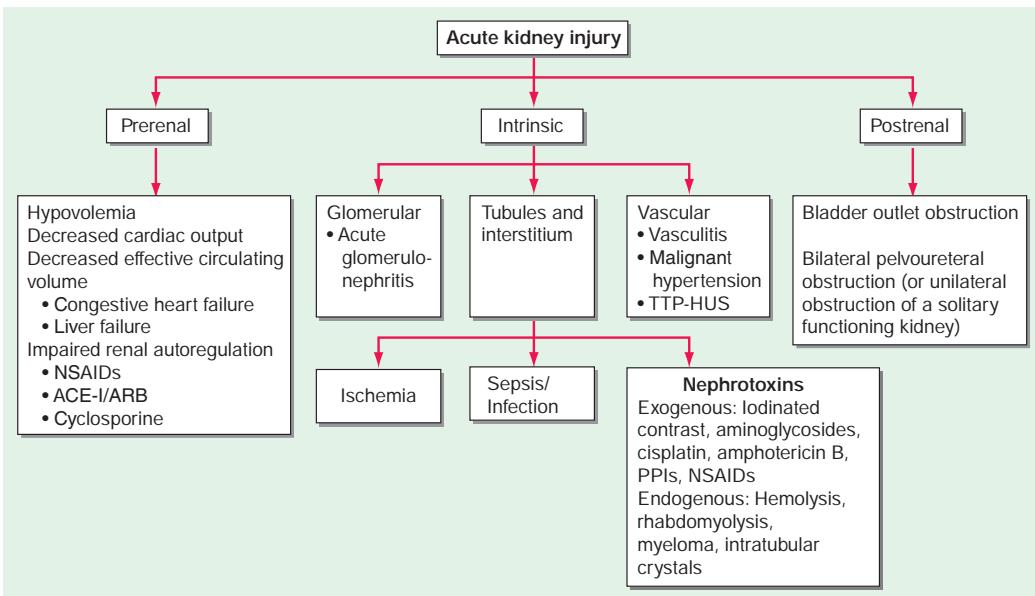


FIGURE 310-1 Classification of the major causes of acute kidney injury. ACE-I, angiotensin-converting enzyme inhibitor-I; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitors; TTP-HUS, thrombotic thrombocytopenic purpura-hemolytic-uremic syndrome.

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 E₂), kallikrein and kinins, and possibly nitric oxide (NO) also increases 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. 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

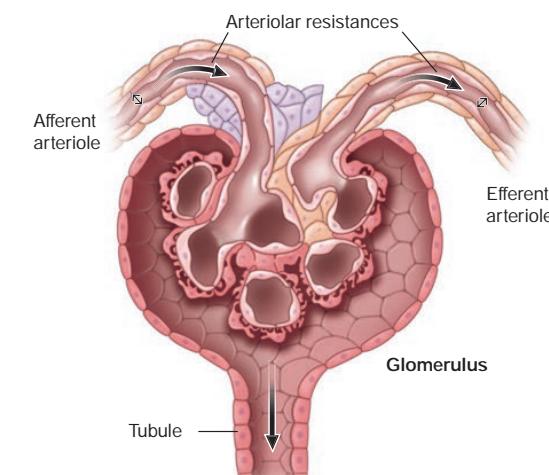
total-body volume overload. Systemic vascular resistance is markedly reduced due to primary arterial vasodilation in the splanchnic circulation, resulting ultimately in activation of vasoconstrictor responses similar to those seen in hypovolemia. AKI is a common complication in this setting, and it can 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 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.

INTRINSIC AKI

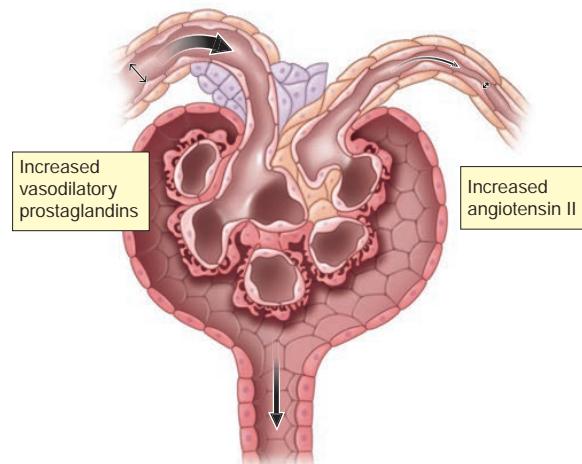
The most common causes of intrinsic AKI are sepsis, ischemia, and nephrotoxins, both endogenous and exogenous (Fig. 310-3). As mentioned previously, in many cases, prerenal azotemia advances to tubular injury. Although often the AKI is attributed to “acute tubular necrosis,” human biopsy confirmation 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 without frank necrosis. There are other potential causes of AKI in settings such as sepsis, including drug-induced interstitial nephritis or glomerulonephritis. These and other causes of intrinsic AKI can be catalogued anatomically according to the major site of renal parenchymal damage: glomeruli, tubulointerstitium, and vessels.

SEPSIS-ASSOCIATED AKI

In the United States, more than 1 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 many cases of severe AKI typically occur in the setting of hemodynamic compromise requiring vasopressor support. While there can be 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.

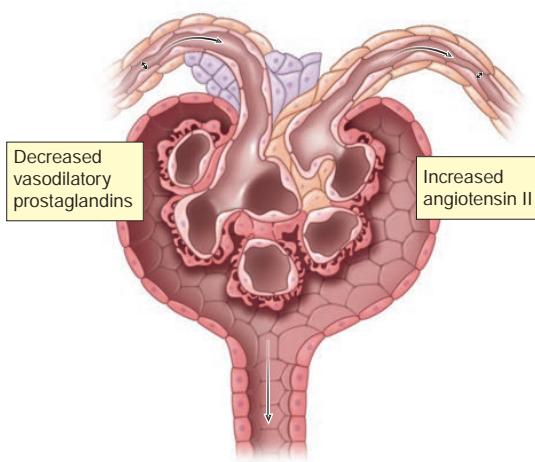


A Normal GFR



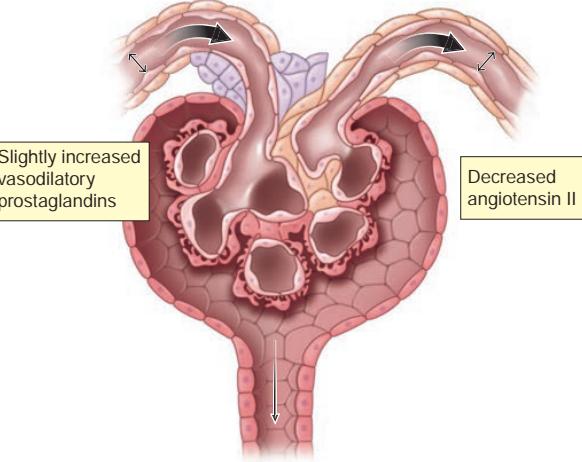
B Normal GFR maintained

Decreased perfusion pressure in the presence of NSAIDs



C Low GFR

Decreased perfusion pressure in the presence of ACE-I or ARB



D Low GFR

FIGURE 310-2 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 vasodilation 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: Normotensive ischemic acute renal failure. *N Engl J Med* 357:797, 2007. Copyright © 2007, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

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, or increased levels of vasoressin or 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.

AKI can be an important complication of viral infections, such as hantavirus, dengue virus, or SARS-CoV-2. The pathophysiology of AKI due to viral infections remains incompletely understood. As an example, some have reported infection of the kidney with SARS-CoV-2

while others have found less direct involvement. SARS-CoV-2 is associated with a large release of cytokines into the circulation (“cytokine storm”), which may cause diffuse intrarenal vasoconstriction. Finally, there is a generalized hypercoagulable state associated with SARS-CoV-2 that may contribute to the impairment of intrarenal blood flow.

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,

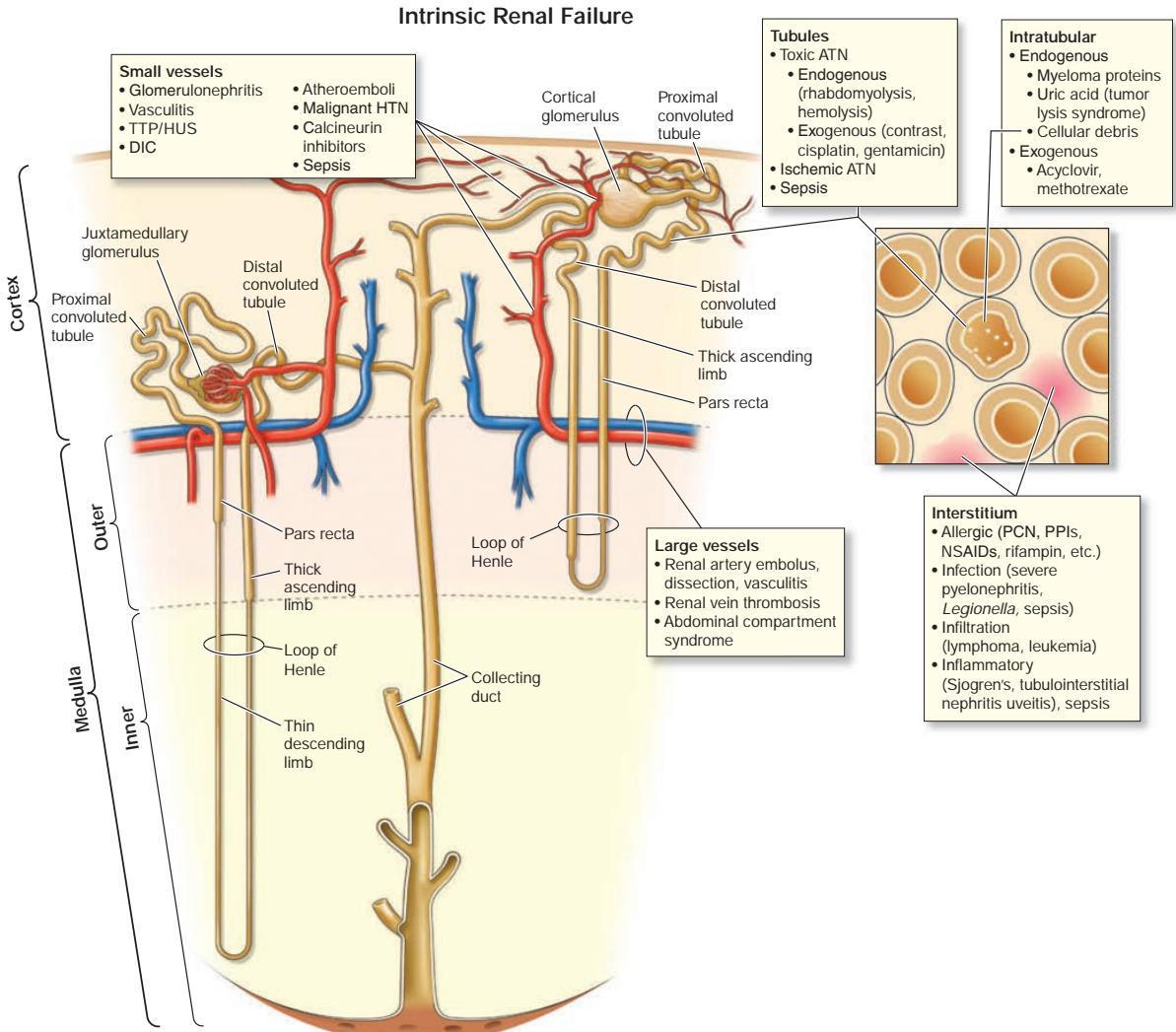


FIGURE 310-3 Major causes of intrinsic acute kidney injury. ATN, acute tubular necrosis; DIC, disseminated intravascular coagulation; HTN, hypertension; PCN, penicillin; PPI, proton pump inhibitors; TINU, tubulointerstitial nephritis-uveitis; TTP/HUS, thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome.

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. Transient 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 tubulo-glomerular 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. 310-4).

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 or vascular surgery. Over time, more of these surgical procedures are performed on older patients with comorbidities that predispose them to AKI and hasten progression of ESKD if they develop AKI. 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

Pathophysiology of Ischemic Acute Renal Failure

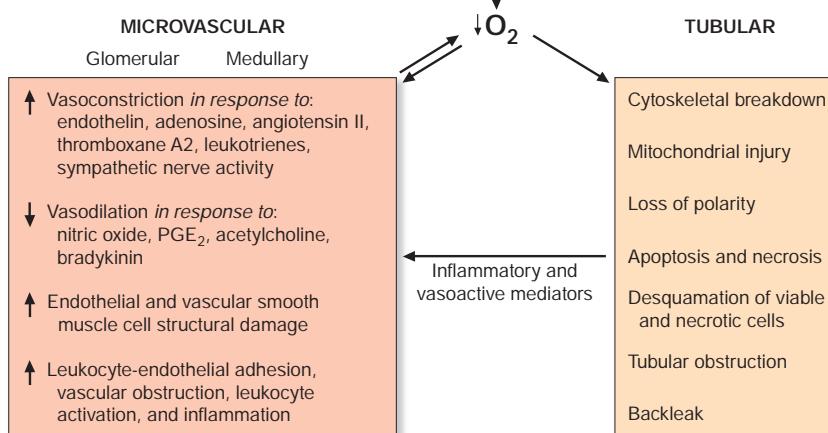


FIGURE 310-4 Interacting microvascular and tubular events contributing to the pathophysiology of ischemic acute kidney injury. PGE₂, prostaglandin E₂. (Republished with permission of American Society of Nephrology, from Recent advances in the pathophysiology of ischemic acute renal failure, JV Bonventre, JM Weinberg, 14:2199, 2003; permission conveyed through Copyright Clearance Center, Inc.)

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. In addition, high doses of exogenous vasopressors and blood-product perfusion increase the risk of AKI. Mortality among cardiovascular patients who require renal replacement therapy can be as high as 40–70%. Even with milder forms of post-operative AKI there is an increased risk of subsequent progression to chronic kidney disease.

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 abdominal compartment syndrome, where markedly elevated intraabdominal pressures, usually >20 mmHg, lead to renal vein compression and reduced GFR.

Diseases of the Vasculature Leading to Ischemia These diseases can compromise oxygen and metabolic substrate delivery to the tubules and glomeruli. Microvascular causes of AKI include the thrombotic microangiopathies (due to cocaine, certain chemotherapeutic agents, antiphospholipid antibody syndrome, radiation nephritis, malignant hypertension nephrosclerosis, thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome [TTP-HUS]), scleroderma, some chemotherapeutic agents and atheroembolic disease. Large-vessel diseases associated with AKI include renal artery dissection, thromboembolism, or thrombosis, and renal vein compression or thrombosis. Renal angiography is the gold standard for direct visualization of the renal vasculature and is important for the diagnosis of renal artery stenosis, large vessel vasculitis, fibromuscular disease, or renal vein obstruction.

NEPHROTOXIN-ASSOCIATED AKI

The kidney has very high susceptibility to nephrotoxic agents due to extremely high blood perfusion and concentration of filtered substances

along the nephron where filtrate water is reabsorbed and in the medullary interstitium, where water flows from the descending blood vessels into the concentrated 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/or 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. Gadolinium has been associated with development of nephrogenic systemic fibrosis (NSF) in subjects with advanced kidney disease, but the majority of these cases were associated with group I gadolinium-based contrast media, which are rarely used now in the United States and have been withdrawn from the market in many other countries. The risk of AKI associated with standard doses of group II gadolinium-based contrast media is very low.

Antibiotics Several antimicrobial agents are commonly associated with AKI. *Vancomycin* may be associated with AKI from tubular injury, particularly when trough levels are high and when used in combination with other nephrotoxic antibiotics. Vancomycin can also crystallize in tubules and cause intratubular obstruction. *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 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. Immune checkpoint inhibitors, such as *ipilimumab*, *tremelimumab*, *nivolumab*, and *pembrolizumab* can cause immune-related adverse events, often manifesting in the kidney as acute interstitial nephritis.

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. 75). 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 glomerular damage and/or 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 sometimes, 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.

Anticoagulant-Related Nephropathy Excessive anticoagulation with warfarin or other classes of anticoagulants has been reported to cause AKI through glomerular hemorrhage resulting in the formation of obstructing red blood cell casts within the kidney tubule and tubular injury.

Glomerulonephritis Diseases involving the glomerular podocytes, mesangial, and/or 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 and decrease subsequent longer term injury.

POSTRENAL AKI

(See also Chap. 319) 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. 310-5). 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 moderate to severe AKI to occur in individuals with two healthy functional kidneys, obstruction must affect both kidneys in order to observe large increases in SCr, unless there is asymmetric kidney function with one chronically diseased, and the other obstructed. 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 obstruction 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 310-2)

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 $<0.5 \text{ mL/kg per h}$ for longer than 6 h. As indicated previously, it is important to recognize that given this definition, some patients

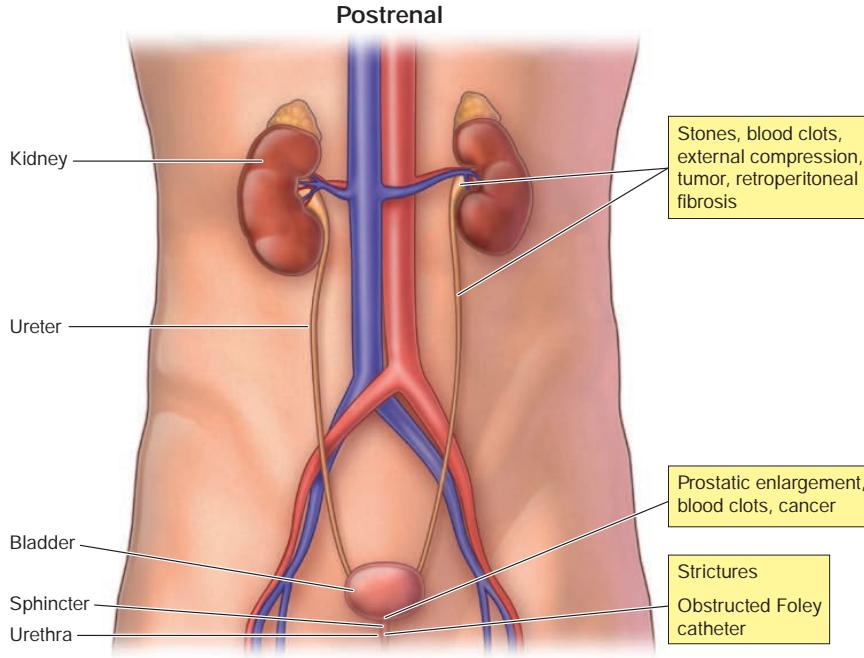


FIGURE 310-5 Anatomic sites and causes of obstruction leading to postrenal acute kidney injury.

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 represent clear evidence of AKI. Once the diagnosis of AKI is established, its cause needs to be determined because the elevation of SCr or reduction in urine output can be due to a large number of physiological and pathophysiological processes as described previously.

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 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 that estimate GFR because those equations are dependent on SCr and the patient being in a steady state. With AKI, changes in 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, a diagnosis facilitated by measurement of bladder pressure. Signs and/or symptoms 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 $<400 \text{ mL}/24 \text{ h}$) 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 (see Fig. 310-6 and Chap. A4). In the absence of preexisting proteinuria from CKD, AKI from ischemia or nephrotoxins leads to mild proteinuria ($<1 \text{ g/d}$). 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. Heavy proteinuria ("nephrotic range," $>3.5 \text{ g/d}$)

TABLE 310-2 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 or other test confirming infection; 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, vancomycin, zoledronate, ethylene glycol, aristolochic acid, 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
Other Causes of Intrinsic AKI			
Glomerulonephritis/vasculitis	Variable (Chap. 314) features include skin rash, arthralgias, sinusitis (AGBM disease), lung hemorrhage (AGBM, ANCA, lupus), recent skin infection or pharyngitis (poststreptococcal), thrombotic microangiopathies including those related to drugs, such as cocaine, anti-VEGF agents	ANA, ANCA, AGBM antibody, hepatitis serologies, cryoglobulins, blood culture, complement abnormalities, 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, <i>Legionella</i> infection	Eosinophilia, sterile pyuria; often nonoliguric	Urine eosinophils have limited diagnostic accuracy; kidney biopsy may be necessary
TPP/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 <i>Escherichia coli</i> or other bacteria; "atypical HUS" is due to inherited or acquired complement dysregulation. "TPP-HUS" refers to sporadic cases in adults. Diagnosis may involve screening for ADAMTS13 activity, Shiga toxin-producing <i>E. coli</i> , 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; TPP/HUS, thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome.

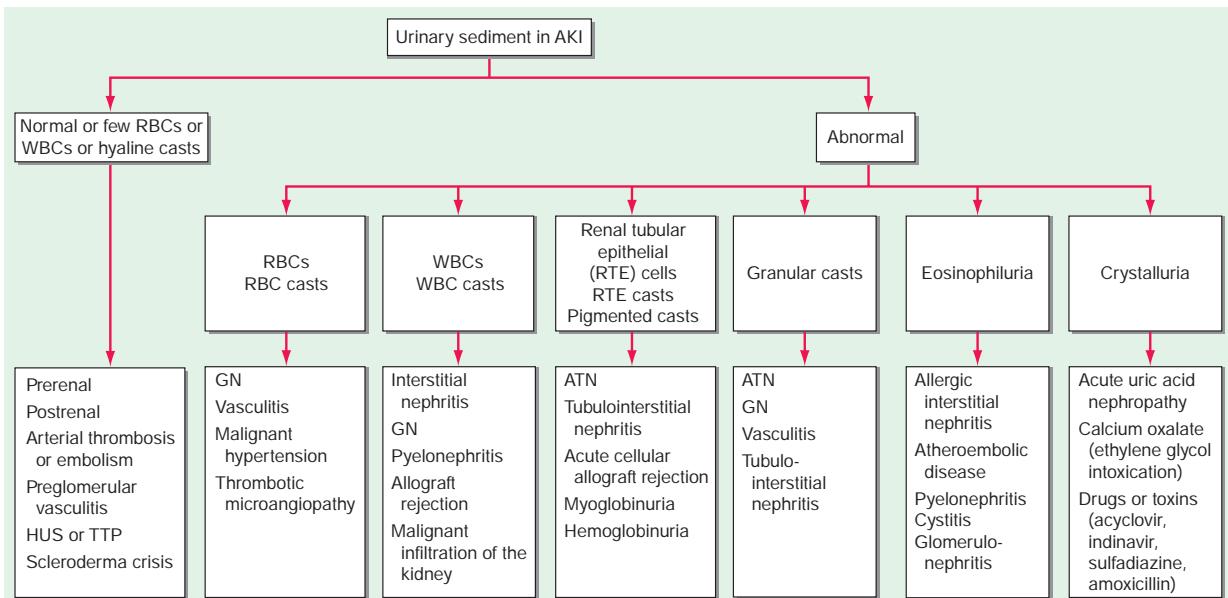


FIGURE 310-6 Interpretation of urinary sediment findings in acute kidney injury (AKI). ATN, acute tubular necrosis; GN, glomerulonephritis; HUS, hemolytic-uremic syndrome; RBCs, red blood cells; RTE, renal tubular epithelial; TTP, thrombotic thrombocytopenic purpura; WBCs, white blood cells. (Adapted 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.)

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 often associated with low serum albumin concentrations (Chap. 309). 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 be associated with 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 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. Myeloma can be diagnosed with serum immunoelectrophoresis or free light chain assay, and it can often be suspected if the blood anion gap is low due to unmeasured cationic proteins. 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 may suggest rhabdomyolysis or tumor lysis syndrome. Serum creatine kinase and uric acid levels are often elevated in rhabdomyolysis, while tumor lysis syndrome can be associated with 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 (ANCA), antiglomerular basement membrane (anti-GBM) antibodies, and cryoglobulins. Anti-phospholipase A2 receptor antibodies will point to a diagnosis of membranous nephropathy.

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 not 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 of, 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 impaired ability 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 relies 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 by passive diffusion from the collecting duct into a concentrated medullary interstitium, 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 this 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 scan 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 hydroureretonephrosis. 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 suggest the possibility of acute interstitial nephritis or infiltrative diseases. As described previously, 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 (GBCAs) 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. The recommendations regarding use of GBCAs in subjects with CKD remain controversial.

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, but the diagnostic and prognostic information obtained can be invaluable.

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 urine and blood 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 <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. Protein biomarkers of kidney injury have also been identified in animal models of AKI and have been used in humans and found to be particularly useful in toxicity identification. *Kidney injury molecule-1* (KIM-1) is a type 1 transmembrane protein that is abundantly expressed in proximal tubular cells injured by ischemia or multiple, distinct nephrotoxins, such as cisplatin. KIM-1 is not expressed in appreciable quantities in the absence of tubular injury or in extrarenal tissues. KIM-1 can be detected after ischemic or nephrotoxic injury in the urine and plasma. *Neutrophil gelatinase associated lipocalin* (NGAL, also known as lipocalin-2 or siderocalin) is another 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. Soluble urokinase plasminogen activator receptor (suPAR) is a signaling glycoprotein expressed in multiple cell types and thought to be involved in the pathogenesis of certain kidney diseases; suPAR has been measured in the plasma and found to predict the subsequent development of AKI. In 2014, the U.S. Food and Drug Administration (FDA) 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. In 2018 the FDA also qualified a panel of urinary markers including KIM-1, NGAL, N-acetyl-beta-D-glucosaminidase, osteopontin, cystatin-C, and clusterin for the detection of kidney tubular injury in phase 1 trials in healthy volunteers. The optimal use of 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.

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 is often heralded by an increase in urine output. This "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 ESKD 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 310-3**). Common to all are several principles. Optimization of hemodynamics, correction of fluid and electrolyte imbalances, discontinuation of nephrotoxic medications, and dose adjustment of administered medications are all critical. Common causes of AKI such as sepsis and ischemic ATN do not yet have specific therapies once injury is established, but meticulous clinical attention is needed to support the patient until (if) AKI resolves. The kidney possesses 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, undergo maladaptive repair processes and 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. Severe acute blood loss should be treated with packed red blood cells. In AKI, oliguria alone is not an indication for fluid administration. Intravascular hypovolemia should be the only indication. Optimal fluid composition is not well defined. Crystalloid solutions are less expensive than albumin-containing solutions, and albumin does not provide a survival benefit compared to crystalloid. Albumin may decrease fluid requirements but does not reduce the need for renal replacement therapy. Buffered crystalloid solutions (e.g., Ringer's Lactate, Hartmann's solution, Plasma-Lyte) are recommended for patients with AKI who are not hypochloremic; 0.9% saline is recommended for hypovolemic hypochloremic patients if the serum chloride concentration is closely monitored. Excessive chloride administration from 0.9% saline may lead to hyperchlormic metabolic acidosis and may impair GFR. Hydroxyethyl starch solutions increase the risk of severe AKI and are contraindicated. Bicarbonate-containing solutions (e.g., dextrose water with 150 mEq sodium bicarbonate) can be used if metabolic acidosis is a concern.

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

TABLE 310-3 Management of Acute Kidney Injury

General Issues	
1.	Optimization of systemic and renal hemodynamics through volume resuscitation and judicious use of vasopressors
Specific Issues	
2.	Elimination of nephrotoxic agents (e.g., ACE inhibitors, ARBs, NSAIDs, aminoglycosides) if possible
3.	Initiation of renal replacement therapy when indicated
1.	Nephrotoxin-specific <ul style="list-style-type: none"> a. Rhabdomyolysis: aggressive intravenous fluids; consider forced alkaline diuresis b. Tumor lysis syndrome: aggressive intravenous fluids and allopurinol or rasburicase
2.	Volume overload <ul style="list-style-type: none"> a. Salt and water restriction b. Diuretics c. Ultrafiltration
3.	Hyponatremia <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> a. Restriction of dietary phosphate intake b. Phosphate binding agents (calcium acetate, sevelamer hydrochloride, aluminum hydroxide—taken with meals)
7.	Hypocalcemia <ul style="list-style-type: none"> a. Calcium carbonate or calcium gluconate if symptomatic
8.	Hypermagnesemia <ul style="list-style-type: none"> a. Discontinue Mg²⁺ containing antacids
9.	Hyperuricemia <ul style="list-style-type: none"> a. Acute treatment is usually not required except in the setting of tumor lysis syndrome (see above)
10.	Nutrition <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> 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; AKI, acute kidney injury; ARBs, angiotensin receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs; THAM, tris (hydroxymethyl) aminomethane.

transplantation. Bridge therapies that have shown promise include terlipressin (a vasopressin analog), with albumin, or, when terlipressin is not available, combination therapy with octreotide (a somatostatin analog) and midodrine (an α_1 -adrenergic agonist), 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, β -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. Kidney injury biomarkers described previously 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. 309). 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 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. 53. 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. 55**), 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). Symptomatic hypocalcemia should be treated with calcium gluconate or calcium chloride. Ionized calcium should be monitored rather than total calcium when hypoalbuminemia is present.

Malnutrition Increased catabolism with protein energy wasting is common in severe 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 proton 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 generally be avoided if possible.

Dialysis Indications and Modalities (See also Chap. 312) 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). 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. In randomized controlled trials, earlier versus later initiation of dialysis has not been demonstrated to improve survival, and may increase the risk of adverse events. The initiation of dialysis should not, however, 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). 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 choice of modality is often dictated by the immediate availability of technology and the expertise of medical staff.

The optimal dose of dialysis for AKI for any particular patient 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 when measuring survival rates. 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. It is rarely used in the United States for AKI in adults (although it was "rediscovered" during the COVID-19 pandemic owing to inadequate numbers of continuous and intermittent hemodialysis machines). 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. AKI is also associated with an increased risk of later cardiovascular disease events, though the mechanisms are not well understood. 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 ESKD requiring dialysis or transplantation. AKI and CKD are increasingly seen as interrelated syndromes: CKD is a major risk factor for the development of AKI, and AKI is a risk factor for the future development of CKD. Measurement of albuminuria after an AKI episode can help predict the risk of kidney disease progression and can serve as a valuable risk-stratification tool. Postdischarge care after AKI under the supervision of a nephrologist for aggressive secondary prevention of kidney disease is prudent.

FURTHER READING

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311 Chronic Kidney Disease

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Chronic kidney disease (CKD) encompasses a spectrum of pathophysiological processes associated with abnormal kidney function, often with a progressive decline in glomerular filtration rate (GFR). The risk of worsening CKD is closely linked to both the GFR and the amount of albuminuria. **Figure 311-1** provides a staging of CKD stratified by the estimates for further progressive decline of GFR based on these two 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. 312 and 313. 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 mechanisms of damage: (1) specific initiating mechanisms particular to the underlying

etiology (e.g., genetic abnormalities in kidney development, immune complex deposition, and inflammation in certain types of glomerulonephritis, or toxin exposure in certain diseases of the renal tubules and interstitium), and (2) nonspecific mechanisms involving hyperfiltration and hypertrophy of the remaining viable nephrons, which are common consequences of long-term reduction of renal mass, irrespective of underlying etiology. The responses to reduction in nephron number are mediated by vasoactive hormones, cytokines, and growth factors. Eventually, the 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. 311-2**). 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 and the efficacy of pharmacologic approaches that attenuate this response (**Fig. 311-3**).

IDENTIFICATION OF RISK FACTORS AND STAGING OF CKD

There has been significant recent progress in the identification of risk factors that increase the risk for CKD, even in individuals with normal GFR (**Table 311-1**).

Adults with such risk factors should be monitored at least every 2 years for albuminuria, decline in eGFR, and blood pressure abnormalities, so that a clinical management pathway can be planned.

Most recently identified risk factors for which there is now a consensus include a past episode of apparently recovered acute kidney injury (AKI), tobacco use, and many forms of apparently resolved childhood and adolescent kidney disease. There is also an increasing awareness of the role of genetic risk factors, which account for 15–40% of adult-onset CKD, with the percentage often depending on the contribution of demographic structure and history to the genetic variation for any population. Many rare inherited forms of CKD follow a Mendelian inheritance pattern, often as part of a systemic syndrome, with the most

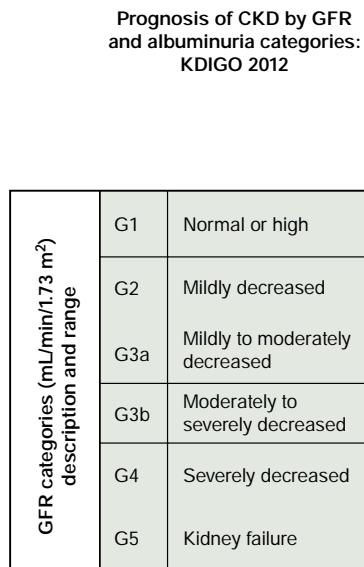


FIGURE 311-1 Kidney Disease Improving Global Outcome (KDIGO) classification of chronic kidney disease (CKD). Gradation of color from green to red corresponds to increasing risk and progression of CKD. GFR, glomerular filtration rate. (Reproduced with permission from KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 3:5, 2013.)

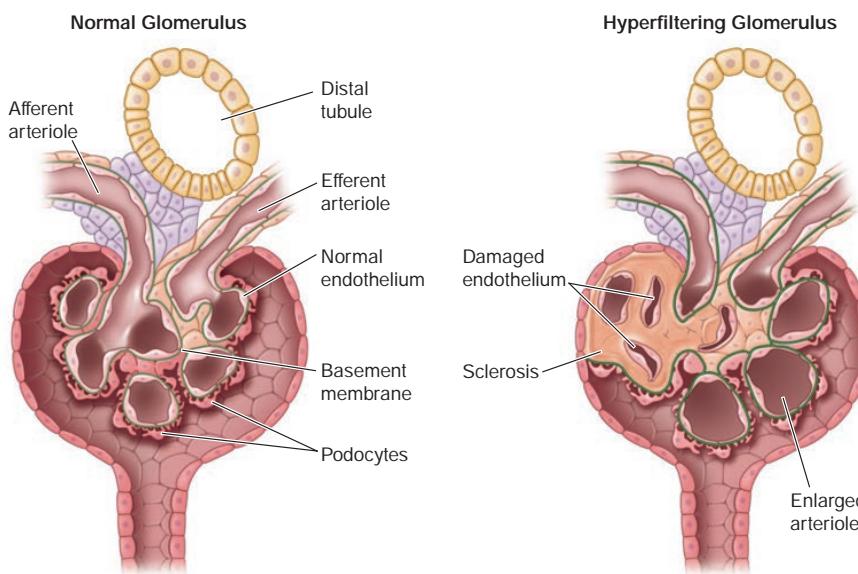


FIGURE 311-2 Left: Schema of the normal glomerular architecture. Right: Secondary glomerular changes associated with a reduction in nephron number, including enlargement of capillary lumens and focal adhesions, which are thought to occur consequent to compensatory hyperfiltration and hypertrophy in the remaining nephrons. (From JR Ingelfinger: Is microanatomy destiny? N Engl J Med 348:99, 2003. Copyright © 2003, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

common in this category being autosomal dominant polycystic kidney disease (ADPKD). In addition, it is now appreciated that many unique, kindred-specific, site-specific copy number variants and microdeletions, as well as functional variants at >60 genetic loci known to harbor systemic and kidney-only disease pathogenic mutations, also contribute to risk for pleiotropic presentations of CKD (**Table 311-2**). Many of the genes with identified CKD-causing mutations are expressed in the podocytes of the renal glomeruli or in the glomerular basement

membrane, but others are expressed in tubule segments with a primary tubulointerstitial process and secondary glomerular injury. Given the significant contribution of monogenic disease etiologies, consideration is now given to chromosomal microarray and genome or exome sequencing for CKD of unknown cause in young adults, as noted below under Evaluation and Management of Patients with CKD.

In addition, recent research in the genetics of predisposition to common complex diseases has revealed DNA sequence variants at a

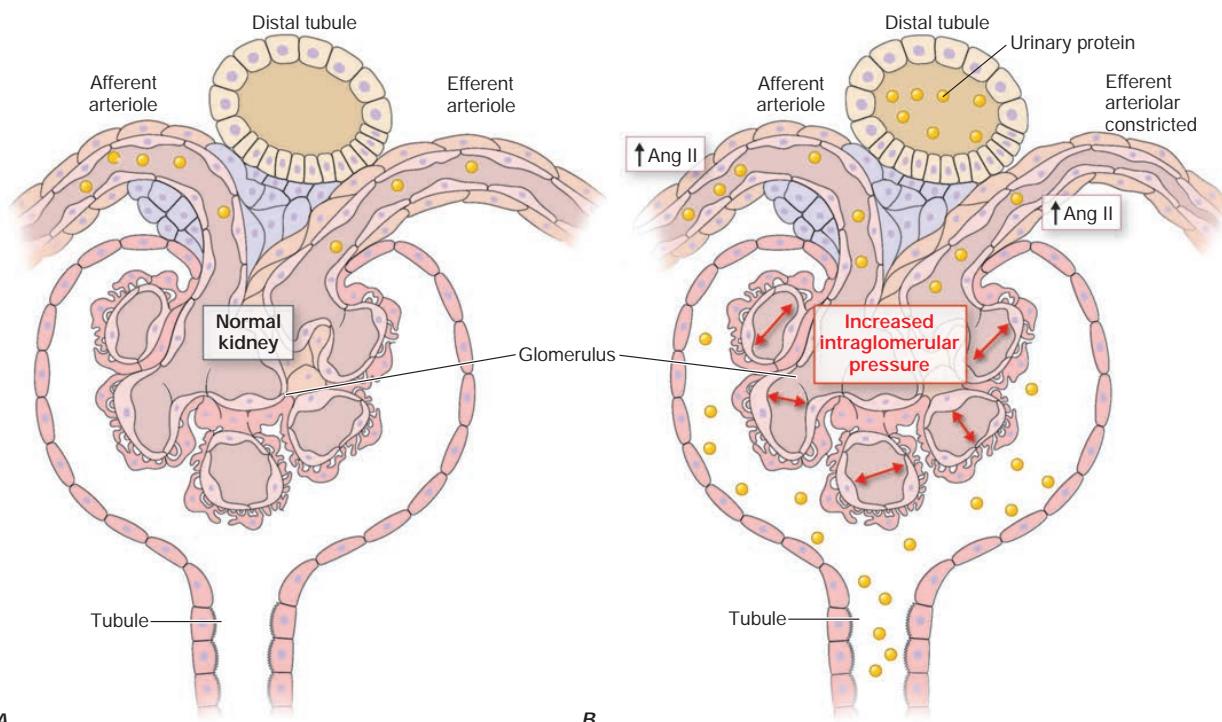


FIGURE 311-3 Schematic representation of the effect of intraglomerular hypertension on nephron survival.

TABLE 311-1 Risk Factors for Chronic Kidney Disease (CKD) in Adulthood by Category^a

Chronic Nonrenal (Systemic) Disease	
Diabetes and metabolic syndrome	
Autoinflammatory disease (e.g., lupus, vasculitis, cancer immunotherapy)	
Infections (e.g., HIV, HBV, HCV)	
Absence of infection (JCV)	
Nephrotoxic exposure (including many antineoplastic therapies)	
Hypertension (risk, cause, or consequence)	
Demographic, Anthropomorphic, Ancestry, Geographic	
Age	
Sex	
Population ancestry	
Family history	
Region-specific CKD risk of uncertain etiology (e.g., Central America, Sri Lanka, and indigenous peoples of Australia and New Zealand)	
Childhood and Adolescent States and Diseases	
Premature and SGA birth	
Increased BMI	
Persistent asymptomatic microscopic hematuria	
Elevated blood pressure	
Childhood kidney disease (even resolved)	
Treated childhood cancer	
Adult Onset	
Prior acute kidney injury	
Preeclampsia	
Kidney donation (or other acquired nephrectomy)	
Genetic	
Monogenic Mendelian inheritance	
Polygenic complex inheritance	
Viral Infection	
HIV infection (HIVAN)	
SARS-CoV-2 (COVAN)	
Lifestyle	
Smoking	
Diet	
Physical activity	

^aNot biomarkers.

Abbreviations: BMI, body mass index; COVAN, COVID-19-associated nephropathy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIVAN, HIV-associated nephropathy; JCV, JC virus; SGA, small for gestational age.

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 (e.g., 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 311-3**). 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 societal implications of adjustment for a construct of race have been the subject of important recent discourse, with the idea that more individually sound adjustments without potentially negative racial categorizations be developed.

The normal annual mean decline in GFR with age from the peak GFR (~120 mL/min per 1.73 m²) attained during the third decade of life is ~1 mL/min per year per 1.73 m², reaching a mean value of 70 mL/

TABLE 311-2 Monogenic Risk Loci for Chronic Kidney Disease

Copy number variants	
17q12	
22q11.2	
16p11.2	
Single nucleotide variants at four most predominant genetic loci with mendelian inheritance	
Genes for autosomal dominant polycystic kidney disease	
<i>ADPKD1</i>	
<i>ADPKD2</i>	
<i>GANAB</i>	
<i>DNAJB11</i>	
<i>ALG9</i>	
Genes for type IV collagen-associated nephropathy	
<i>COL4A3</i>	
<i>COL4A4</i>	
<i>COL4A5</i>	
Genes for autosomal dominant tubulointerstitial kidney disease	
<i>UMOD</i>	
<i>MUC1</i>	
<i>REN</i>	
<i>HNF1B</i>	
<i>SEC61AI</i>	
Genes with known common variants that confer increased risk with odds ratio exceeding 2 with non-Mendelian inheritance patterns	
<i>APOL1</i>	

min per 1.73 m² at age 70, with considerable interindividual 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 m². 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 urinary dipstick tests for protein, persistent UACR >2.5 mg/mmol (male) or >3.5 mg/mmol (female) on two to three occasions serves as a marker not only for early detection of primary kidney disease but for systemic microvascular disease as well.

TABLE 311-3 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**

$$\text{Estimated GFR (mL/min per } 1.73 \text{ m}^2) = 1.86 \times (S_{\text{Cr}})^{-1.154} \times (\text{age})^{-0.203}$$

Multiply by 0.742 for women

Multiply by 1.21 for African ancestry (currently under review)

2. CKD-EPI Equation

$$\text{GFR} = 141 \times \min(S_{\text{Cr}}/\kappa, 1)^\alpha \times \max(S_{\text{Cr}}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}}$$

Multiply by 1.018 for women

Multiply by 1.159 for African ancestry (currently under review)

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.

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, www.kidneyfailurerisk.com) and uses age, sex, region (North American or non-North American), GFR, and UACR. 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 with easy fatigability; decreased appetite with progressive malnutrition; abnormalities in calcium, phosphorus, and mineral-regulating hormones, such as $1,25(\text{OH})_2\text{D}_3$ (calcitriol), parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF-23); and abnormalities in sodium, potassium, water, and acid-base homeostasis. Many patients, especially older individuals, will have eGFR values compatible with stage 2 or 3 CKD. However, the majority of these patients will show no further deterioration of kidney function. In this setting, it is advised to recheck kidney function, and if it is stable and not associated with proteinuria, the patient can usually be followed with interval repeat testing without referral to a nephrologist. However, caution should be exercised in terms of potential exposure to potential nephrotoxins or interventions that risk 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 (GFR <15 mL/min), toxins accumulate such that patients usually experience a 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 311-4** 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 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 some of these patients may have a subclinical primary glomerulopathy, such as focal segmental or global glomerulosclerosis. In other patients, progressive nephrosclerosis and hypertension are the renal correlates of a systemic vascular disease, often also involving large and small vessels elsewhere, such as the heart and brain. This latter combination is especially common in older patients, among whom chronic kidney ischemia as a cause of CKD may be underdiagnosed.

TABLE 311-4 Leading Categories of Etiologies of Chronic Kidney Disease (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

^aRelative contribution of each category varies with geographic region and race.

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 symptoms and signs that characterize the uremic syndrome in advanced CKD. 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 nonvolatile 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 are also impaired and can result 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 morbidity 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 care 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 kidney function, tubular excretion of filtered sodium and water matches intake. Many forms of kidney disease disrupt this balance such that dietary intake of sodium exceeds its excretion, leading to sodium retention and attendant extracellular fluid volume (ECFV) expansion. This expansion may contribute to hypertension, which itself can accelerate nephron hyperfiltration and injury. As long as water intake does not exceed the capacity for renal water clearance, the ECFV expansion will be isonatric 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 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.

Rarely, patients with CKD may 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. Any depletion of ECFV, whether due to GI losses, renal sodium loss, 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, 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 hyperfiltration and progression of CKD often favor their cautious and judicious use with very close monitoring of plasma potassium concentration. Coadministration of potassium-lowering agents such as patiromer may allow for the use of RAS inhibitors with reduced risk of hyperkalemia.

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 CKD. The majority of patients can still acidify the urine, but they produce less ammonia and, therefore, cannot excrete the quantity of protons required to maintain acid-base balance in most diets. Hyperkalemia, if present, further depresses ammonia production. The combination of hyperkalemia and hyperchloremic metabolic acidosis is often present, even at earlier stages of CKD, in patients with diabetic nephropathy or in those with predominant tubulointerstitial disease or obstructive uropathy. With further declining GFR, the total urinary net daily acid excretion may be severely limited to less than 30–40 mmol, and the accumulation of 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. Studies have suggested that even modest degrees of metabolic acidosis may be associated with the development of protein catabolism and progression of CKD.

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 euolemia. Water restriction is indicated only if there is hyponatremia.

Hyperkalemia often responds to dietary restriction of potassium, the use of kaliuretic diuretics, and both avoidance of potassium supplements (including occult sources, such as dietary salt substitutes) and dose reduction or avoidance of potassium-retaining medications (especially RAS inhibitors). 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. The sodium load in sodium bicarbonate supplementation needs to be taken into account, when ECFV expansion is present.

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 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.

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 effect 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 series of interrelated mechanisms: (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 of PTH and also stimulates growth of parathyroid gland mass; and (3) PTH production is stimulated by decreased levels of ionized calcium, which, in turn, result from decreased levels of renal calcitriol production with reduced kidney mass and suppression of calcitriol production due to phosphate retention and elevated levels of FGF-23, which also increases degradation of calcitriol. Low calcitriol levels contribute to hyperparathyroidism, both by leading to hypocalcemia and also by a direct effect on PTH gene transcription. In addition, the normal inhibitory effect of FGF-23 on PTH production is Klotho-dependent and is also attenuated in CKD. These changes start to occur when the GFR falls below 60 mL/min, though some studies point to retention of phosphate as an event antedating measurable reduction in GFR, together with early elevation of FGF-23 as well. FGF-23 is part of a family of phosphatoinositides that promotes phosphate excretion, and high levels of FGF-23 are an independent risk factor for left ventricular hypertrophy and are associated with increased mortality due to several classes of complications in CKD, dialysis, and kidney transplant patients.

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 resistance to erythropoiesis-stimulating agents (ESA) in part related to the bone marrow fibrosis. Furthermore, PTH itself is considered a uremic toxin, and high levels are associated



FIGURE 311-4 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.

with muscle weakness, fibrosis of cardiac muscle, and constitutional symptoms.

Adynamic bone disease is increasing in prevalence, especially among diabetics and older patients. 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. 311-4). Patients with adynamic bone disease often experience the most severe symptoms of musculoskeletal pain, owing to the inability to repair the microfractures that occur normally as a part of healthy skeletal homeostasis with regular physical activity. Patients with advanced CKD experience more frequent fractures than their age-matched controls. Osteomalacia is a distinct process, consequent to reduced production and action of $1,25(\text{OH})_2\text{D}_3$, leading to accumulation of nonmineralized osteoid.

Calcium, Phosphorus, and the Cardiovascular System There is a strong association between hyperphosphatemia and increased cardiovascular mortality in patients with 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 in the media of coronary arteries and even heart valves that appears 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 extrasseous sites, such as the vascular bed and soft tissues. There is a similar 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 painful livedo reticularis and subcutaneous nodules that advance to patches of ischemic necrosis, especially on the legs, thighs, abdomen, and breasts (Fig. 311-5). Pathologically, there is evidence of vascular occlusion



FIGURE 311-5 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.

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. Warfarin is still used in some dialysis patients in whom direct oral anticoagulants (DOACs) are contraindicated, and one of the effects of warfarin therapy is to decrease the vitamin K-dependent activation of matrix GLA protein. This latter protein is important in preventing vascular calcification. Thus, warfarin treatment is considered a risk factor for calciphylaxis, and if a patient develops this syndrome, this medication should be discontinued and alternative means of anticoagulation should be chosen, depending on the specific underlying indication for anticoagulation.

TREATMENT

Disorders of Calcium and Phosphate Metabolism

The optimal management of secondary hyperparathyroidism and osteitis fibrosa is prevention. Once the parathyroid gland mass is very large, it is difficult to control the disease. Careful attention should be paid to the plasma phosphate concentration in CKD patients, who should be counseled on a low-phosphate diet as well as the appropriate use of phosphate-binding agents, which are taken with meals and complex 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. Tenapanor is a sodium-proton inhibitor that decreases GI phosphate absorption and may be useful to manage hyperphosphatemia in CKD and dialysis patients.

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 parathyroid cells to the suppressive effect of calcium. This class of drug, which includes cinacalcet and etelcalcetide, 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 2 and 9 times the upper limit of normal, 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 (Fig. 311-6) before ever reaching stage 5 CKD. Between 30 and 45% of those patients who do reach stage 5 CKD have advanced significant cardiovascular complications. Thus, the focus of patient care in earlier CKD stages should be directed to prevention of cardiovascular complications.

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, diabetes mellitus, hypervolemia, dyslipidemia, sympathetic overactivity, and hyperhomocysteinemia. The CKD-related risk factors comprise anemia, hyperphosphatemia, hyperparathyroidism, increased FGF-23, sleep apnea, and systemic 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 acute myocardial infarction but, instead, is the result of congestive heart failure and sudden death. ECG monitoring studies have suggested that asystole and bradycardias are the principal causes of sudden cardiac death in dialysis patients.

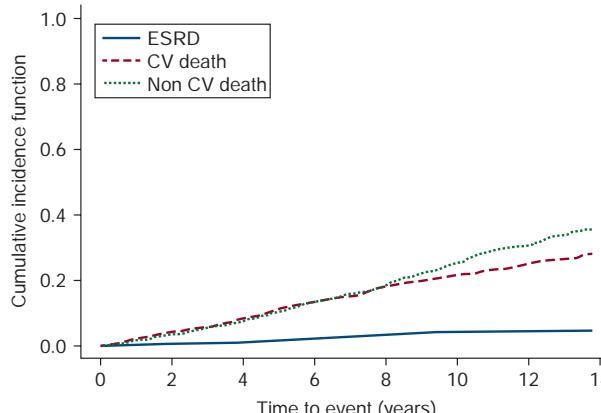


FIGURE 311-6 The cumulative incidence of end-stage renal disease (ESRD), cardiovascular (CV) death, and non-CV death during follow-up in cohort of 1268 participants with an estimated glomerular filtration rate (eGFR). (Reproduced with permission from LS Dalrymple et al: Chronic kidney disease and the risk of end-stage renal disease versus death. *J Gen Intern Med* 26:379, 2010.)

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.

Heart Failure Abnormal cardiac function secondary to myocardial ischemia, left ventricular hypertrophy, diastolic dysfunction, and frank cardiomyopathy, in combination with 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 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 are the most common complications of CKD. Hypertension 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 high-output 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 the attendant poor prognosis.

The use of exogenous ESAs 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. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (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 reduction in the intraglomerular hyperfiltration and hypertension. Occasionally, introduction of ACE inhibitors and ARBs can actually precipitate an episode of AKI, especially when used in combination in patients with ischemic renovascular disease.

Slight reduction of GFR (<30% of baseline) may signify a salutary reduction in intraglomerular 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 patiromer, can improve potassium excretion in addition to improving blood pressure control. Potassium-sparing diuretics, such as amiloride and triamterene, should be avoided in most patients, and mineralocorticoid receptor blockers should also be used with great caution and with careful monitoring of serum potassium concentration, weighing potential cardiovascular benefits against risk for lethal hyperkalemia.

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 use of the gliflozins (SGLT2 inhibitors) in patients with diabetes mellitus has recently been associated with kidney protection and a reduction in cardiovascular events, including heart failure. Currently under study is the feasibility of using gliflozins in nondiabetic CKD.

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, nonadherent patients than in those starting dialysis.

TABLE 311-5 Causes of Anemia in Chronic Kidney Disease (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

TREATMENT

Pericardial Disease

Uremic pericarditis is an absolute indication for the urgent initiation of dialysis or for intensification of the dialysis prescription in those already receiving dialysis. Because of the propensity to hemorrhage in pericardial fluid, hemodialysis should be performed without heparin. A pericardial drainage procedure should be considered in patients with recurrent pericardial effusion, especially with echocardiographic signs of impending tamponade. Nonuremic causes of pericarditis and effusion include viral, malignant, tuberculous, and autoimmune etiologies. It may also be seen after myocardial infarction and as a complication of treatment with the antihypertensive drug minoxidil. Consideration could be given to the use of colchicine or nonsteroidal anti-inflammatory drugs, although the latter agents could adversely affect renal function.

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 erythropoietin (EPO) by the diseased kidneys. Additional factors are reviewed in **Table 311-5**.

The anemia of CKD is associated with a number of adverse pathophysiological 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 ESAs 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 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 kidney 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 parenteral 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 B₁₂ 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.

A new class of agents to treat the anemia of CKD are the prolyl-hydroxylase inhibitors of endogenous hypoxia-inducible factors (HIFs). This inhibition leads to an increase in both endogenous production of EPO and an increase in GI absorption of iron. Studies are in progress comparing the efficacy of these agents to the standard ESAs.

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 or 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 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. 118**).

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 disturbances in concentration and sleep. 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 or iron deficiency) 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, consequences of low protein and caloric intake, are common in advanced CKD and are 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 bioimpedance analysis 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. The gliflozins, discussed above, that inhibit sodium-glucose transport in the proximal tubule result in glucose lowering, accompanied by striking reductions in kidney function decline and in cardiovascular events.

2318 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 reactivation of the tubuloglomerular feedback loop. This represents a fortunate convergence of pathophysiology of glomerular hyperfiltration in diabetes with drug discovery. A similar effect on hyperfiltration by residual nephrons in certain nondiabetic forms of CKD may explain the salutary role of this class of medications more broadly in CKD. Other studies have also pointed to a more direct effect on proximal tubule metabolic pathways that alleviate cell injury.

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. Recently, agonists of kappa opioid receptors have shown promise in reducing pruritis in hemodialysis patients.

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 patients 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's or Fabry's 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, funduscopic and precordial examination should be carried out. Funduscopic is especially important in the diabetic patient, because it may show evidence of diabetic retinopathy, which is associated with diabetic 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 old 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 B₁₂, 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 and also is associated with a higher risk of progression.

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 kidney 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. 315*). A discrepancy >1 cm in kidney length suggests either a unilateral developmental abnormality or a 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, although these agents may not be as effective as previously thought.

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, polyarthritides, 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 is another 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 using a combination of chromosomal microarray and whole exome sequencing 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 (Table 311-2).

TREATMENT

Chronic Kidney Disease

Treatments aimed at specific causes of CKD are discussed elsewhere. Two recent developments in the etiology-directed therapy of CKD include the now-proven role of gliflozins in diabetic kidney disease and the emergence of genome-specific therapies now established for certain patients with ADPKD ([Chap. 315](#)), which are

at the clinical trial stage for *APOL1*-mediated kidney disease and certain forms of hyperoxaluria. 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 is 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 AKI 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.

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 recommended choices, and another in which proteinuria is mild or absent initially (e.g., ADPKD 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.

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. 313) 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 diet carries a risk of malnutrition; 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 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. Encephalopathy and pericarditis are very late complications, so it is now rare that they serve as indications for initiation of renal replacement therapy.

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 to most jurisdictions 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. 313) 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 population genetic risk, endemic nephrotoxins, exposure to pesticides, NSAID use, and chronic volume depletion have all been suggested to contribute.

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312 Dialysis in the Treatment of Kidney 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 (CRRTs) 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. 310. 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. 310](#).

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 kidney disease (ESKD).

With the widespread availability of dialysis, the lives of hundreds of thousands of patients with ESKD have been prolonged. In the United States alone, there are now ~750,000 patients with treated ESKD (kidney failure requiring dialysis or transplantation), the vast majority of whom require dialysis. Since 2000, the prevalence of treated ESKD has increased 65%, which reflects both a small increase in the incidence rate and marginally enhanced survival of patients receiving dialysis. The crude incidence rate for treated ESKD in the United States is 370 cases per million population per year; ESKD is disproportionately higher in African Americans as compared with white Americans. In the United States, the leading cause of ESKD is diabetes mellitus, currently accounting for approximately 45% of newly diagnosed cases of ESKD. Approximately 30% of patients have ESKD 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 ESKD include glomerulonephritis, polycystic kidney disease, and obstructive uropathy. A fraction of the excess incidence of ESKD in African Americans is likely related to transmission of high-risk alleles for the *APOL1* gene.

Globally, mortality rates for patients with ESKD 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 somewhat, but remains extremely high, with a mortality rate of 167 per 1000 patient-years for patients receiving hemodialysis and 156 per patient-years for patients receiving peritoneal dialysis. Deaths are due mainly to cardiovascular diseases and infections. Older age, male sex, nonblack race, diabetes mellitus, malnutrition, and underlying heart disease are important predictors of death.

TREATMENT OPTIONS FOR PATIENTS WITH ESKD

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 m² (see [Chap. 311](#) for estimating equations). Timely referral to a nephrologist for advanced planning and creation of a dialysis access, education about ESKD 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 ESKD cases result following episodes of acute kidney injury, 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 m² compared to initiating dialysis for symptoms of uremia.

In ESKD, 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. 313](#)). Although there are significant geographic variations and differences in practice patterns, in-center hemodialysis remains the most common therapeutic modality for ESKD (>85% 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. 312-1](#)). 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 (vs 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 0–4 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,

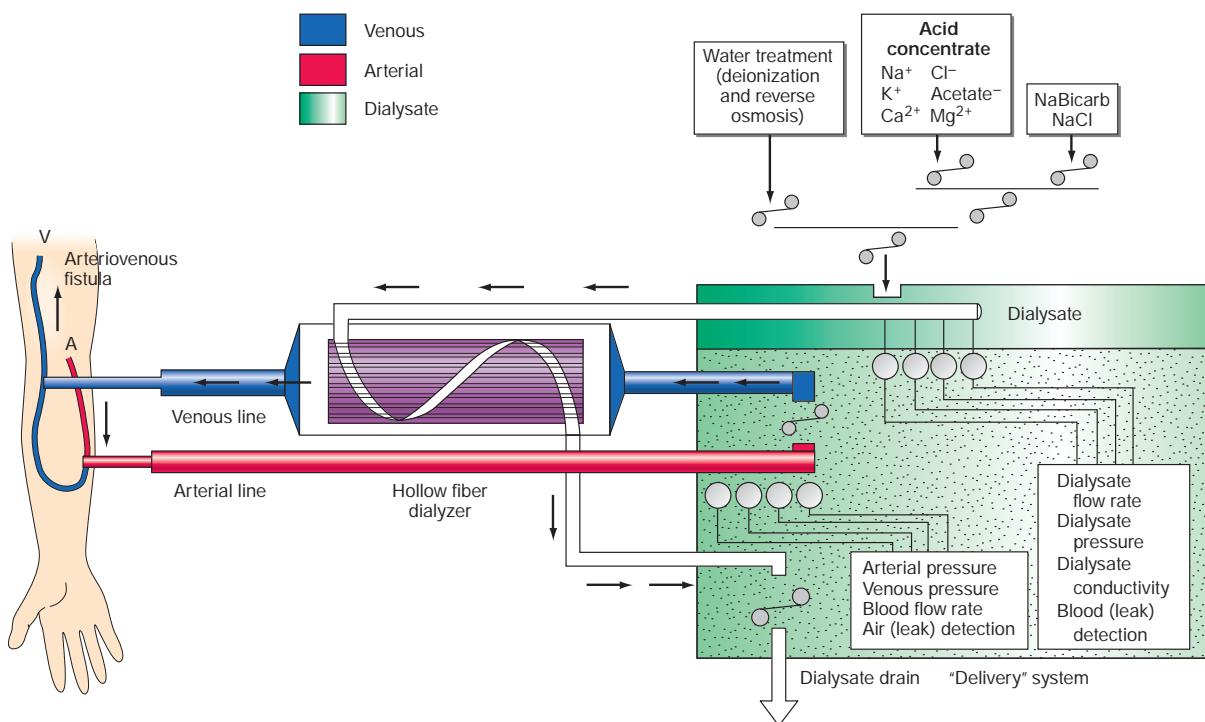


FIGURE 312-1 Schema for hemodialysis.

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 250–450 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, 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 universally 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. Infection, venous thrombosis, and venous stenosis resulting in swelling of the extremity or superior vena cava syndrome are complications best avoided by limiting the time during which catheters are employed.

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 ESKD, 9–12 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, although the latter is generally unavailable in outpatient settings. 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 α_1 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 cellulose-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 by-products 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 1.5–3 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,

2324 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 ($100/\text{mm}^3$, 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 ESKD.

LONG-TERM OUTCOMES IN ESKD

Cardiovascular disease constitutes the major cause of death in patients with ESKD. 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 patients with ESKD; none has demonstrated consistent benefit. Two clinical trials of statin agents in ESKD 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 non-dialysis-requiring CKD, showed a 17% reduction in the rate of major cardiovascular events or cardiovascular death with simvastatin-ezetimibe treatment. Most experts recommend conventional cardioprotective strategies (e.g., lipid-lowering agents, aspirin, inhibitors of the renin-angiotensin-aldosterone system, and -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 ESKD include a high incidence of infection, progressive debility and frailty, protein-energy malnutrition, and impaired cognitive function.

GLOBAL PERSPECTIVE

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

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TABLE 313-1 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

^aKidneys 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 Kidney Donor Profile Index (KDPI) score >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.

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Transplantation in the Treatment of Renal Failure

Jamil Azzi, Naoka Murakami, Anil Chandraker

Kidney transplantation is the treatment of choice for patients with end-stage kidney disease (ESKD). Worldwide, tens of thousands of kidney transplants have been performed, and >220,000 patients are living with a functioning kidney transplant in the United States today. The first successful kidney transplant was performed in Boston in 1954 between identical twins without the need of immunosuppression. The introduction of immunosuppressive therapies such as azathioprine and prednisone in the 1960s established kidney transplantation across non-identical individuals (allografts). However, the results with properly matched familial donors remained significantly superior to those with organs from deceased donors. During the 1970s and 1980s, the success rate at the 1-year mark for deceased-donor allografts rose progressively after the introduction of calcineurin inhibitors. Currently, 1-year survival rates for living-donor and deceased-donor allografts are 98% and 93%, respectively, in the United States. However, long-term survival has not improved as much over time, and average allograft survival times are 14 and 10 years for living-donor and deceased-donor grafts, respectively.

Age-related mortality rates after transplantation are highest in the first year due to the surgical risks: 2% for ages 18–34 years, 3% for ages 35–49 years, and 6.8% for ages 50–60 years. Despite these outcome statistics, the actual survival benefit of transplantation compared to chronic dialysis becomes apparent within days to months following transplantation, even after risk adjustments for age, diabetes, and cardiovascular status. While the loss of kidney transplant due to acute rejection is now a rare event, most allografts eventually succumb at varying rates to a chronic process consisting of interstitial fibrosis, tubular atrophy, vasculopathy, and glomerulopathy, the pathogenesis of which in varying degrees is likely a combination of an alloimmune response, drug toxicity, and the end result of a variety of other insults. Overall, transplantation results in an improved life expectancy with a higher quality of life compared to patients whom remain on dialysis.

RECENT ACTIVITY AND RESULTS

In 2019, >16,000 deceased-donor kidney transplants and 6800 living-donor transplants were performed in the United States, with the ratio of deceased-donor to living-donor transplants remaining stable over the past few years. As the number of patients with ESKD increases, the number of patients on the transplant waitlist also increases, and the donor shortage remains a critical challenge. As of 2019, there were nearly 59,000 active adult candidates on the waiting list, with <23,000 patients being transplanted yearly. This imbalance is set to worsen over the coming years with the predicted increased rates of kidney failure associated with obesity and diabetes worldwide. In an attempt to increase utilization of marginal kidneys and allocate organs

equitably, a new allocation system within the United States was implemented in 2014. The guiding principles of the changes were to offer an opportunity for transplantation to patients who were highly sensitized and, thus, less likely to find a suitable donor, while at the same time to allow patients expected to survive the longest to receive the best-quality deceased donor organs. The Kidney Donor Profile Index (KDPI) score, which ranges from 0 to 100%, was introduced to estimate the potential risk of graft failure after kidney transplant based on 10 donor factors. The lower KDPI values are associated with higher expected posttransplant survival. Hence, the kidneys with a KDPI <20% are allocated to the 20% of the potential recipients with the highest expected posttransplant survival. Kidneys with a KDPI >85% (previously called expanded criteria donor [ECD] kidneys) are directed toward patients who are expected to fare less well on dialysis and would benefit from being transplanted earlier even if it means accepting a lower-quality organ. A variety of other means to increase the donor pool and equity in terms of wait time for a transplant have also become more popular. Kidneys from donors after cardiac death (DCD) are being increasingly used to overcome the demand for organs (Table 313-1). Furthermore, with the advancement of the direct-acting antiviral therapies for hepatitis C virus (HCV), transplantation from HCV-positive donors to HCV-positive or -negative recipients has been performed since 2017 in order to increase the donor pool. Now this practice is incorporated in several centers in the United States. Recently, the HOPE (Human Immunodeficiency Virus [HIV] Organ Policy Equity) Act authorized organ donation from HIV-positive candidates, and >100 transplants have been performed. Finally, in the new kidney allocation system, B blood type candidates who have low anti-A titer are eligible for an allograft from A blood type donors. This helps improve access and reduce disparities in wait time for minorities, especially for the African-American ESKD population, in whom blood type B is more common than in other ethnicities.

The overall results of transplantation are presented in Table 313-2. At the 1-year mark, allograft survival is higher for living-donor recipients. This is most likely related to decreased damage of the organ related to less ischemic injury. The introduction of more effective drugs and more sensitive matching between recipients and donors has almost equalized the risk of graft rejection in the majority of patients within the first year. At 5- and 10-year follow-up, however, there remains a steeper decline in survival of those with deceased-donor kidneys.

RECIPIENT EVALUATION

Virtually all patients with ESKD benefit from transplantation with a longer life expectancy and a better quality of life. While the mortality rate after transplantation is highest in the first year due to perioperative complications, recipient evaluation is critical in identifying patients at risk. It involves a multidisciplinary approach that requires thorough medical, surgical, social, and psychosocial evaluations to identify the risk factors that prohibit transplantation or mandate treatment before proceeding, as well as ensuring the appropriate use of limited organs.

There are a few absolute contraindications to kidney transplantation: chronic illness that limits predicted survival for <2 years, active

TABLE 313-2 Mean Rates of Graft and Patient Survival for Kidneys Transplanted in the United States from 1999 to 2015^a

	1-YEAR FOLLOW-UP		5-YEAR FOLLOW-UP		10-YEAR FOLLOW-UP	
	GRAFTS, %	PATIENTS, %	GRAFTS, %	PATIENTS, %	GRAFTS, %	PATIENTS, %
Deceased donor	93	96	75	85	48	64
Living donor	98	99	85	92	65	79

^aAll 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, 2018 Annual Reports, Scientific Registry of Transplant Recipients.

malignancy, active infection, psychosocial issues affecting adherence to the medical care, and active substance abuse. Another critically important factor to consider is cardiovascular risk during both the perioperative and postoperative periods. Patients with ESKD are at higher cardiovascular mortality risk, and thorough cardiovascular evaluation for coronary artery diseases, valvular diseases, and heart failure is critical.

At most centers, there is no official age limit for transplantation, with >20% of waitlisted candidates currently being older than 65. However, overall physical and cognitive function of the candidates needs to be fully assessed. While history of malignancy itself is not a contraindication for kidney transplantation, potential recipients should be treated and cured with a waiting time of 2–5 years depending on the type of malignancy to decrease the risk of recurrence of the disease. Latent or indolent infection (HIV, hepatitis B or C, tuberculosis) should be a routine part of the candidate workup. While historically transplant centers considered overt AIDS and active hepatitis absolute contraindications to transplantation because of the high risk of opportunistic infection, with the introduction of potent antiviral regimens, many centers are now transplanting individuals with hepatitis and HIV infection under strict protocols.

One of the few “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. Removal of these antibodies directed at donor tissue through a variety of strategies (desensitization) is now routinely performed with varying levels of success.

TISSUE TYPING AND CLINICAL IMMUNOGENETICS

Matching for antigens of the HLA major histocompatibility complex (Chap. 350) is an important criterion for the selection of donors. Each mammalian species has a single chromosomal region that encodes the strong, or major, transplantation antigens, and this region on the human chromosome 6 codes the HLA genes. HLA is highly polymorphic; therefore, it can be an immunologic target of organ rejection when mismatched between the donor and the recipient. Historically, HLA antigens have been defined by serologic techniques by adding sera of a recipient (potentially containing anti-HLA antibodies) with a “library” of leukocytes with known serotypes. However, currently, molecular typing of HLA by genomic sequencing is almost universally used. Other “minor,” non-HLA antigens may also elicit an alloimmune response in addition to the ABH(O) antigens and endothelial antigens that are not expressed on lymphocytes. The number of HLA antigen mismatches in A, B, and DR loci correlates with allograft survival; the more mismatches, the higher is the risk of allograft rejection. Nevertheless, some HLA-identical renal allografts are rejected, often within the first few weeks after transplantation. These failures may 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. If prior exposure to the antigen and priming of the recipient immune system has occurred, secondary exposure at the time of transplantation may lead to an immune response refractory to treatment.

DONOR EVALUATION

LIVING-DONOR EVALUATION

Living kidney donors experience the immediate risk of surgery and the long-term potential risk of developing kidney dysfunction prematurely; thus, the basic principle of “first, do no harm” (Chap. 11) is important. Therefore, donor evaluation must take every effort to exclude any medical conditions that may cause morbidity and mortality after kidney donation, such as hypertension, diabetes, and/or proteinuria. Although studies have shown that the risk of ESKD after kidney donation is not greater than that of the general population, donation is associated with a small but significant potential lifetime risk of ESKD (0.3–0.4%; absolute risk increased by 0.2–0.3% compared to that of healthy non-donors). The mechanism of premature renal failure is thought to be due to increased blood flow and hyperfiltration injury 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. In family members of type 1 diabetics, anti-insulin and anti-islet cell antibodies should be measured, and a glucose tolerance test should be performed. African-American donors have a higher risk of ESKD after donation (in line with their higher risk of kidney failure in general), and the genetic screening for APOL1 risk alleles may be appropriate (Chap. 314). From the surgical perspective, selective renal arteriography is essential to reveal any anatomic anomaly and to assess the size imbalance and laterality of donor kidneys. In most cases, donor nephrectomy is performed laparoscopically to minimize the surgical scar and to enhance a faster postsurgical recovery. Lastly, although financial and nonfinancial conflicts of interest between kidney donors and recipients are strictly prohibited, removing financial disincentives is increasingly accepted as a means to reduce barriers toward living donation (Chap. 11).

DECEASED-DONOR EVALUATION

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

In the United States, there is a national system of regulations, allocation support, and outcomes analysis for kidney transplantation called the Organ Procurement Transplant Network. Studies have shown that it is possible to remove deceased-donor kidneys and maintain them for up to 48 h on cold pulsatile perfusion or with simple flushing and cooling, but these practices are not part of clinical care as of yet. Generally, an ischemic time of <24 h is preferred; this approach permits adequate time for typing, cross-matching, transportation, and selection issues to be resolved.

PRESENSITIZATION

The presence of antibodies against donor antigens, either HLA or non-HLA, can be a potential cause of allograft injury following transplantation, and hence, it is important to carry out cross-matching prior to transplantation. For the purposes of cross-matching, donor T lymphocytes, which express class I but not class II HLA, are used as a surrogate target for detection of circulating anti-class I (HLA-A and -B) antibodies in the recipient. Note that T cells are used as surrogate cells

for the detection of class I HLA as a matter of convenience and this is unrelated to the risk of T cell-mediated rejection. A positive cytotoxic cross-match of recipient serum with donor T lymphocytes indicates the presence of preformed donor-specific anti-HLA class I antibodies and is usually predictive of an acute vasculitic event termed *hyperacute rejection*. This finding represents the only widely accepted absolute immunologic contraindication for kidney transplantation. Recently, an increasing number of tissue-typing laboratories have shifted to a more sensitive flow cytometric-based cross-match assay, which detects the presence of anti-HLA antibodies that are not necessarily detected on a cytotoxic cross-match assay and may not be an absolute contraindication to transplantation. The known sources of sensitization are blood transfusion, a prior transplant, pregnancy, and, less commonly, vaccination/infection.

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 (again, used for convenience), which express both class I and class II HLA, are used as a surrogate target in these assays. 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 prior to transplantation by reducing the level of anti-donor antibodies utilizing plasmapheresis and/or the administration of pooled immunoglobulin (IV immunoglobulin [IVIG]) has been useful in reducing the risk of hyperacute rejection following transplantation.

IMMUNOLOGY OF REJECTION

Both T cell-mediated and antibody-mediated effector mechanisms can play roles in kidney transplant rejection.

T cell-mediated rejection is caused by recipient T lymphocytes that respond to donor HLA antigens expressed on the organ. CD4+ lymphocytes respond to class II (HLA-DR) incompatibility by proliferating and releasing proinflammatory cytokines that augment the proliferative response of the immune system. CD8+ cytotoxic lymphocytes respond primarily to class I (HLA-A, -B) antigens and mature into cytotoxic effector cells that cause organ damage through direct contact and lysis of donor target cells. Full T-cell activation requires not only T-cell receptor binding to the alloantigens presented by self or donor HLA molecules (known as indirect and direct presentation, respectively), but also engagement of costimulatory molecules such as CD28 on T cells and CD80 and CD86 ligands on antigen-presenting cells (Fig. 313-1). 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 (IL) 2 and interferon γ . 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 still have rejection episodes and require maintenance immunosuppression, whereas true 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.

Antibody-mediated rejection is caused by circulating antibodies against donor antigens. After transplantation, donor-derived antigens are delivered to the recipient's draining lymph nodes and activate an alloimmune response. A subset of CD4+ T cells called follicular helper T cells (T_{fh}) are activated and promote differentiation of B cells into antibody-secreting plasma cells. Plasma cells produce donor-targeting antibodies against HLA and non-HLA antigens, which can deposit in allograft kidney and cause injury via complement-dependent and independent mechanisms. C4d deposition in peritubular capillaries and glomerular basement membrane is a footprint of complement activation and is one of the diagnostic criteria of antibody-mediated rejection, together with the presence of circulating donor-specific antibody.

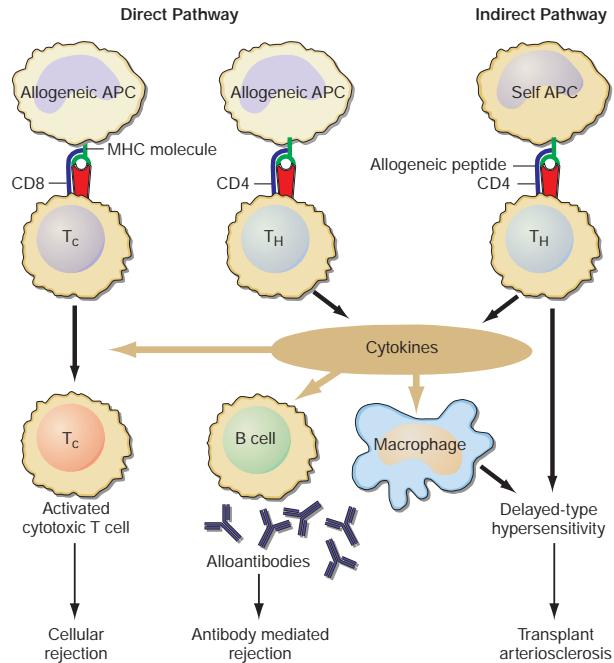


FIGURE 313-1 Recognition pathways for major histocompatibility complex (MHC) antigens. Graft rejection is initiated by CD4 helper T lymphocytes (T_H) having antigen receptors that bind to specific complexes of peptides and MHC class II molecules on antigen-presenting cells (APC). In transplantation, 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 T_H 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 (T_c). In the indirect pathway, the incompatible MHC molecules are processed into peptides that are presented by the self-APCs of the recipient. The indirect, but not the direct, pathway is the normal physiologic process in T-cell recognition of foreign antigens. Once T_H cells are activated, they proliferate and, by secretion of cytokines and direct contact, exert strong helper effects on macrophages, TC, and B cells. (From MH Sayegh: The role of T-cell costimulatory activation pathways in transplant rejection. *N Engl J Med* 338:1813, 1998. Copyright © 1998, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

IMMUNOSUPPRESSIVE TREATMENT

Kidney transplant recipients need to take immunosuppressive drugs for life, except identical twins and simultaneous bone marrow–kidney transplant recipients. Immunosuppressive therapy, as currently available, suppresses all immune responses nonspecifically, including those to bacteria, fungi, and even malignant tumors. In general, all clinically available drugs are more selective to primary rather than to memory immune responses. Agents to suppress the immune response are divided into induction and maintenance agents. Those currently in clinical use are listed in Table 313-3.

INDUCTION THERAPY

Induction therapy is 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 and depleting or nondepleting.

Depleting Agents Antithymocyte globulin (ATG) is a lymphocyte-depleting agent. Peripheral human lymphocytes, thymocytes, or lymphocytes from spleens or thoracic duct fistulas are injected into horses or rabbits to produce antilymphocyte serum, from which the immunoglobulin fraction is then separated. Those polyclonal antibodies induce lymphocyte depletion, and the immune system may take several months, if not years, to fully recover.

Monoclonal antibodies against defined lymphocyte subsets offer a more precise and standardized form of therapy. Alemtuzumab is

TABLE 313-3 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 prodrug	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.

directed to CD52, widely expressed on immune cells such as B and T cells, natural killer cells, macrophages, and some granulocytes.

Nondepleting Agents Another more selective approach is to target the 55-kDa alpha chain of the IL-2 receptor, which is expressed only on activated T cells. This approach is used as prophylaxis for (but not treatment of) acute rejection in the immediate posttransplant period and is effective at decreasing the early acute rejection rate with few adverse side effects.

MAINTENANCE THERAPY

The most frequently used combination is a calcineurin inhibitor (CNI), usually tacrolimus, and an antimetabolite, usually mycophenolic acid, with or without early steroid withdrawal. More recently, the U.S. Food and Drug Administration (FDA) approved a new costimulatory blocking antibody, belatacept, as a new strategy to prevent long-term CNI toxicity. The mTOR inhibitors sirolimus and everolimus are infrequently used as first-line maintenance immunosuppression.

Antimetabolites *Azathioprine* is a prodrug that must first be activated to form thioguanine nucleotides. Thiopurine S-methyltransferase (TPMT) inactivates azathioprine. Patients with two nonfunctional TPMT alleles experience life-threatening myelosuppression when treated with azathioprine, and those who carry one nonfunctional TPMT allele may also have significant side effects; therefore, the FDA recommends TPMT genotyping or phenotyping before starting treatment with azathioprine. Azathioprine, which inhibits synthesis of DNA and RNA and thereby inhibits T-cell proliferation, was the keystone of immunosuppressive therapy in kidney transplant recipients until the 1990s but has been replaced by more effective agents. Concomitant use of allopurinol should be avoided, owing to inhibition of xanthine oxidase.

Mycophenolate mofetil and *mycophenolate sodium*, both of which are metabolized to mycophenolic acid, are now used in place of azathioprine based on superior efficacy. Mycophenolic acid has a similar mode of action as azathioprine and is associated with a mild degree of gastrointestinal toxicity but less bone marrow suppression.

Steroids *Glucocorticoids* are important adjuncts to immunosuppressive therapy and used as both induction and maintenance therapy. In general, methylprednisolone 250–500 mg is given immediately before or at the time of transplantation, and the dose is tapered to 20 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. Early discontinuation or avoidance of steroids is common to avoid long-term adverse effects on bone, skin, and

glucose metabolism. 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 per day are the rule. A major effect of steroids is preventing the release of 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 inhibit transcription of IL-2 and other proinflammatory cytokines, thereby inhibiting T-cell proliferation. It works synergistically with glucocorticoids and mycophenolate. Among its toxic effects (nephrotoxicity, hepatotoxicity, hirsutism, tremor, gingival hyperplasia, and diabetes), nephrotoxicity presents a serious management problem and is further discussed below.

Tacrolimus (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; in contrast, it can be associated with hair loss. *De novo* diabetes mellitus following transplantation more commonly occurs with tacrolimus. An extended-release formulation of tacrolimus is now available and is given once daily. Owing to its nephrotoxicity and narrow therapeutic window, the drug level of CNIs should be monitored, and drug-drug interactions should be carefully examined. Antibiotics and antifungals (e.g., erythromycin, ketoconazole, fluconazole) and nondihydropyridine calcium channel blockers (e.g., diltiazem, verapamil) inhibit the activity of cytochrome P450 C3A enzyme and cause elevated levels of CNIs. On the other hand, antiepileptics, such as phenytoin and carbamazepine, increase metabolism, resulting in lower levels.

mTOR Inhibitors *Sirolimus* (previously called rapamycin) is another fungal macrolide but has a different mode of action from tacrolimus; 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 CNIs.

Everolimus is another mTOR inhibitor with similar mechanism of action as *sirolimus* but with better bioavailability. mTOR inhibitors are modestly tolerated and are associated with gastrointestinal disturbance, stomatitis, mucositis, and pneumonitis. Poor wound healing associated with mTOR inhibitors makes them less preferable agents during the perioperative period. While the PI3K-mTOR is the most commonly mutated cellular pathway in malignant cells, mTOR inhibitors have been used more frequently in transplant patients who develop cancers, in particular recurrent skin cancers.

Belatacept *Belatacept* is a fusion protein composed of the Fc fragment of human IgG1 immunoglobulin and the extracellular domain of cytotoxic T-lymphocyte associated protein 4 (CTLA-4). It binds to its

costimulatory ligands (CD80 and CD86) 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-year follow-up of the Belatacept Evaluation of Nephroprotection and Efficacy as First-Line Immunosuppression Trial (BENEFIT) showed improved patient and graft survival for the belatacept-treated group compared to patients treated with cyclosporine, despite short-term risks of higher rates of acute rejection.

CLINICAL COURSE AND MANAGEMENT OF THE RECIPIENT

Adequate hemodialysis should be performed within 48 h of surgery as needed to control serum potassium to prevent cardiac arrhythmias. During the transplantation surgery, the kidney allograft is usually placed in recipient's iliac fossa using a retroperitoneal approach. An anastomosis is made between donor renal artery and recipient external iliac artery, and donor renal vein to recipient external iliac vein. The donor ureter is anastomosed to the recipient bladder mucosa. Native kidney nephrectomy is rarely performed except in the case of an extremely enlarged polycystic kidney or chronic pyelonephritis. In many cases, especially after living kidney transplantation, the allograft starts to produce urine immediately after anastomosis. The allograft

often has some degree of acute tubular injury due to ischemia, which accounts for postoperative diuresis. Large amounts of sodium, potassium, and water may be lost postoperatively, which requires close monitoring and replacement. The recipient's serum creatinine should start to fall as the allograft starts to function, and recovery usually occurs within 2 weeks, although periods as long as 6 weeks have been reported. Slow recovery or oliguria should prompt an allograft biopsy, because superimposition of rejection on acute tubular injury is common and difficult to distinguish without an allograft biopsy. Induction immunosuppression therapy and maintenance steroids and antimetabolites start on the day of surgery, and it is usually safe to delay introduction of a CNI for a few days if a lymphocyte-depleting induction agent is used. **Figure 313-2** illustrates a typical algorithm followed by transplant centers for early posttransplant management of recipients at high or low risk of early renal dysfunction.

MANAGEMENT OF REJECTION

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,

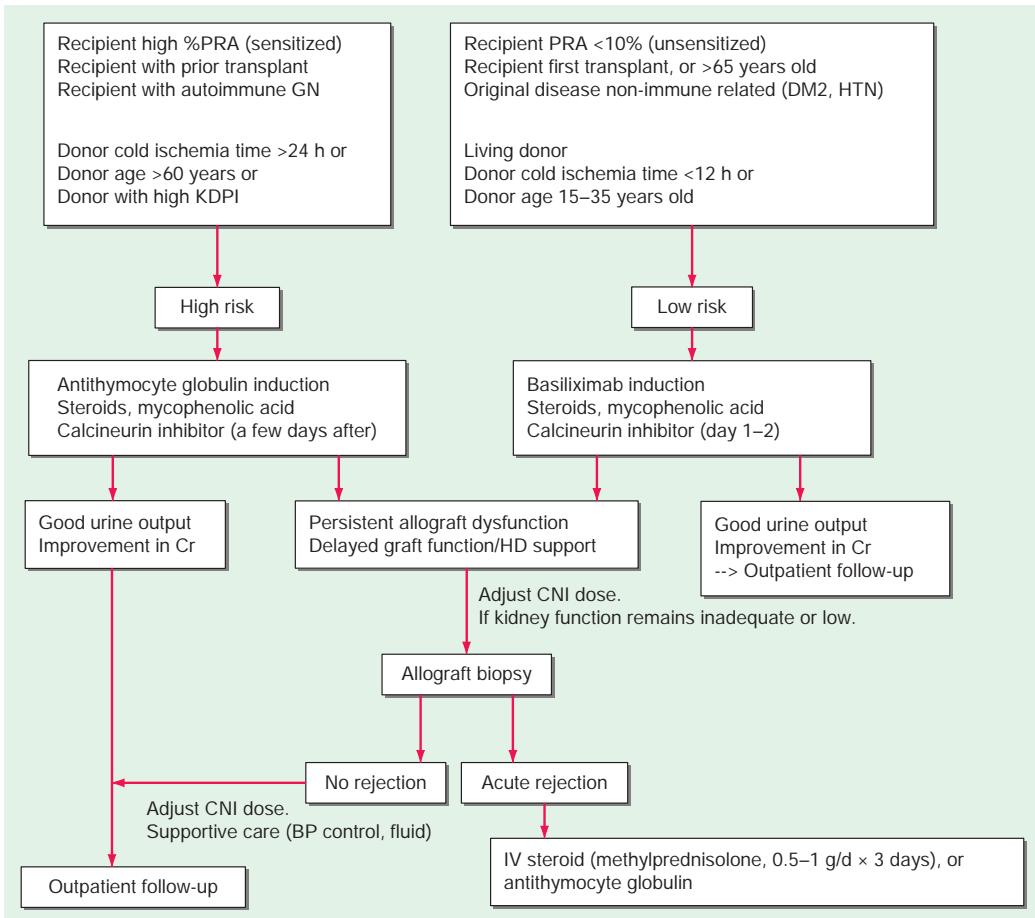


FIGURE 313-2 A typical algorithm for early posttransplant care of a kidney recipient. If any of the recipient or donor "high-risk" factors exist, more aggressive management is called for. Low-risk patients can be treated with a standard immunosuppressive regimen with no or less-potent induction therapy (e.g., basiliximab). Patients at higher risk of rejection or early ischemic transplant dysfunction are often induced with an antithymocyte globulin to provide more potent early immunosuppression or to spare calcineurin use in the immediate posttransplant period. *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. BP, blood pressure; CNI, calcineurin inhibitor; Cr, creatinine; DM2, type 2 diabetes; GN, glomerulonephritis; HD, hemodialysis; HTN, hypertension; KDPI, Kidney Donor Profile Index.

2330 such as acute tubular injury, calcineurin toxicity, BK nephropathy, and recurrent glomerular diseases.

Doppler ultrasonography is 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 also helpful in identifying urinary obstruction or the presence of perirenal collections of urine (urinoma), blood (hematoma), or lymph (lymphocele).

Allograft biopsy is the gold standard for diagnosis of acute T cell-mediated and antibody-mediated rejection. Acute T cell-mediated rejection is diagnosed by the presence of immune cell infiltration in the interstitial, tubular, or vascular compartments, according to the Banff classification. Treatment of T cell-mediated rejection involves a high-dose steroid, e.g., IV administration of methylprednisolone, 500–1000 mg daily for 3 days. Failure to respond is an indication for antibody therapy, usually with ATG.

Evidence of antibody-mediated rejection is present when endothelial injury and deposition of complement component C4d is detected in peritubular capillaries. This is usually accompanied by detection of the circulating donor-specific antibody in the recipient's blood. Treatment of antibody-mediated rejection remains a challenge, and aggressive use of plasmapheresis, IVIG, anti-CD20 monoclonal antibody (rituximab) to target B lymphocytes, and bortezomib to target antibody-producing plasma cells is indicated. Recently, noninvasive biomarkers such as circulating donor-derived cell-free DNA, urine chemokine markers (e.g., CXCL9), and characterization of the urine exosome have been used as adjunct diagnostic markers for rejection.

MANAGEMENT OF CHRONIC COMPLICATIONS

Cardiovascular events (29%), infection (18%), and malignancy (17%) are the major causes of death in kidney transplant recipients. Typical time courses of opportunistic infections after transplantation are shown in **Table 313-4**.

The signs and symptoms of infection may be atypical due to immunosuppression, which makes diagnosis challenging. In addition to commensal infections, opportunistic infections should be considered based on the clinical presentation. Diagnostic measures such as culture (blood, urine, drain fluids), viral load in plasma, and imaging (allograft ultrasound and CT) should be obtained. Overall therapy involves adequate source control, anti-microorganism therapy, and reduction of immunosuppression.

Pneumocystis jirovecii is a rare but critical opportunistic infection (**Chap. 220**). Aggressive diagnostic procedures, including transbronchial and open-lung biopsy, are frequently indicated. Trimethoprim-sulfamethoxazole (TMP-SMX) is the treatment of choice; amphotericin B has been used effectively in systemic fungal infections. Prophylaxis against *P. jirovecii* with daily low-dose TMP-SMX for 6 months is effective. Involvement of the oropharynx with *Candida* (**Chap. 216**) may be treated with local nystatin. Tissue-invasive fungal infections require treatment with systemic agents such as fluconazole or one of the newer

antifungal agents. *Aspergillus* (**Chap. 217**), *Nocardia* (**Chap. 174**), and especially cytomegalovirus (CMV) (**Chap. 195**) infections also occur.

CMV infection is a serious complication after kidney transplantation associated with increased morbidity and mortality. While the seronegative recipients of seropositive donors are at the highest risk, presentation varies from asymptomatic CMV viremia to a systemic syndrome (fever, leukopenia) and tissue-specific manifestation (hepatitis, gastroenteritis, and retinopathy). Plasma viral load and a rise in IgM antibodies to CMV are diagnostic. Valganciclovir has proved effective in both prophylaxis and treatment of CMV disease. Acyclovir is an effective therapy for herpes simplex virus infections.

BK virus is a latent polyomavirus that lies dormant in the kidney and urothelial tract and can be activated in the setting of immunosuppression. Reactivation of BK, if left untreated, will lead to progressive fibrosis and loss of the graft within 1 year in most cases. However, as risk of reactivation of BK infection is associated with the overall degree of immunosuppression, in most cases, BK infection can be managed by regular testing of BK viral load and judicious reduction of maintenance immunosuppression. Renal biopsy can be useful in examining for the presence of interstitial nephritis, tubular cytopathic changes of BK nephropathy, and viral antigens in the allograft. In difficult to treat cases beyond reduction in immunosuppression, a variety of therapies including leflunomide, cidofovir, and quinolone antibiotics (which are effective against polyoma helicase) and IVIG have been tried but with inconsistent results.

CHRONIC LESIONS OF THE TRANSPLANTED KIDNEY

Although current 1-year transplant survival is excellent, most recipients experience a progressive decline in kidney function over time thereafter. Chronic renal transplant dysfunction can be caused by chronic active antibody-mediated rejection, recurrent glomerular disease, hypertension, CNI nephrotoxicity, secondary focal glomerulosclerosis, or a combination of these pathophysiolgies. Chronic vascular changes with intimal proliferation and medial hypertrophy are commonly found. Control of systemic and intrarenal hypertension with angiotensin-converting enzyme (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. Hence, surveillance for skin cancers and protection from ultraviolet radiation are necessary. Solid organ transplant recipients are at higher risk to develop posttransplant lymphoproliferative disease, most frequently seen early (<1 year) or late (7–10 years) after transplantation. Most cases are associated with EBV infection, and the prognosis is poor. The overall malignancy risks are increased in proportion to the total immunosuppressive load administered and the time elapsed since transplantation. Treatment of cancer after transplant involves the reduction of immunosuppression, surgery, conventional cytotoxic chemotherapy, and radiotherapy. Cancer immunotherapy is associated with a high risk of allograft rejection (30–40%), and the multidisciplinary risk-benefit discussion should be made before the initiation of therapy.

OTHER COMPLICATIONS

Both chronic dialysis and renal transplant patients have a higher incidence of death from myocardial infarction and stroke than the population at large, and this is particularly true of 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 recipients increase. More than 30% of kidney transplant recipient mortality

TABLE 313-4 The Most Common Opportunistic Infections in Renal Transplant Recipients

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

is attributable to cardiovascular disease. Strict control of blood pressure and blood sugar and lipid levels is essential in this population.

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 CNI toxicity, which may improve with reduction in dose. Whereas ACE inhibitors may be useful in the longer term, 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 when it occurs 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 mTOR inhibitors. 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 to have 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 HCV 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 HCV antiviral medications reduced this risk significantly.

In conclusion, while kidney transplantation has progressed significantly toward the goals of longer patient survival and better quality of life, the field still has significant challenges and unmet needs. Advanced immunologic and genetic studies have led and will continue to lead us to detailed understanding of alloimmunity at the molecular level. Noninvasive biomarkers for monitoring and diagnosing rejection and novel therapeutic targets will continue to evolve. Further effort is needed to achieve equity and improve personalized care of kidney transplant recipients.

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314 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. 314-1). 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. 309). 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

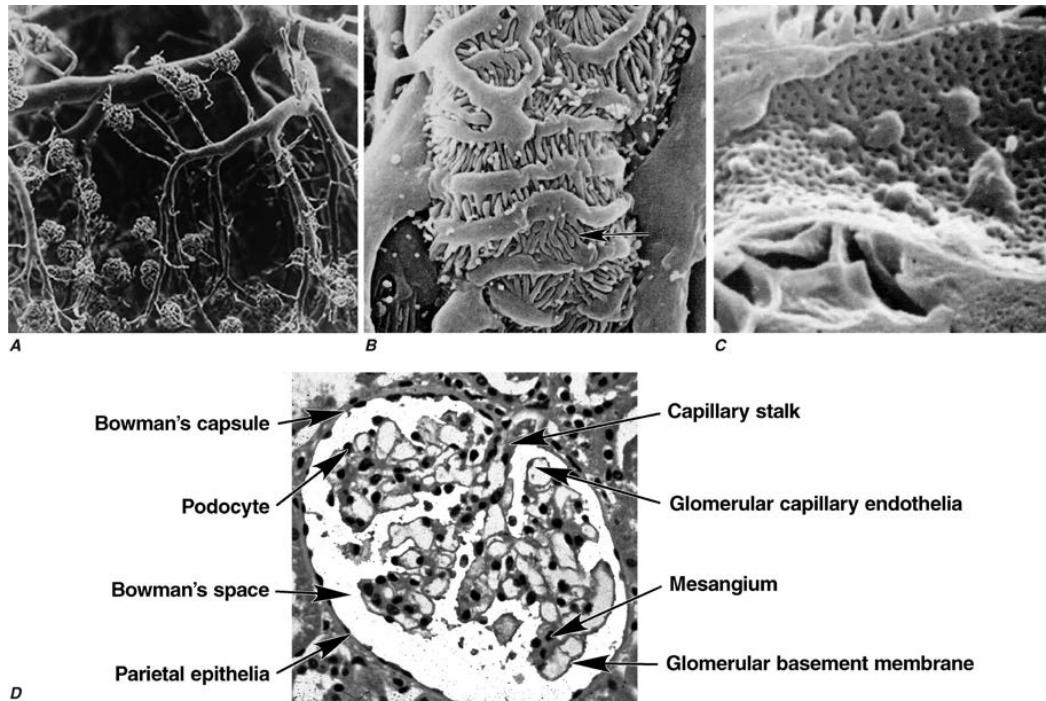


FIGURE 314-1 Glomerular architecture. **A.** The glomerular capillaries form from a branching network of renal arteries, arterioles leading to an afferent arteriole, glomerular capillary bed (tuft), and a draining efferent arteriole. (From VH Gattone II et al: Hypertension 5:8, 1983.) **B.** Scanning 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.)

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) affects 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*; monogenetic causes of *FSGS* are increasingly linked to early age of onset and to genes encoding type IV collagen in older adults, suggesting that much of *FSGS* may be hereditary; mutations in control of the complement pathway increasingly associate with various forms of *membranoproliferative glomerulonephritis* (*MPGN*) and C₃ glomerulopathies including dense deposit disease, or *atypical hemolytic-uremic syndrome* (*aHUS*); type II partial lipodystrophy from mutations in genes encoding lamin A/C or PPAR cause a metabolic syndrome associated with *MPGN*; Alport's syndrome, from mutations in the genes encoding for the 3, 4, or 5 chains of type IV collagen, produces *split basement membranes* with *glomerulosclerosis*; and lysosomal storage diseases, such as -galactosidase A deficiency causing Fabry's disease and *N-acetylneuraminiac acid hydrolase* deficiency causing nephrosialidosis, produce *FSGS*.

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

Inflammation of the glomerular capillaries is called *glomerulonephritis*. Most glomerular or mesangial antigens involved in *immune-mediated glomerulonephritis* are unknown (Fig. 314-2). 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 such as *idiopathic membranous glomerulonephritis* (*MGN*) or *MPGN* are confined to the kidney, whereas systemic inflammatory diseases such as *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 3 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 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.

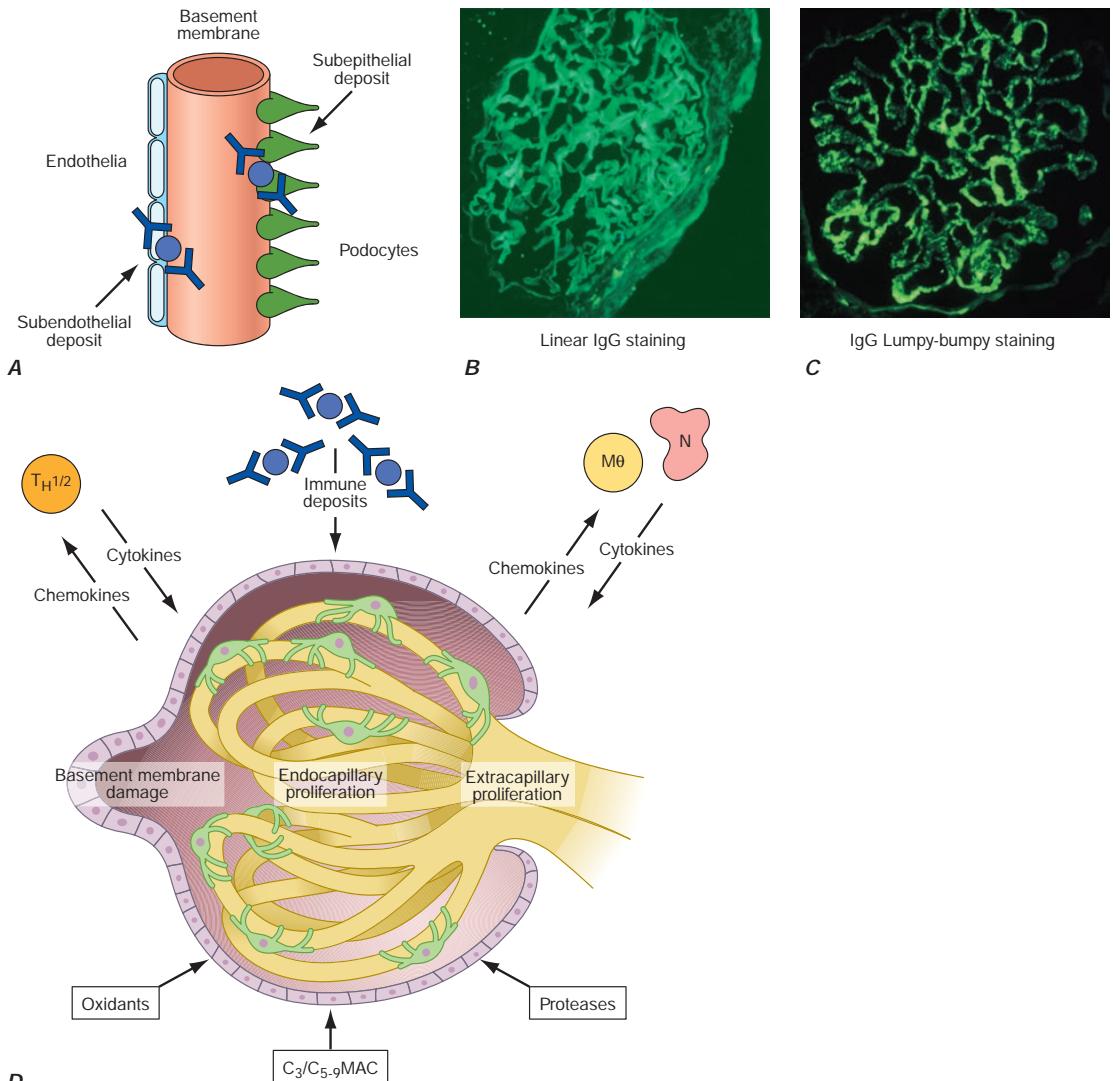


FIGURE 314-2 The glomerulus is injured by a variety of mechanisms. **A.** Preformed immune deposits can precipitate from the circulation and collect along the glomerular basement membrane (GBM) in the subendothelial space or can form in situ along the subepithelial space. **B.** Immunofluorescent staining 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.

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 C₅₋₉ 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. A4-27). 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.

2334 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. A4-27) suggests potentially recoverable renal function, whereas the development of *chronic interstitial fibrosis* prognosticates permanent loss (see Fig. A4-30).

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 (TGF- β), fibroblast growth factor 2 (FGF-2), hypoxemia-inducible factor 1 (HIF-1 α), 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. A4-34) 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 314-1).

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 314-1). 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 314-2). 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 antibody (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,

TABLE 314-1 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+	–/150
Proteinuria	>300	>300	Trace–3+	>150

^aAlbumin detected by radioimmunoassay. ^bAlbumin represents 20–60% of the total protein excreted in the urine.

TABLE 314-2 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	+/++	++/+++ ^c	++++
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	+/++	++/+++ ^c	++++
Cryoglobulinemia ^a	+/++	++/+++	++++
Nephrotic Syndromes			
Minimal change disease	++++	-	-
Focal segmental glomerulosclerosis	+++/++++	+	-
Membranous glomerulonephritis	++++	+	-
Diabetic nephropathy	++/++++	/+	-
AL and AA amyloidosis	+++/++++	+	+/++
Light chain deposition disease	+++	+	-
Fibrillary-immunotactoid disease	+++/++++	+	+
Fabry's disease	+	+	-
Basement Membrane Syndromes			
Anti-GBM disease ^a	++	++/+++	-
Alport's syndrome	++	++	-
Thin basement membrane disease	+	++	-
Nail-patella syndrome	++/+++	++	-
Glomerular Vascular Syndromes			
Atherosclerotic nephropathy	+	+	+++
Hypertensive nephropathy ^b	+/++	/++	++
Cholesterol emboli	+/++	++	+++
Sickle cell disease	+/++	++ ^c	+++
Thrombotic microangiopathies	++	++	+++
Antiphospholipid syndrome	++	++	+++
ANCA small-vessel vasculitis ^a			
Granulomatosis with polyangiitis (Wegener's)	+/++	++/+++	++++
Microscopic polyangiitis	+/++	++/+++	++++
Churg-Strauss syndrome	+++	++/+++	++++
Henoch-Schönlein purpura ^a	+/++	++/+++ ^c	++++
Cryoglobulinemia ^a	+/++	++/+++	++++
AL and AA amyloidosis	+++/++++	+	+/++
Infectious Disease-Associated Syndromes			
Poststreptococcal glomerulonephritis ^a	+/++	++/+++	-
Subacute bacterial endocarditis ^a	+/++	++	-
HIV	+++	/++	-

(Continued)

TABLE 314-2 Patterns of Clinical Glomerulonephritis (Continued)

GLOMERULAR SYNDROMES	PROTEINURIA	HEMATURIA	VASCULAR INJURY
Hepatitis B and C	+++	+/++	-
Syphilis	+++	+	-
Leprosy	+++	+	-
Malaria	+++	+/++	-
Schistosomiasis	+++	+/++	-

^aCan present as rapidly progressive glomerulonephritis (RPGN); sometimes called crescentic glomerulonephritis. ^bCan present as a malignant hypertensive crisis producing an aggressive fibrinoid necrosis in arterioles and small arteries with microangiopathic hemolytic anemia. ^cCan present with gross hematuria.

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

and microscopic hematuria; if only large amounts of proteinuria are present without clinical manifestations, the condition is sometimes called *nephrotic-range proteinuria*. The glomerular filtration rate (GFR) in these patients may initially be normal or, rarely, higher than normal, but with persistent hyperfiltration and continued nephron loss, it typically declines over months to years. Patients with a *basement membrane syndrome* either have genetically abnormal basement membranes (Alport's syndrome) or an autoimmune response to basement membrane collagen IV (Goodpasture's syndrome) associated with microscopic hematuria, mild to heavy proteinuria, and hypertension with variable elevations in serum creatinine. *Glomerular-vascular syndrome* describes patients with 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) or antibodies (anti-GBM, antiphospholipid, antistreptolysin O [ASO], PLA2R, THSD7A, 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 (PLA2R, THSD7A, and DNAJB9). 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.

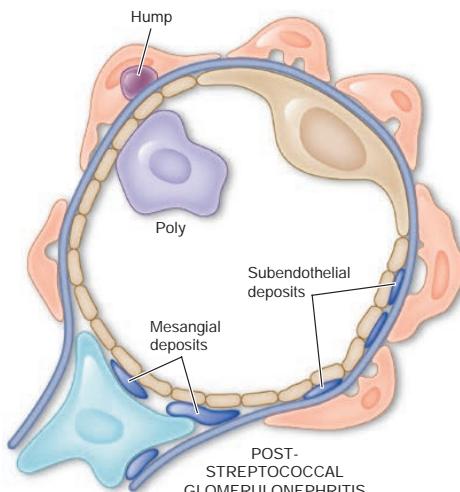
POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

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 nephritis in underdeveloped countries is epidemic and usually affects children between the ages of 2 and 14 years. In developed countries, it 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 more commonly throat infections with particular M types of streptococci (nephritogenic strains) antedate glomerular disease. Antibiotic therapy does not reduce the occurrence of nephritis. Poststreptococcal glomerulonephritis due to pharyngitis develops 1–3 weeks after infection and 2–6 weeks after impetigo.

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, C₃, C₄, and C₅₋₉; and subepithelial deposits (which appear as “humps”) (see Fig. A4-6). (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 are a cationic cysteine proteinase known as streptococcal pyrogenic exotoxin B (SPEB) and NAPlr, the nephritis-associated plasmin receptor. The nephritogenic antigen SPEB has been demonstrated inside the subepithelial “humps” on biopsy.

The classic presentation is an acute nephritic picture with hematuria, pyuria, red blood cell casts, edema, hypertension, and oliguric renal failure, which may be severe enough to appear as RPGN. Systemic symptoms of headache, malaise, anorexia, and flank pain (due to swelling of the renal capsule) are reported in as many as 50% of cases. Five percent of children and 20% of adults have proteinuria in the nephrotic range. In the first week of symptoms, 90% of patients will have a depressed CH₅₀ and decreased levels of C₃ with normal levels of C₄. Positive rheumatoid factor (30–40%), cryoglobulins, 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 C₃ complement levels.

Glomerular schematic 1



Treatment is supportive, with control of hypertension, edema, and dialysis as needed. Antibiotic treatment for active streptococcal infection should be given to 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. Complete resolution of the azotemia, 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. Overall, the prognosis is good, with ESRD being very uncommon in children and adults. 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 C₃. 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). Clinical manifestations of renal disease are present in 30% of patients at the time of diagnosis, and the majority will develop renal abnormalities in the course of their disease; it is more common in blacks, Asians, and Hispanics than it is in whites. Lupus nephritis results from the deposition of circulating immune complexes composed of primarily DNA and anti-DNA, which activate the complement cascade, leading to complement-mediated damage,

2338 leukocyte infiltration, activation of procoagulant factors, and release of various cytokines. In situ immune complex formation also plays a role in renal injury. These immune deposits may occur in the mesangial, subendothelial, and/or subepithelial spaces.

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. 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. A kidney biopsy should be performed in most patients with renal involvement to establish the histologic subtype, which guides therapy.

The World Health Organization (WHO) workshop in 1974 first outlined several distinct patterns of lupus-related glomerular injury, and this classification was modified in 2004. This latest version of lesions seen on biopsy (**Table 314-3**) forms the basis for modern treatment recommendations. Class I nephritis describes normal glomerular histology by 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.

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 involving <50% of the glomeruli with proliferation or scarring*, often involving only a segment of the glomerulus (**see Fig. A4-12**). Class III lesions have the most varied course. Hematuria and proteinuria are present, and some patients also have an active urinary sediment, nephrotic syndrome, hypertension, and a decreased GFR. Patients with mild proliferation involving a small percentage of glomeruli respond well to therapy with steroids alone, and <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. Class IV describes *diffuse lesions with >50% of the glomeruli involved and proliferative endocapillary lesions with or without extracapillary lesions that may be segmental (IV-S), involving <50% of the glomerular tuft, or global (IV-G), involving >50%*. 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. A4-12**).

TABLE 314-3 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.

Without treatment, this aggressive lesion has the worst renal prognosis, with class IV-S worse than class IV-G. However, if a remission—defined as a return to near-normal renal function and proteinuria

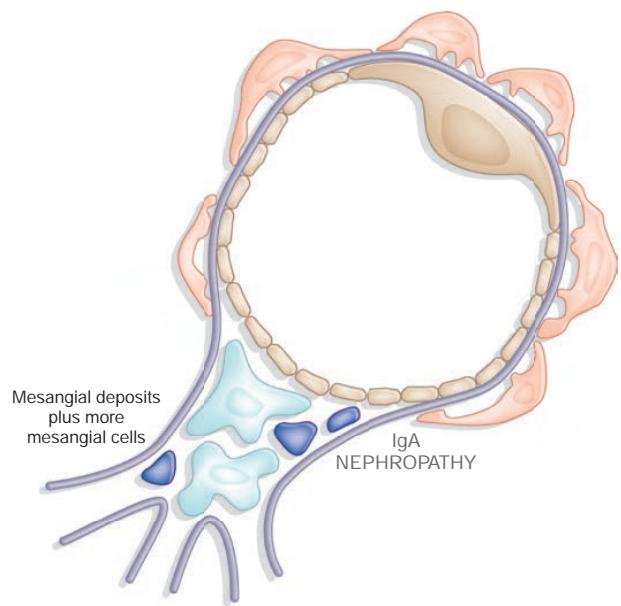
330 mg/dL per day—is achieved with treatment, renal outcomes are excellent. Current evidence suggests that inducing a remission with administration of high-dose steroids and either cyclophosphamide or mycophenolate mofetil for 2–6 months, followed by maintenance therapy with lower doses of steroids and 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, or rituximab. 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. A4-11**); 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 thrombotic microangiopathy. 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. Up to 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 3 NC1 domain of collagen IV. Indeed, anti-GBM disease may be considered an autoimmune “conformeropathy” that involves the perturbation of quaternary structure of the 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. Younger patients are more likely to present with the full Goodpasture's syndrome, with hemoptysis, a sudden fall in hemoglobin, fever, dyspnea, and hematuria, and older patients are more likely to present with isolated glomerulonephritis. 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. A4-14). 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 3 NC1 domain of collagen IV alone be used as the target. This is because nonnephritic antibodies against the 1 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. 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. Patients who present with hemoptysis should be treated for their lung hemorrhage, as it responds to plasmapheresis. Treated patients with less severe disease typically respond to 8–10 treatments of plasmapheresis accompanied by oral prednisone and cyclophosphamide. Maintenance therapy with low-dose immunosuppressants should be considered until antibody titers are negative. There are scarce data alternatively using rituximab, azathioprine, or mycophenolate mofetil. Kidney transplantation 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. This may reflect variation in detection or a true variation 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, celiac disease, chronic bronchiectasis, idiopathic interstitial pneumonia, dermatitis herpetiformis, mycosis fungoides, ankylosing spondylitis, HIV infection, and Sjögren's syndrome. IgA deposition in these entities is not usually associated with clinically significant renal disease. IgG A-dominant *Staphylococcus*-associated postinfectious glomerulonephritis is associated with clinically significant renal disease.

The pathognomonic finding on kidney biopsy is dominant or codominant mesangial IgA deposits, either alone or with IgG, IgM, or C₃ (See Glomerular Schematic 2.) IgA deposits are typically J-chain containing polymeric IgA. 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-galactosamine 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. A second hit, such as a viral or other antigen exposure, or hereditary defects in alternative complement pathway proteins may affect the manifestation of disease. 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. A4-8), 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 and 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, and older age of onset. Mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular interstitial fibrosis (T), and crescents (C) have predictive value as established by the Oxford Classification and the MEST-C score. 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

2340 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. 363](#)). 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. Remission is induced in 85–90% of patients, but relapse is common. Steroids are tapered soon after acute inflammation subsides. Maintenance therapy includes low-dose steroids and 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, hematuria, and subnephrotic proteinuria; occasionally, there may be cutaneous purpura and mononeuritis multiplex. Patients may present without renal involvement, although most of these patients develop 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. A4-13](#)). 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 (eosinophilic granulomatosis with polyangiitis [EGPA]) 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* without immune deposits 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.

C₃ GLOMERULOPATHIES

C₃ glomerulopathy is a recent disease classification that is defined by the glomerular accumulation of C₃ with little or no immunoglobulin and encompasses dense deposit disease (DDD), formerly MPGN type II (see below), and C₃ glomerulonephritis (C₃GN) ([Table 314-4](#)). DDD is defined morphologically by dense deposits forming ribbons in the GBM. In the absence of this specific morphology, the entity is categorized as C₃GN. Both are associated with the presence of a complement mutation believed to cause the renal pathology, including mutations in the complement factor H regulatory (CFHR) protein genes. DDD is primarily a disease of children and young adults, whereas the other C₃ glomerulopathies are reported to present in an older age group (mean age 30). By definition, kidneys with C₃ glomerulopathy show sole or dominant staining for C₃ but can have variable light microscopy, with mesangial proliferative or membranoproliferative patterns seen most commonly. Morphologically, many cases are not distinguishable from recovering postinfectious glomerulonephritis. Patients with DDD present with proteinuria, which may be nephrotic range, and/or hematuria, which may be macroscopic or microscopic. Partial lipodystrophy and Drusen bodies in the retina may also be present. Prognosis is poor, with 50% of patients progressing to ESRD. C₃GN patients are clinically less well defined, but approximately two-thirds have hematuria and one-third have proteinuria. C₃ levels are low with normal C₄ and C₃ nephritic factor is present in most patients with DDD and less commonly in C₃GN. Abnormalities in factor H, soluble C5b-9, paraprotein detection, and specific CFHR genetic mutations should be assessed as well. Screening family members may be indicated. The optimal therapies remain undefined but include inhibition of the renin-angiotensin

TABLE 314-4 Membranoproliferative Glomerulonephritis: Immunoglobulin-Mediated

Type I Disease—Most Common

Idiopathic

Infection: Subacute bacterial endocarditis, hepatitis B and C, fungal and parasitic infections

Autoimmune diseases: Systemic lupus erythematosus, cryoglobulinemia, Sjögren's

Monoclonal gammopathies: Monoclonal gammopathy of undetermined significance, myeloma, monoclonal gammopathy of renal significance

Cancer: Lung, breast, and ovary (germinal)

Type II Disease

Idiopathic

Dense deposit disease (immunoglobulin-mediated)

Type III Disease

Idiopathic

C₃ Glomerulopathy: C₃ Dominant, Non-Immunoglobulin-Mediated

Dense Deposit Disease (C₃ dominant)

Idiopathic

Specific genetic mutations and/or autoantibodies to alternate complement pathway factors or regulatory factors of alternate complement pathway

C₃ Glomerulonephritis

Specific genetic mutations and/or autoantibodies to alternate complement pathway factors or regulatory factors of alternate complement pathway

system, lipid lowering, steroids, and other immunosuppressants. Evidence suggests a benefit of therapy with eculizumab, a monoclonal antibody directed at C₅, which is activated by C₃.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

MPGN is characterized by thickening of the GBM with mesangio-proliferative changes often leading to a lobular appearance of the glomerular tuft; 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 based on histology into type I, type II, and type III disease. *Type I MPGN* is immune complex-mediated and commonly associated with persistent hepatitis B and C, fungal and parasitic infections, SBE, autoimmune diseases such as lupus or cryoglobulinemia, or monoclonal gammopathies, including monoclonal gammopathy of renal significance (MGRS), where the only clinically apparent manifestations are in the kidney (Table 314-4). *Types II and III MPGN* can be idiopathic and immunoglobulin-mediated disease (driven by the classical complement pathway), but the vast majority of cases formerly defined as MPGN type II or III are non-immunoglobulin-mediated and driven by the alternate complement pathway.

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. A4-9). (See **Glomerular Schematic 3**) Subendothelial deposits with low serum levels of C₃ are typical, although 50% of patients have normal levels of C₃ and occasional intramesangial deposits. Low serum C₃ and a dense thickening of the GBM containing ribbons of dense deposits and C₃ characterize type II MPGN, *dense deposit disease* (see Fig. A4-10). 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 as well as subendothelial 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 C₃ 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 supports the efficacy of treatment of *primary MPGN* with steroids, particularly in children. There are reports of efficacy with other immunosuppressive drugs. If defects in the complement pathway are found, treatment with eculizumab is of benefit. In *secondary MPGN*, treating the associated infection, autoimmune disease, or neoplasms is of demonstrated benefit. Patients with primary MPGN are well known to be at risk for not only a histologic recurrence in the transplanted kidney 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. Mesangioproliferative pathology 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.

NEPHROTIC SYNDROME

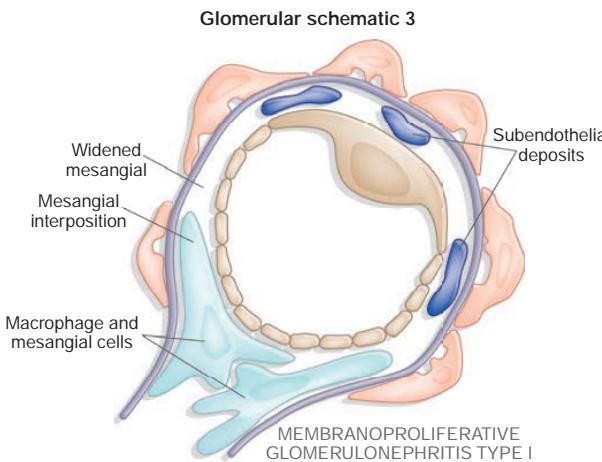
Nephrotic syndrome classically presents with heavy proteinuria, minimal hematuria, hypoalbuminemia, hypercholesterolemia, edema, and hypertension. If left undiagnosed or untreated, some of these syndromes will progressively damage enough glomeruli to cause a fall in GFR, producing renal failure. Multiple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

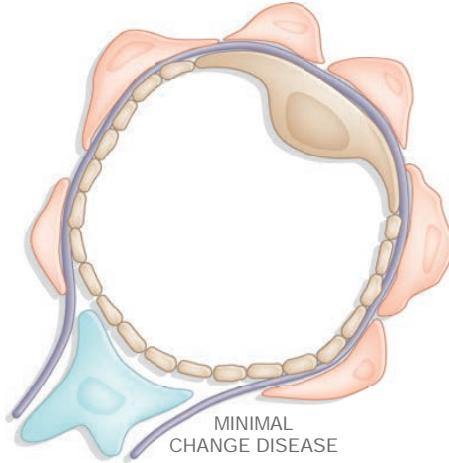
Therapies for various causes of nephrotic syndrome are noted under individual disease headings below. In general, all patients with hypercholesterolemia secondary to nephrotic syndrome should be treated with lipid-lowering agents because they are at increased risk for cardiovascular disease. Edema secondary to salt and water retention can be controlled with the 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 conditions, including Hodgkin's disease, allergies, use of nonsteroidal anti-inflammatory agents or lithium, infections, and other glomerular diseases. MCD on renal biopsy shows no 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. A4-1). (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 pathogenesis of this lesion is unclear. Most agree there is a disturbance related to T-cell responses, or expression of CD80 or CD40/40L may alter capillary charge and podocyte integrity; interestingly, the use of checkpoint inhibitors as chemotherapy is associated with MCD. There also is some circumstantial evidence for the presence of preceding allergies, altered cell-mediated immunity during viral infections, and a 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 (25–40%), which often returns to normal after remission of the nephrotic syndrome. The appearance of acute renal failure in adults is often seen more commonly in patients with low serum albumin and intrarenal edema (nephrosarca) that is responsive to 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, most children today are treated with steroids; only children who are nonresponders are biopsied. Primary responders are patients who have a complete remission (<0.2 mg/24 h of proteinuria), often abruptly 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. 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 (focal); the clinical findings of FSGS largely manifest as proteinuria. When the secondary and genetic causes of FSGS are eliminated (Table 314-5), 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

TABLE 314-5 Focal Segmental Glomerulosclerosis

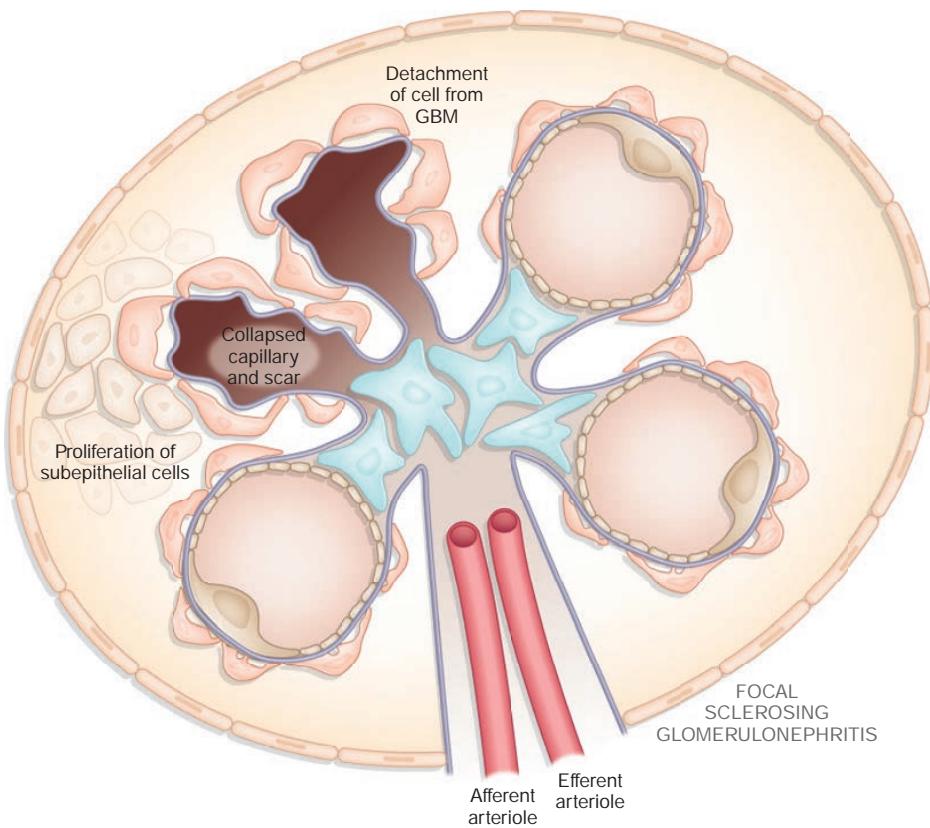
Primary focal segmental glomerulosclerosis
Secondary focal segmental glomerulosclerosis
Adaptive response to hyperfiltration/reduced renal mass, obesity
Viruses: HIV/hepatitis B/papovavirus
Hypertensive nephropathy
Reflux nephropathy
Cholesterol emboli
Drugs: Heroin/analgesics/bisphosphonates/ecstasy
Oligomegaly
Sickle cell disease
Radiation nephritis
Familial podocytopathies
<i>NPHS1</i> mutation/nephrin
<i>NPHS2</i> mutation/podocin
<i>PLCE1</i> mutation/phospholipase Cε1
<i>INF2</i> mutation/inverted formin 2
<i>WT1</i> mutation/Wilms tumor
<i>TRPC6</i> mutation/cation channel
<i>ACTN4</i> mutation/actinin
α-Galactosidase A deficiency/Fabry's disease
<i>N-Acetylneurameric acid hydrolase</i> deficiency/nephrosialidosis

nephrotic syndrome in African Americans. The pathogenesis of FSGS has multiple possible mechanisms including a circulating permeability factor, an adaptive response to glomerular hypertrophy or hyperfiltration, and podocyte abnormalities associated with direct toxic injury or genetic mutations. Risk polymorphisms at the *APOL1* locus expressed in podocytes substantially explain the increased burden of FSGS among African Americans.

The pathologic changes of FSGS are most prominent in glomeruli located at the corticomedullary junction (see Fig. A4-2), so if the renal biopsy specimen is from superficial tissue, the lesions can be missed, which sometimes leads to misdiagnosis of MCD. In addition to focal and segmental scarring, other variants have been described, including cellular lesions with *endothelial hypercellularity* and heavy proteinuria; *collapsing glomerulopathy* (see Fig. A4-3) with segmental or global glomerular collapse and a rapid decline in renal function; a hilar stalk lesion (see Fig. A4-4); or the *glomerular tip lesion* (see Fig. A4-5), which may have a better prognosis. (See Glomerular Schematic 5.)

FSGS can present with hematuria, hypertension, any level of proteinuria, and 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 FSGS should include inhibitors of the renin-angiotensin system. Patients with primary FSGS 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 6–12 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 established. Immunosuppressive therapy is not indicated in secondary or genetic FSGS. FSGS recurs in 30% of renal transplants, more commonly in primary FSGS, less commonly in secondary FSGS, and rarely in genetic FSGS. In recurrent posttransplant FSGS, many patients will achieve a full or partial remission with plasmapheresis. The treatment of secondary FSGS typically involves treating the underlying cause and controlling proteinuria. There is no role for steroids or other immunosuppressive agents in secondary FSGS.

Glomerular schematic 5

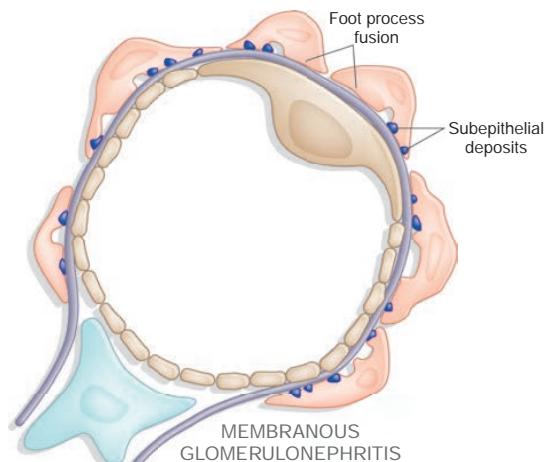
**MEMBRANOUS GLOMERULONEPHRITIS**

MGN, or *membranous nephropathy* as it is sometimes called, accounts for ~25% 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 such as lupus or rheumatoid arthritis, IgG4 diseases, or drug exposure (Table 314-6).

Uniform thickening of the basement membrane along the peripheral capillary loops is seen by light microscopy on renal biopsy (see Fig. A4-7); 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 C₃,

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 A₂

Glomerular schematic 6

**TABLE 314-6 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, antitumor necrosis factor agents

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, IgG4 disease

receptor circulate and bind to a conformational epitope present in the PLA2R on human podocytes, producing characteristic *in situ* deposits. Three to 10% of IMN patients alternatively have autoantibodies to thrombospondin type-1 domain containing 7A (THSD7A). 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, cancer, 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 makes treatment decisions difficult. One-third of patients continue to have relapsing nephrotic syndrome but maintain normal renal function, and approximately another third of patients develop renal failure or die from the complications of nephrotic syndrome. Male gender, older age, hypertension, and the persistence of nephrotic-range 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 hypoalbuminemia.

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 ($>3.0\text{ g}/24\text{ h}$). 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. Attaining remission is associated with a good long-term prognosis.

DIABETIC NEPHROPATHY

Diabetic nephropathy is the single most common cause of chronic renal failure in the United States and worldwide. The dramatic increase in the number of patients with diabetic nephropathy reflects the epidemic increase in obesity and type 2 diabetes mellitus. Approximately 40% of patients with 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.

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 nephropathy. The composition of the GBM is altered notably with a loss of heparan sulfate moieties that form the negatively charged filtration barrier resulting in increased filtration of serum proteins into the urine. The expansion of the mesangium due to the accumulation of extracellular matrix correlates with the clinical manifestations of diabetic nephropathy (see stages in Fig. A4-20). 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 diabetic nephropathies with albuminuria are largely indistinguishable. Patients with type 2 diabetes without albuminuria

are classified as having diabetic kidney disease as opposed to diabetic nephropathy and may have myriad pathologic findings.

Multiple lines of evidence support an important role for changes in glomerular hemodynamics including increases in glomerular capillary pressure and glomerular hyperfiltration in these pathologic changes. Hyperglycemia activates the renin-angiotensin-aldosterone system and also alters insulin-like growth factor, reactive oxygen species, and endothelin 1. Diabetes upregulates the sodium-glucose cotransporters (SGLT1 and SGLT2) in the proximal tubule, resulting in decreased distal delivery of sodium to the macula densa and further glomerular hyperfiltration. Sustained glomerular hypertension increases matrix production and alterations in the GBM with disruption in the filtration barrier. Other factors that alter matrix production include the accumulation of advanced glycosylation end products, circulating factors including growth hormone, connective tissue growth factor, TGF- β , and dyslipidemia.

The natural history of diabetic nephropathy has been historically well characterized in the ~40% of diabetics who develop it as a progression from glomerular hyperfiltration and renal hypertrophy to increasing albuminuria followed by declining GFR and ESRD. 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*. Albuminuria and decreased GFR are potent risk factors for cardiovascular disease, with some patients dying before they reach ESRD. Furthermore, contemporary studies reveal that up to 24% of patients with type 1 diabetes and 50% with type 2 diabetes and chronic kidney disease may be normoalbuminuric. It is unknown whether this alteration in the natural history reflects contemporary effective interventions or perhaps other kidney diseases that happen to occur in patients with diabetes. The degree of early glomerular hyperfiltration does correlate with the development of albuminuria and declining GFR. Albuminuria in the range of 30–300 mg/24 h is called *microalbuminuria* (Table 314-1). 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. Microalbuminuria classically progresses over 5–10 years to proteinuria and declining GFR, but in contemporary studies, greater heterogeneity is reported with regression to normoalbuminuria; however, albuminuria remains the single most important predictor of a faster decline in GFR. Regression of albuminuria with a treatment intervention is a good prognostic sign. Proteinuria in diabetic nephropathy can be variable, ranging from 500 mg to 25 g/24 h. 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. A4-20). Even with advanced chronic kidney disease, patients with diabetic nephropathy will have enlarged kidneys. Using the above data, and in the absence of other clinical or serologic data suggesting another disease, diabetic nephropathy is usually diagnosed without a renal biopsy. The risk of progression to ESRD is influenced by treatment and other risk factors, and reports vary from a decline of 1.8–14 mL/min per year. Survival on dialysis is worse for patients with diabetes. Renal transplantation results in better survival than dialysis.

Good evidence supports the benefits of blood sugar and blood pressure control, inhibitors of the renin-angiotensin-aldosterone system (RAAS), and inhibitors of SGLT2 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 to achieve this goal. Drugs that inhibit the RAAS (ACE inhibitors, angiotensin receptor blockers [ARBs]), independent of their effects on systemic blood pressure, have been shown in large clinical trials to slow the progression of diabetic nephropathy at early (microalbuminuria) and late (proteinuria with reduced glomerular filtration) stages. Evidence suggests increased risk for cardiovascular adverse events without increased efficacy in patients with a combination of two drugs (ACE inhibitors, ARBs, or renin inhibitors) that suppress several components of the RAAS. In patients with type 2 diabetes and kidney disease with albuminuria, the risk of kidney failure and cardiovascular events was lower in those receiving SGLT2 in addition to inhibitors of the RAAS. Ongoing trials are examining the hypotheses that other agents may be of benefit, including 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 confer renal injury; that of either *cast nephropathy* (see Fig. A4-17), which causes renal failure but not heavy proteinuria or amyloidosis, or light chain deposition disease (LCDD) (see Fig. A4-16), which produces proteinuria 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 or, more prominently, in the tubular basement membrane and Bowman's capsule. Light chain deposits are not fibrillar and do not stain with Congo red, but they are easily detected with anti-light chain antibody. A combination of the light chain rearrangement, self-aggregating properties at neutral pH, and abnormal metabolism probably contributes to the deposition.

Monoclonal Plasma Cell Disorders Multiple myeloma, Waldenström's macroglobulinemia, or lymphoma may be present, as well as heart, liver, and pulmonary involvement. The monoclonal protein may be found with serum electrophoresis or with serum free light chain analysis. Nephrotic syndrome may develop, and ~70% of patients progress to dialysis. Treatment for LCDD is treatment of the primary disease and, if possible, autologous stem cell transplantation. Rarely, truncated heavy chains similarly cause nonamyloid deposits.

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. 112). Even though both occur for different reasons, their clinicopathophysiology is quite similar. 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 contrast to LCDD, amyloid renal deposits are fibrillar, stain with Congo red, and contain predominantly the variable region of lambda chains (see Fig. A4-15). 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. Approximately 10% of patients have overt myeloma as defined by CRAB (hypercalcemia, renal insufficiency, anemia, or lytic bone lesions). Nephrotic syndrome is common, and ~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 -pleated sheets of serum amyloid A protein, an acute phase reactant. Patients with AA amyloid have associated inflammatory diseases including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, juvenile inflammatory arthritis, and

familial Mediterranean fever. An increasing proportion of patients have unidentified chronic inflammation; this may reflect better treatments for the previously associated diseases or a rise in chronic inflammation due to obesity. 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 ~40–60% of patient's progress to dialysis. Serum-free light chain analysis is 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 ~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 (HCT) can delay the course of disease. Patients who are not candidates for HCT often receive bortezomib-based regimens. 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 and Immunotactoid Glomerulopathies Fibrillary and immunotactoid glomerulopathies are rare (<1.0% of renal biopsies), morphologically defined diseases characterized by glomerular accumulation of nonbranching randomly arranged fibrils that are Congo red negative. Fibrillary glomerulopathy accounts for 85–90% of cases and is identified by the presence of the protein Dnaj heat shock protein family B9 (DNAJB9) in the glomeruli, which is absent in the rarer immunotactoid glomerulopathy. In both, glomerular and mesangial deposits contain oligoclonal or oligotypic immunoglobulins and complement, with 12- to 24-nm fibrils in fibrillary glomerulopathy and >30-nm fibrils organized into microtubules in immunotactoid glomerulopathy. The cause of this "nonamyloid" glomerulopathy is mostly idiopathic; reports of fibrillary glomerulonephritis describe associations with malignancy, autoimmune disease, and monoclonal gammopathy, and immunotactoid glomerulopathy has been associated with lymphoma or plasma cell disorders. Both disorders appear in adults aged 40–80 years old, with moderate to heavy proteinuria (100%), hematuria (70%), renal insufficiency (50%), and a wide variety of histologic lesions, including DPGN, MPGN, MGN, or mesangioproliferative glomerulonephritis. Most patients have disease limited to the kidney. Patients should be screened for associated disorders. Half of patients develop renal failure over a few years. There is no consensus on treatment of this uncommon disorder, although rituximab has been reported to remit proteinuria. These diseases can recur in the renal transplant.

FABRY'S DISEASE

Fabry's disease is an X-linked inborn error of globotriaosylceramide metabolism secondary to deficient lysosomal -galactosidase A (alpha-Gal 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, cornea verticillate, 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 alpha-Gal 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. A4-18). 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

2346 polarized light (Maltese cross). Measurement of alpha-Gal A activity and mutational analysis of the gene is diagnostic, with renal biopsies sometimes helpful. Progression to renal failure occurs by the fourth or fifth decade. Treatment with inhibitors of the renin-angiotensin system is recommended. Treatment with recombinant alpha-Gal A or migalastat, a chaperone that facilitates trafficking of alpha-Gal 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 disease are similar to those of 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 1. 1. 2(IV) collagen. Some specialized tissues undergo a developmental switch replacing 1. 1. 2(IV) protomers with an 3. 4.

5(IV) collagen network; this switch occurs in the kidney (glomerular and tubular basement membrane), lung, testis, cochlea, and eye, while an 5. 5. 6(IV) network appears in skin, smooth muscle, and esophagus and along Bowman's capsule in the kidney. This switch probably occurs because the 3. 4. 5(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.

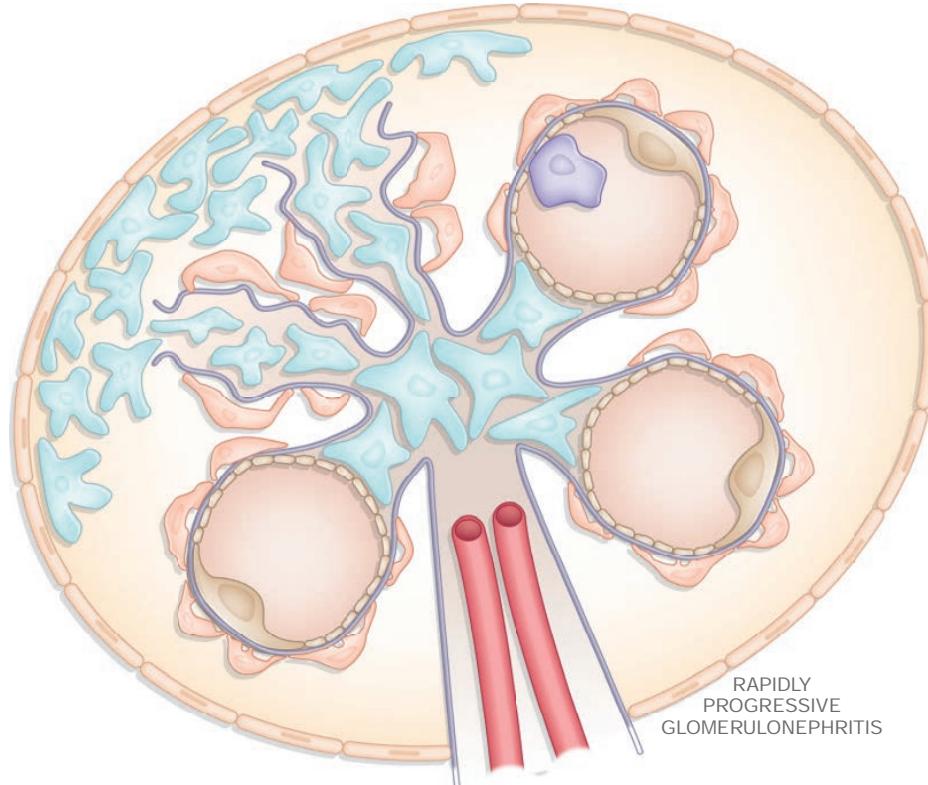
ANTI-GBM DISEASE

Autoimmune disease where antibodies are directed against the 3 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, and mild proteinuria (<1–2 g/24 h), which appears late in the course, followed by chronic glomerulosclerosis leading to renal failure in association with sensorineural deafness. Some patients develop lenticonus of the anterior lens capsule, "dot and fleck" retinopathy, and rarely, leiomyomatosis. Approximately 85% of patients with Alport's syndrome have an X-linked inheritance of mutations in the 5(IV) collagen chain on chromosome Xq22–24. Female

Glomerular schematic 7



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 3(IV) or 4(IV) chains on chromosome 2q35–37. Rarely, some kindred have an autosomal dominant inheritance of dominant-negative mutations in 3(IV) or 4(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, lenticus, 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 5(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 5(IV) collagen chain on immunofluorescent analysis. Patients with mutations in 3(IV) or 4(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. A4-19), 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), a relatively common disorder characterized by persistent or intermittent, asymptomatic, usually microscopic hematuria and rarely macroscopic hematuria with flank pain, is not typically associated with proteinuria, hypertension, or loss of renal function or extrarenal disease. TBMD is often familial, with pedigrees exhibiting an autosomal dominant pattern. It usually presents in childhood in multiple family members and is also called *benign familial hematuria*. Many cases of TBMD have genetic defects in type IV collagen, but in contrast to Alport's syndrome, the disease behaves as an autosomal dominant disorder that in ~40% of families segregates with the COL(IV) 3/COL(IV) 4 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. A4-19). 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 3 and 4 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 in 30–40% of patients and rarely progress to renal failure. Proteinuria or isolated hematuria is discovered throughout life but usually by the third decade. On renal biopsy, pathognomonic rarefactions containing clusters of collagen fibrils within the lamina densa of the GBM are found, and FSGS may be present. Treatment is nonspecific, but renin-angiotensin system inhibition is recommended. 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 ~6% of patients with elevated blood pressure. As many as 27% of patients with end-stage kidney disease have hypertension as a primary cause, and it is the second most common cause of ESRD after diabetic nephropathy. *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 explain 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. A4-21). 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 blood pressure <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. A4-24). The hemodynamic stress of malignant hypertension leads to fibrinoid necrosis of

2348 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. A4-22). 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 vaso-occlusive 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. Early changes in the kidney include glomerular hyperfiltration, hyposthenuria, micro- or macroscopic hematuria, and microalbuminuria. Later changes can include papillary necrosis, renal infarction and proteinuria, and most commonly, FSGS on renal biopsy and rarely MPGN. 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 vaso-occlusive disease in the kidney leads to varying degrees of renal failure. Their prognosis on dialysis is poor, and anemia management with erythropoiesis-stimulating agents is complicated. Treatment is directed to reducing the frequency of painful crises and administering ACE inhibitors and hydroxyurea 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), Shiga toxin-mediated *hemolytic-uremic syndrome* (HUS), and complement-mediated HUS represent a spectrum of thrombotic microangiopathies (TMAs). TTP and HUS share the general features of idiopathic thrombocytopenic purpura, hemolytic anemia, fever, renal failure, and neurologic disturbances. Clinically, when patients, particularly children, have evidence of renal injury, HUS is suspected, and in adults with neurologic disease, TTP is suspected. 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. A4-23). These tissue findings are similar to what is seen in preeclampsia/HELLP (*hemolysis*, elevated liver

enzymes, and *low platelet count syndrome*), malignant hypertension, and the antiphospholipid syndrome. TMA is also seen postpartum (and may be complement mediated); 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; in patients taking the antiplatelet agents ticlopidine and clopidogrel; and following HIV infection. The implicated drug should be discontinued.

Shiga toxin-mediated 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, 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. Patients can be tested for ADAMTS13 activity, and if low, the presence of antibodies to ADAMTS13 distinguishes the deficiency from the immune-mediated disease. Complement-mediated TMA/HUS is a rare hereditary deficiency of one of the regulatory proteins that restrict the activation of the alternate complement pathway and can present in children or adults often preceded by an infection. The treatment of adult TTP 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. There is an anecdotal role in relapsing patients for using splenectomy, steroids, immunosuppressive drugs, bortezomib, or rituximab. Patients without antibodies and a genetic deficiency of ADAMTS13 production can be treated with fresh frozen plasma alone. Patients with Shiga toxin-mediated HUS are not given antibiotics and are treated with supportive care because antibiotics are thought to accelerate the release of the toxin and the diarrhea is usually self-limited. Patients with complement-mediated TMA/HUS are treated with eculizumab, an anticomplement therapy.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME (SEE CHAP. 357)

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. A4-3) 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, linked to *APOL1* polymorphisms. HIV immune complex kidney disease (HIVICK) is a group of immune complex-mediated glomerular lesions seen in HIV patients that, 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 an 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 or MPGN. Viral antigens, most commonly HBeAG, are found in the renal deposits. Cryoglobulinemic glomerulonephritis has also been reported. Treatment is with antiviral agents. Children have a better prognosis than adults.

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 MPGN, but polyarteritis nodosa (PAN), IgA nephropathy, and FSGS have been reported. With the availability of direct-acting antivirals, 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, new cases of leprosy appear primarily in developing countries. 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 lepromatos, and lepromatos. 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 lepromatos and lepromatos 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 multidrug 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 C₃ 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 as follows: 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 class 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. Filarisis 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.

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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 underlie this group of genetic diseases collectively termed *ciliopathies* (Table 315-1).

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Etiology and Pathogenesis (Fig. 315-1) ADPKD is characterized by progressive formation of epithelial lined cysts in the kidney. Although cysts occur in only 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 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 hairlike 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. Recent evidence suggests a 1:3

stoichiometry for PC1:PC2 in the PC1/2 channel complex. 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 aquaporin 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 lifetimes. 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, are underdiagnosed. 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. Two additional genes, *GANAB* and *DNAJB11*, have been found in patients with autosomal dominant form of polycystic kidney disease. The *GANAB* gene encodes the glucosidase IIa subunit and the *DNAJB11* gene produces a cofactor of BiP, a key chaperone in the endoplasmic reticulum controlling folding, trafficking, and degradation of secreted and membrane proteins. Both proteins appear to affect PC1 trafficking. However, these mutations have only been found in a very small number of families.

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 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 such as 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. 315-2). Enlarged kidneys can each reach a four-fold increase in length and weigh up to 20 times the normal weight.

TABLE 315-1 Inherited Diseases Commonly Associated with a Cystic Phenotype

DISEASE	MODE OF INHERITANCE	RENAL ABNORMALITIES	OTHER CLINICAL FEATURES	GENES
Autosomal dominant polycystic kidney disease	AD	Bilaterally enlarged kidneys with cortical and medullary cysts	Liver, pancreatic cysts, hypertension, subarachnoid hemorrhage	<i>PKD1, PKD2</i>
Autosomal dominant polycystic kidney disease-like	AD	Normal to smaller sized kidneys with fewer cortical and medullary cysts	Liver cysts at variable degree (from absent to severe)	<i>GANAB, DNAJB11</i>
Autosomal recessive polycystic kidney disease	AR	Distal and collecting duct cysts	Oligohydramnios if severe, hypertension, ascending cholangitis, liver fibrosis	<i>PKHD1</i>
Autosomal dominant tubulointerstitial kidney disease	AD	Small fibrotic kidneys; medullary cysts	In adults, gout	<i>UMOD, MUC1, REN, HNF1^A, SEC61A1</i>
Renal cysts and diabetes syndrome	AD	Kidney cysts, aberrant nephrogenesis, irregular collecting systems, abnormal renal calyces, hyperuricemic nephropathy. Highly variable.	Diabetes	<i>HNF1B</i>
Nephronophthisis	AR	Small fibrotic kidneys; medullary cysts	Growth retardation, anemia (In syndromic forms: visual loss, liver fibrosis, cerebellar ataxia, other)	<i>NPHP1-20, IQCB1, CEP290, GLIS2, RPGRIP1L, NEK8, SDCCAG8, TMEM67, TTC21B</i>
Senior-Loken syndrome	AR	Renal cysts	Juvenile nephronophthisis, Leber amaurosis	<i>NPHP1-6, SDCCAG8</i>
Leber congenital amaurosis	AR	Renal cysts	Visual impairment in first year of life; pigmentary retinopathy	<i>GUCLY2D, RPE65, LCA3-14</i>
Meckel-Gruber syndrome	AR	Cortical and medullary cysts	CNS anomalies, polydactyly, congenital heart defects	<i>MKS1, TMEM216, TMEM67, TMEM231, TMEM107, CEP290, RPGRIP1L, CC2D2A, TCTN2, B9D1, B9D2, NPHP3, KIF14</i>
Bardet-Biedl syndrome	AR	Renal cysts	Obesity, polydactyly, retinitis pigmentosa, anosmia, congenital heart defects, mental retardation	<i>BBS1, 2, ARL6, BBS4, 5, MKKS, BBS7, TTC8, BBS9, 10, TRIM32, BBS12, MKS1, CEP290, C2ORF86</i>
Oral-facial-digital syndrome type I	X-linked dominant	Renal cysts	Oral cavity, face, and digit anomalies; CNS abnormalities; cystic kidney disease; X-linked with male lethality, primary ciliary dyskinesia	<i>OFD1</i>
Tuberous sclerosis	AD	Renal cysts	Angiomyolipomas; renal cell carcinoma Facial angiofibromas; CNS hamartomas	<i>TSC1, TSC2</i>
Von Hippel-Lindau disease	AD	Renal cysts	Renal cell carcinoma, retinal angiomas; CNS hemangioblastomas; pheochromocytomas	<i>VHL</i>

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

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 lifetimes. 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. Mutations in *GANAB* and *DNAJB11* genes result in milder cystic kidney disease than that in classic ADPKD with small renal cysts and normal-sized kidneys. Sometimes patients with *GANAB* mutations present with ADPLD-like phenotype. Patients with *DNAJB11* develop renal fibrosis, characteristic of autosomal dominant tubulointerstitial disease (ADTKD) discussed below. 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 hypocitaturia 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. Radiologic imaging is often not helpful in distinguishing cyst infection and cyst hemorrhage because of their complexity. CT scan and 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

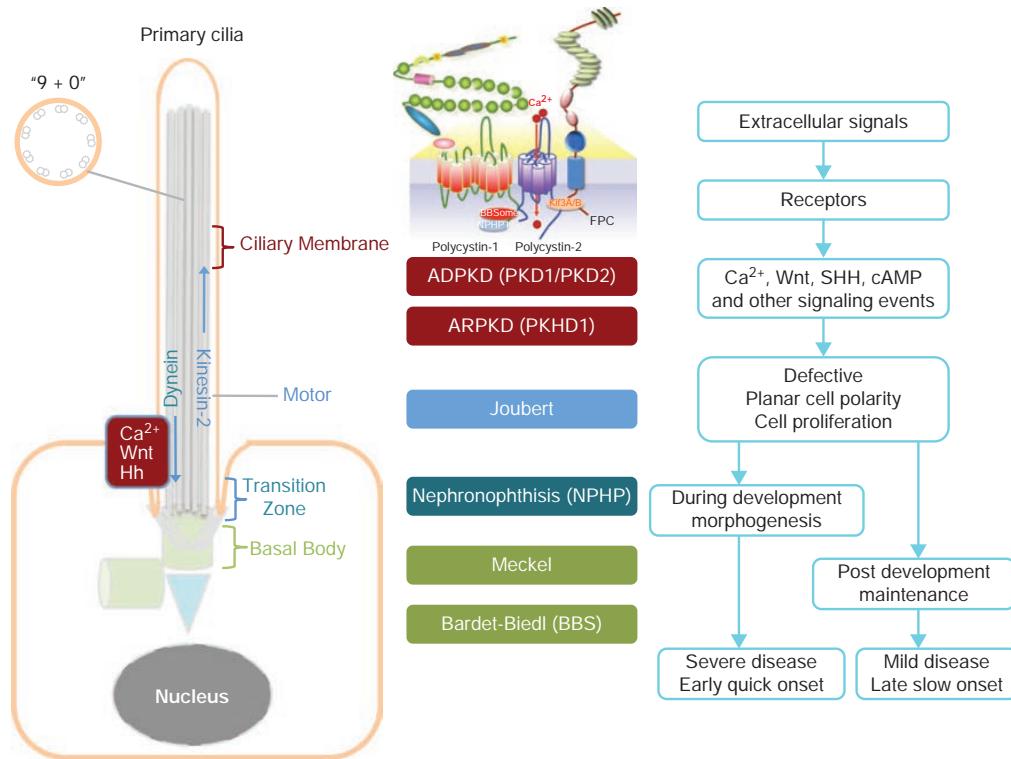


FIGURE 315-1 Scheme of the primary cilium and cystic kidney disease proteins. **Left:** A scheme of the primary cilium. Primary cilia share a "9+0" organization of microtubule doublets. Proteins are transported into the cilium by motor protein kinesin 2 and transported out of the cilium by dynein. The cilium is connected to the basal body through the transition zone. **Middle:** Topology of ADPKD and ARPKD proteins polycystin 1, polycystin 2, and FPC is shown. Localizations 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.

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 GII and *SEC63*, and each appears to affect PC1 biogenesis.

Intracranial aneurysm (ICA) occurs four to five times more frequently in ADPKD patients than in the general population and causes 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 radiologic screening for ICA in asymptomatic patients with ADPKD remains unclear. ADPKD patients with a positive family history of ICAs may undergo presymptomatic 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 is also increased in ADPKD patients.

Diagnosis A 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 presymptomatic 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, is 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 of 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 is 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.



FIGURE 315-2 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.

TREATMENT

Autosomal Dominant Polycystic Kidney Disease

No specific treatment to prevent cyst growth or the decline of renal function has been approved by the 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 of penetrating 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 (nonnarcotic and narcotic analgesics) and nonpharmacologic (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 for 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 reduce 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 multicenter 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. Notably, treatments may vary depending on the patient population. For example, the FDA has indicated tolvaptan to be only for patients at risk of rapidly progressing disease. Combining genotypic and imaging information may predict kidney growth rates and help in selecting this patient population.

Additional preclinical studies in animal models include the use of inhibitors to nonreceptor tyrosine kinase Src, B-raf, cycline-dependent kinase (CDK), transcription factors STAT3 and STAT6 (pyrimethamine and leflunomide), purinergic receptors, hepatocyte growth factor receptor, glucosylceramide, agonists to peroxisome proliferator-activated receptor-gamma (PPAR γ) receptors (thiazolidinediones), and targeting microRNAs. Reprogramming the metabolic pathway through studies of transcription regulator super enhancer as well as dietary control including time-restricted feeding, have been shown in murine models 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

2354 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 oligohydramnios 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. Macrocytosis 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 portosystemic 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 <1:5000 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 majority of TS-causing mutations are found in *TSC2*.

Renal cysts are observed in about 20–30% of people with 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 a rare problem, 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. Everolimus, an mTOR inhibitor, has been approved in the United States for treatment of TSC-associated kidney tumors as well as nonkidney manifestations of TS. Regular surveillance is perhaps the most important component of the clinical management of the kidney 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. The VHL protein plays a critical role in the regulation of hypoxia pathways and oxygen sensing via the transcription factor hypoxia-inducible factor (HIF). Like many other 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 affect the majority of VHL patients. Nonrenal features of VHL include pheochromocytomas, cerebellar hemangioblastomas, and retinal hemangiomas. While much rarer than ADPKD, VHL is an entity that should 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 TUBULOINTERSTITIAL KIDNEY DISEASE (MEDULLARY CYSTIC KIDNEY DISEASE)

The term *autosomal dominant tubulointerstitial kidney disease* (ADTKD) has replaced the phrase *medullary cystic kidney disease* (MCKD) as the preferred designation for a group of autosomal dominant disorders characterized by progressive kidney failure and a benign urine sediment. 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. This leads to the production of a large “neoprotein” fragment that has 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. Disease does not recur in transplanted kidneys.

ADTKD-UMOD ADTKD-UMOD (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 (HNF1) 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). ADTKD-REN patients demonstrate hyporeninemia with mild hyperkalemia, and often have hyperuricemia and gout. Mutations in HNF1 and SEC61A1 are even rarer causes of ADTKD.

Kidney biopsies in patients with any of the various forms of ADTKD 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 and in large panels of kidney disease genes are available in the clinical setting. High cost and complexity in interpretation are the major barriers to the use of such testing.

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 sets of autosomal recessive disorders are referred to as nephronophthises, 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 abnormalities 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. To date, 21 BBS genes have been identified. 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 NPHP. Genetic diagnosis is possible, complicated because of the large number of genes that can be responsible, but now quite 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.

KARYOMEGLIC 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* genes are genetically sensitized to the effect of DNA damage. Kidney histology shows karyomegaly in addition to the nonspecific 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.

CONGENITAL ABNORMALITIES OF THE KIDNEY AND URINARY TRACT

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 that when mutated lead to both nonsyndromic and 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. A nontrivial fraction of children with CKD have an unsuspected genomic imbalance, often disrupting genes known to be relevant to CAKUT and kidney development. It is not uncommon for such genetic lesions to 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. 468]) 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 are 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, hypercalcemia, glycosuria, and tubular proteinuria. Decreased urine concentrating ability is common.

DIAGNOSTIC CONSIDERATIONS

Recent studies using new DNA sequencing technologies suggest that variants in Mendelian kidney disease genes contribute to a nontrivial fraction of CKD cases, even when a clear Mendelian disease phenotype or family history of disease is lacking. Many studies also lead to the conclusion that various rare genetically mediated kidney diseases are difficult to categorize by phenotype alone. These diseases may mimic each other, an argument for using fairly large panels (or the entire genome) in genetic testing in the setting of kidney disease. The old and complicated nomenclature used to describe human kidney diseases is expected to continue to be replaced by newer, genetically defined, categories.

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 have kidney disease has suggested that a strong genetic component is involved as well.

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Tubulointerstitial Diseases of the Kidney

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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 316-1**).

Acute TIN most often presents with acute kidney injury (**Chap. 310**). 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 ammoniogenesis, as well as progressive azotemia (rising creatinine and blood urea nitrogen [BUN]). There is often modest proteinuria (rarely >2 g/d) attributable to decreased tubular reabsorption of filtered proteins; however, nephrotic-range albuminuria may occur in some conditions due to the development of secondary focal segmental glomerulosclerosis (FSGS). Renal ultrasonography may reveal changes of "medical renal disease," such as increased echogenicity of the renal parenchyma with loss of corticomedullary differentiation, prominence of the renal pyramids, and cortical scarring in some conditions. The predominant pathology in chronic TIN is interstitial fibrosis with patchy mononuclear cell infiltration and widespread tubular atrophy, luminal dilation, and thickening of tubular basement membranes. Because of the nonspecific nature of the histopathology, biopsy specimens rarely provide a specific diagnosis. Thus, diagnosis relies on careful analysis of history, drug or toxin exposure, associated symptoms, and imaging studies.

ACUTE INTERSTITIAL NEPHRITIS

In 1897, Councilman reported on eight cases of acute interstitial nephritis (AIN) in the Medical and Surgical Reports of the Boston City Hospital—three as a postinfectious complication of scarlet fever and two from diphtheria. Later, he described the lesion as "an acute inflammation of the kidney characterized by cellular and fluid exudation in the interstitial tissue, accompanied by, but not dependent 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 316-1**). 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 316-1**).

ALLERGIC INTERSTITIAL NEPHRITIS

Although biopsy-proven AIN accounts for no more than ~15% of cases of unexplained acute kidney injury, 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 kidney biopsy to establish the diagnosis of AIN.

Clinical Features The classic presentation of AIN, namely, fever, rash, peripheral eosinophilia, and oliguric kidney injury occurring

TABLE 316-1 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, H₂ 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
- Tubulointerstitial disease related to checkpoint inhibitors
- Anti-brush border disease (anti-LRP2 nephropathy)
- 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)
- Chronic interstitial nephritis in agricultural communities

Metabolic Disturbances

- Hypercalcemia and/or nephrocalcinosis
- Hyperuricemia
- Prolonged hypokalemia
- Hyperoxaluria
- Cystinosis (**see Chap. 315**)

Cystic and Hereditary Disorders (see Chap. 315)

- Polycystic kidney disease
- Nephronophthisis
- Autosomal dominant tubulointerstitial kidney disease (medullary cystic kidney 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.

2358 after 7–10 days of treatment with methicillin or another -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 kidney injury (**Chap. 310**). Atypical reactions can occur, most notably with nonsteroidal anti-inflammatory drug (NSAID)-induced AIN, in which fever, rash, and eosinophilia are rare, but acute kidney injury 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 316-1 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 kidney injury 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. Kidney biopsy is generally not required for diagnosis but reveals extensive interstitial and tubular infiltration of leukocytes, including eosinophils.

PART 9

Disorders of the Kidney and Urinary Tract

TREATMENT

Allergic Interstitial Nephritis

Discontinuation of the offending agent often leads to reversal of the kidney injury. However, depending on the duration of exposure and degree of tubular atrophy and interstitial fibrosis that has occurred, the kidney damage may not be completely reversible. Glucocorticoid therapy may accelerate kidney recovery but does not appear to impact long-term kidney survival. It is best reserved for those cases with severe kidney injury in which dialysis is imminent or if kidney function continues to deteriorate despite stopping the offending drug (**Fig. 316-1** and **Table 316-2**).

TABLE 316-2 Indications for Corticosteroids and Immunosuppressives in Interstitial Nephritis

Absolute Indications

- Sjögren's syndrome
- Sarcoidosis
- SLE interstitial nephritis
- Adults with TINU
- Interstitial nephritis from IgG4-related disease
- 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: From Treatment of acute interstitial nephritis, S Reddy & DJ Salant: Renal Failure, 07 Jul 2009, Taylor and Francis. Reprinted by permission of the publisher (Taylor and Francis Ltd, <http://www.tandfonline.com>).

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. 361**). TIN with a predominant lymphocytic infiltrate is the most common renal manifestation of Sjögren's syndrome and can be associated with impaired kidney function, distal RTA, and nephrogenic diabetes insipidus. 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. 316-1** and **Table 316-2**).

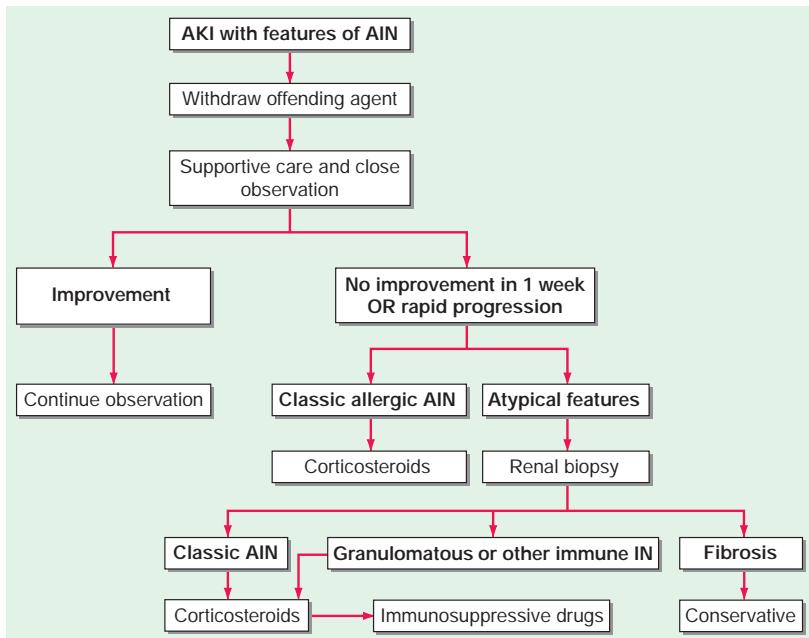


FIGURE 316-1 Algorithm for the treatment of allergic and other immune-mediated acute interstitial nephritis (AIN). AKI, acute kidney injury; IN, interstitial nephritis. See text for immunosuppressive drugs used for refractory or relapsing AIN. (From Treatment of acute interstitial nephritis, S Reddy & DJ Salant: Renal Failure, 07 Jul 2009, Taylor and Francis. Reprinted by permission of the publisher (Taylor and Francis Ltd, <http://www.tandfonline.com>)).

TUBULointerSTITIAL NEPHRITIS WITH UVEITIS

Tubulointerstitial nephritis with uveitis (TINU) is a systemic autoimmune disease of unknown etiology. It accounts for <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. 316-2), 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 kidney 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 kidney disease, such as Sjögren's syndrome, Behcet's disease, sarcoidosis, and systemic lupus erythematosus, have been considered. Clinical symptoms are typically self-limited in children but are more apt to follow a relapsing course in adults. The renal and ocular manifestations generally respond well to oral glucocorticoids, although maintenance therapy with agents such as methotrexate, azathioprine, or mycophenolate may be necessary to prevent relapses (Fig. 316-1 and Table 316-2).

SYSTEMIC LUPUS ERYTHEMATOSUS

An interstitial mononuclear cell inflammatory reaction accompanies the glomerular lesion in most cases of class III or IV lupus nephritis (Chap. 314), and deposits of immune complexes can be identified in tubular 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. Kidney 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

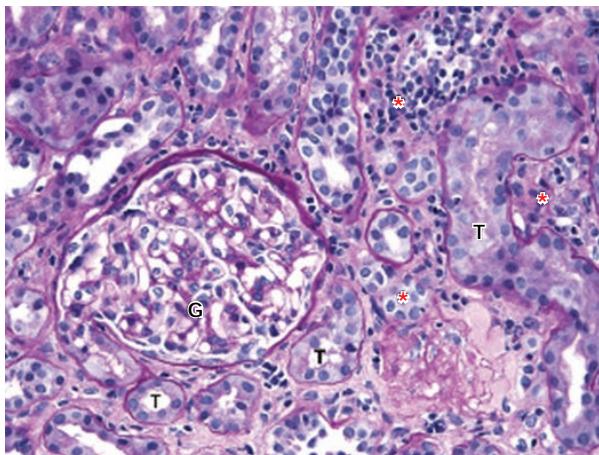


FIGURE 316-2 Acute interstitial nephritis (AIN) in a patient who presented with acute iritis, low-grade fever, erythrocyte sedimentation rate of 103, pyuria and cellular casts on urinalysis, and a newly elevated serum creatinine of 2.4 mg/dL. Both the iritis and AIN improved after intravenous methylprednisolone. This PAS-stained kidney 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.

hypercalcemia. Most patients experience some improvement in kidney function if treated early with glucocorticoids before the development of significant interstitial fibrosis and tubular atrophy (Table 316-2). Other immunosuppressive agents may be required for those who relapse frequently upon steroid withdrawal (Fig. 316-1). Tuberculosis should be ruled out before starting treatment because this too is a rare cause of granulomatous interstitial nephritis.

IgG4-RELATED SYSTEMIC DISEASE

A form of AIN characterized by a dense inflammatory infiltrate containing IgG4-expressing plasma cells can occur as a part of a syndrome known as IgG4-related systemic disease (Chap. 368). 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.

AIN ASSOCIATED WITH THE USE OF IMMUNE CHECKPOINT INHIBITORS

The use of immune checkpoint inhibitors has had a major impact in cancer care by disrupting mechanisms by which tumor cells elude the body's immune surveillance systems. However, such success comes at the cost of increasing the incidence of autoimmune phenomena. While dermatologic, gastrointestinal, and endocrine manifestations prevail, the kidney is impacted in 2% of cases with monotherapy and up to 5% when dual checkpoint inhibitor therapy is used. An acute rise in serum creatinine is typically noted within 15 weeks after starting therapy, although it can occur later during therapy or up to 2 months following the final dose. Biopsy, when performed, typically shows acute interstitial inflammation, although glomerular pathologies may also be found. Patients are often taking medications commonly known to cause acute drug-associated TIN such as proton pump inhibitors or NSAIDs. Treatment for severe acute kidney injury includes corticosteroids, discontinuation of potential inciting medications, and avoidance of further checkpoint inhibitor doses until the kidney function has recovered.

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. 316-1 and Table 316-2). Recently, cases have been identified in which autoantibodies that may be important in disease pathogenesis were seen to target antigens expressed by the collecting duct or proximal tubular brush border.

INFECTION-ASSOCIATED AIN

AIN may also occur as a local inflammatory reaction to microbial infection (Table 316-1) and should be distinguished from acute bacterial pyelonephritis (Chap. 135). Acute bacterial pyelonephritis does not generally cause acute kidney injury unless it affects both kidneys or causes septic shock. Presently, infection-associated AIN is most often seen in immunocompromised patients, particularly kidney transplant recipients with reactivation of polyomavirus BK (Chaps. 143 and 313).

CRYSTAL DEPOSITION DISORDERS AND OBSTRUCTIVE TUBULOPATHIES

Acute kidney injury may occur when crystals of various types are deposited in tubular cells and interstitium or when they obstruct tubules. Impaired kidney function, often accompanied by flank pain from tubular obstruction, may occur in patients treated with

2360 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 birefringent 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 kidney injury 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. 75). 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 kidney function.

Calcium oxalate crystal deposition in tubular cells and interstitium may lead to permanent kidney 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. 318). *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 kidney disease and hypovolemia. Consequently, Phosphosoda should be avoided in patients with chronic kidney disease.

LIGHT CHAIN CAST NEPHROPATHY

Patients with multiple myeloma may develop acute kidney injury 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 kidney injury.

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. 316-3). 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.

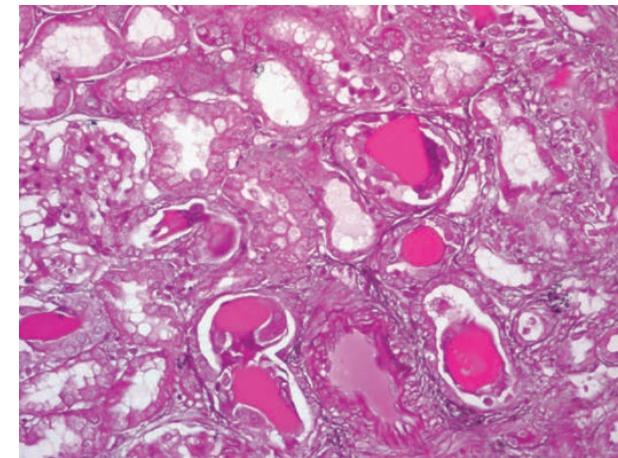


FIGURE 316-3 Histologic appearance of myeloma cast nephropathy. A hematoxylin-eosin-stained kidney biopsy shows many atrophic tubules filled with eosinophilic casts (consisting of Bence-Jones protein), which are surrounded by giant cell reactions. (Courtesy of Dr. Michael N. Koss, University of Southern 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. 111); 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 kidney injury. Although high-dose glucocorticoids and subsequent chemotherapy often result in recovery of kidney 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. 314). 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

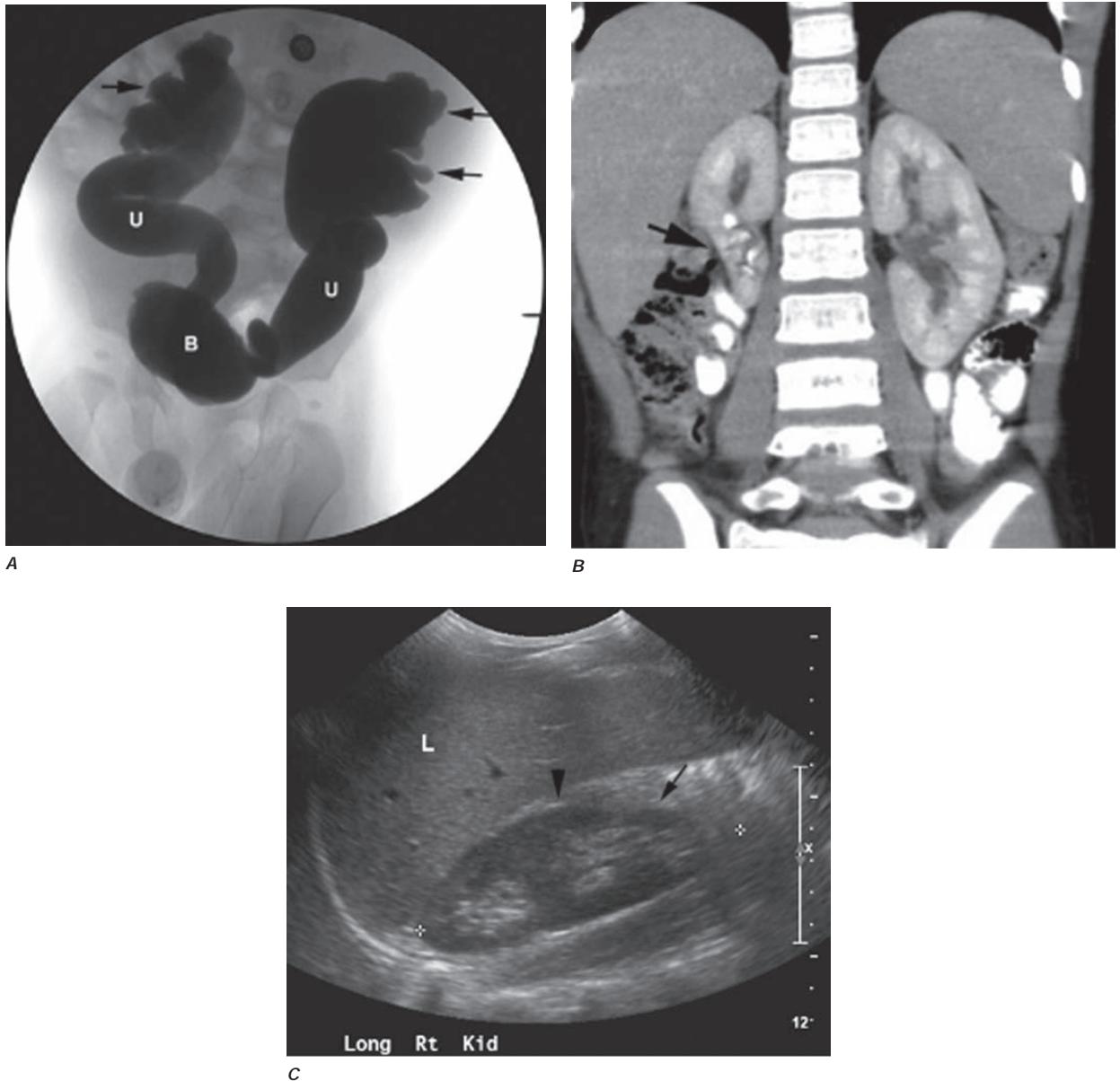


FIGURE 316-4 Radiographs of vesicoureteral reflux (VUR) and reflux nephropathy. *A*, Voiding cystourethrogram in a 7-month-old baby with bilateral high-grade VUR evidenced by clubbed calyces (arrows) and dilated tortuous ureters (U) entering the bladder (B). *B*, Abdominal computed tomography scan (coronal 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.)

abnormal retrograde urine flow from the bladder into one or both ureters and kidneys because of mislocated and incompetent ureterovesical valves (**Fig. 316-4**). 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 may exhibit variable degrees of kidney injury as well as hypertension, mild to moderate proteinuria, and an 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. Kidney ultrasound in adults characteristically shows asymmetric small kidneys with irregular outlines, thinned cortices, and regions of compensatory hypertrophy (Fig. 316-4).

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 kidney function.

SICKLE CELL NEPHROPATHY

The pathogenesis and clinical manifestations of sickle cell nephropathy are described in Chap. 317. 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 hypoxic and hypertonic medullary vasculature and present with gross hematuria and ureteric obstruction by sloughed ischemic papillae (Table 316-3).

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 kidney biopsy in a patient who presents with advanced kidney 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 impaired kidney function, papillary necrosis (Table 316-3) 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. 316-5). 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 kidney failure. Recent cohort studies in individuals with normal baseline kidney 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 kidney disease.

TABLE 316-3 Major Causes of Papillary Necrosis

- Analgesic nephropathy
- Sickle cell nephropathy
- Diabetes with urinary tract infection
- Prolonged NSAID use (rare)

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.



FIGURE 316-5 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 Int 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 kidney 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.

KARYOMEGLIC 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 nuclelease 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 3 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 kidney 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 kidney function.

TREATMENT

Lithium-Associated Nephropathy

Kidney function should be followed regularly in patients taking lithium, and caution should be exercised in patients with underlying kidney 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 deterioration of kidney function can be problematic, as lithium is an effective mood stabilizer that is often incompletely substituted by other agents. Furthermore, despite discontinuation of lithium, chronic kidney 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 kidney function declines.

CALCINEURIN INHIBITOR NEPHROTOXICITY

The calcineurin inhibitor (CNI) immunosuppressive agents cyclosporine and tacrolimus can cause both acute and chronic kidney 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 kidney 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 kidney 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 impaired kidney function 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 kidney function, although either of these two factors may have been the primary event. In 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 kidney 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* is very uncommon nowadays and is 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 kidney 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. 417). This should be distinguished from juvenile hyperuricemic nephropathy, a form of medullary cystic kidney disease caused by mutations in uromodulin (UMOD) (Chap. 315) 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 kidney function.

HYPERCALCEMIC NEPHROPATHY

(See also Chap. 410) Chronic hypercalcemia, as occurs in primary hyperparathyroidism, sarcoidosis, multiple myeloma, vitamin D intoxication, or metastatic bone disease, can cause tubulointerstitial disease and progressive kidney injury. 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 kidney injury. 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. 410**). Acute kidney injury from acute hypercalcemia may be completely reversible. Gradual progressive kidney dysfunction 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

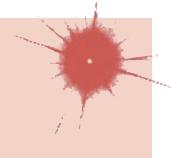
The causes of acute and CIN vary widely across the globe. Analgesic nephropathy continues to be seen in countries where phenacetin-containing compound analgesic preparations are readily available. Adulterants in unregulated herbal and traditional medicaments pose a threat of toxic interstitial nephritis, as exemplified by aristolochic acid contamination of herbal slimming preparations. Contamination of food sources with toxins, such as an outbreak of nephrolithiasis and acute kidney injury 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. In particular, nephropathies with features of CIN have been increasing in prevalence among Pacific coastal plantation workers in Central America (Mesoamerican nephropathy), Sri Lanka (Sri Lankan nephropathy), and southern India (Uddanam nephropathy). Together, these disorders have been called chronic interstitial nephritis of agricultural communities (CINAC) and may be related to repetitive episodes of heat exposure, dehydration, and volume depletion in the field workers. However, toxins, pesticides, and infective agents also remain as possible etiologic agents. Global warming and regional temperature variability have been proposed as contributors to these newly described forms of kidney disease, and tens of thousands of lives have been lost due to ESRD in these resource-poor areas in which renal replacement therapy is often not an option.

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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. 278**). 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, organomegaly, endocrinopathy, 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 neurologic involvement can be 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 aphasia, 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 chemoattractant 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-acetylneurameric 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.

aHUS or complement-mediated HUS is the result of complement dysregulation. The complement dysregulation can be congenital or acquired. The affected patients often have low C3 and 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 (CFH)-related protein 1 (CFHR1), CFHR3, CFHR5, and thrombomodulin, have also been reported. Finally, an autoimmune variant of aHUS, 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 of 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. TTP can be congenital from ADAMTS13 mutation (cTTP) or acquired from autoantibody against ADAMTS13 protein (iTTP).

cTTP, also known as Upshaw-Schulman syndrome, is characterized by congenital deficiency of ADAMTS13. cTTP 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 cTTP. Plasma transfusion is an effective strategy for prevention and treatment. In iTTP, autoantibody to ADAMTS13 (IgG or IgM) either increases its clearance or inhibits its activity. Data from the Oklahoma TTP/HUS Registry suggest an iTTP incidence rate of 2.9 cases/10⁶ patients in the United States. The median age of onset is 40 years. The incidence is more than nine times higher among blacks than nonblacks. Like that of systemic lupus erythematosus, the incidence of iTTP is nearly three times higher among women than among men. If untreated, iTTP has a mortality rate exceeding 90%. Even with modern therapy, 20% of patients die within the first month from complications of microvascular thrombosis.

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., proteasome inhibitors [bortezomib, carfilzomib, and ixazomib], mitomycin C, and 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 (quinine). 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

Hemolytic-Uremic Syndrome/Thrombotic Thrombocytopenic Purpura

Treatment should be based on pathophysiology. iTTP 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. The use of caplacizumab, a monoclonal antibody fragment that binds to the A1 domain of von Willebrand factor, blocking its interaction with platelets, was recently shown to improve platelet count recovery and reduce the composite risk of death, disease exacerbation, and thromboembolic events. It is now approved for use in iTTP in conjunction with plasma exchange and immunosuppressive therapy. Plasma infusion is usually sufficient to replace the ADAMTS13 in cTTP. Plasma exchange should be considered if larger volumes are necessary.

Plasma infusion/exchange is effective in certain types of aHUS because it replaces complement-regulatory proteins. Eculizumab and ravulizumab, anti-C5 monoclonal antibodies, are approved for use in aHUS, and have 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. Combined factor H and ADAMTS13 deficiency has been reported. The affected patients are generally less responsive to plasma infusion, an outcome that illustrates the complexity of the management of these cases.

Drug-induced TMA secondary to endothelial damage typically does not respond to plasma exchange and is treated primarily by discontinuing the use of the agent and, if refractory, a trial of C5 inhibitors. 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 may decrease the duration of bacterial shedding in adults.

HEMATOPOIETIC STEM CELL TRANSPLANTATION-ASSOCIATED THROMBOTIC MICROANGIOPATHY

Hematopoietic stem cell transplantation (HSCT)-associated TMA develops after allogeneic 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 317-1** lists definitions of HSCT-TMA currently used for clinical trials. Diagnosis may be difficult since thrombocytopenia, anemia, and renal

TABLE 317-1 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 above baseline
A sudden and persistent increase in LDH	Negative direct and indirect Coombs test
Decrease in hemoglobin or increased RBC transfusion requirement	Concurrent renal and/or neurologic dysfunction without other explanations
Decrease in haptoglobin concentration	

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

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) are recommended. There are increasing reports of successful use of eculizumab, but clinical trial data are lacking.

HIV-RELATED THROMBOTIC MICROANGIOPATHY

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. Angiotensin II receptor antagonists are less effective at preventing renal failure; thus, they are only recommended if the patient is intolerant of ACE inhibitors. ACE inhibition alone does not prevent scleroderma renal crisis, but it does reduce the impact of hypertension. In addition, it has been observed that patients on ACE inhibitors have a higher renal recovery rate after initiation of dialysis, and thus, ACE inhibitors are continued even after starting dialysis. 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. Bosentan (endothelin-1 antagonist) and eculizumab have both been investigated for use in this disease.

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (Chap. 357) 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-2 glycoprotein I antibodies (anti-2GPI). Patients with both anticardiolipin antibodies and anti-2GPI 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, a condition recently found to be pathophysiologically linked to uncontrolled complement activation. 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 thrombosis may form in the vascular access and the renal allografts. Hypertension is common. Treatment entails lifelong anticoagulation; however, neither safety nor effectiveness of novel oral anticoagulants has been established. 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. More recently, the efficacy of rituximab has been reported in several cases. A pilot phase 1/2 study has shown rituximab to be safe in these patients. Similarly, eculizumab had been shown to be efficacious in reversing the acute kidney injury in a number of cases, including in patients with catastrophic antiphospholipid syndrome. Some of these patients were refractory to rituximab. Further studies are needed for both of these medications.

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% occur postpartum. 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 Purtzscher-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; in addition, complement gene mutations and complement pathway dysfunction 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 (<10%). 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 postpartum. 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. Eculizumab has been reported to be effective in a small number of cases, but dosing, efficacy, and indications remain undetermined.

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), 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 is 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. Extramedullary hematopoiesis can sometimes be seen, especially in patients with myelofibrosis. MPN-related glomerulopathy may develop while patients are on treatment with hydroxyurea and JAK2 inhibitors. No standard treatment is available. Renin-angiotensin system 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 motor-sensory deficit is the hallmark of the disease. Patients also commonly have elevated IL-6 and vascular endothelial growth factor (VEGF) levels at diagnosis. Another characteristic is that >95% of monoclonal light chain is of the lambda isotype. IgA also makes up ~50% of the monoclonal proteins involved. 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 volumetric 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 increasing 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. CRISPR gene editing therapy was used for the first time in a patient with sickle cell anemia in 2019; long-term results of this novel therapy are pending.

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.

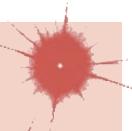
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Nephrolithiasis

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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 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 B₆ 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, whereas calcium phosphate stones are more likely to form when the urine pH is >6.5. 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 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 ureteropelvic 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. 318-1). 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. 318-2). Helical CT detects stones as small as 1 mm that may be missed by other imaging modalities.

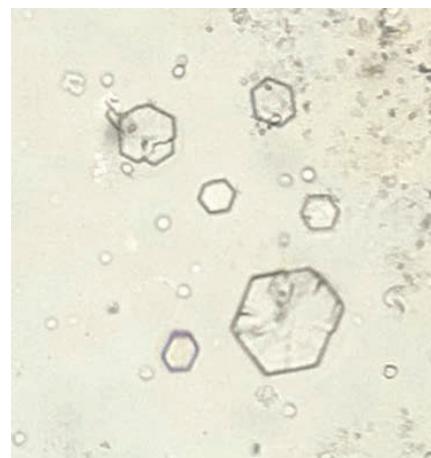
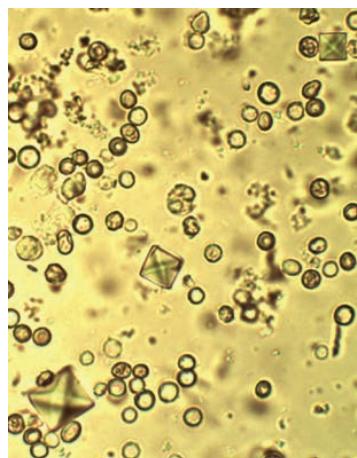


FIGURE 318-1 Urine sediment from a patient with calcium oxalate stones (*left*) and a patient with cystine stones (*right*). Calcium oxalate dihydrate crystals are bipyramidal shaped, and cystine crystals are hexagonal. (*Left panel* image courtesy of Dr. Mark Perazella, Yale School of Medicine; *Right panel* image courtesy Dr. John Lieske, Mayo Clinic.)

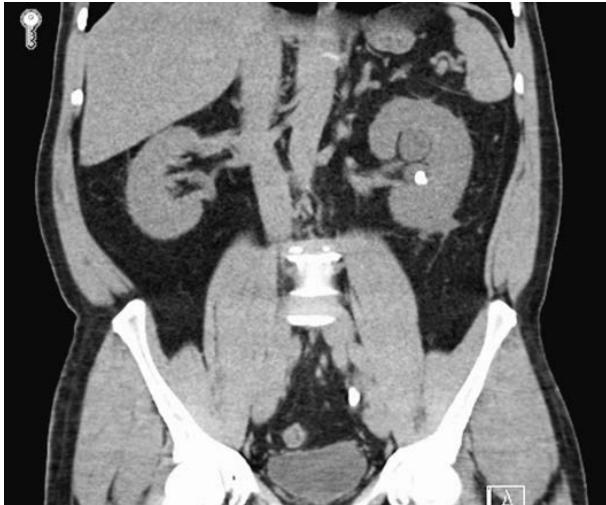


FIGURE 318-2 Coronal noncontrast CT image from a patient who presented with left-sided renal colic. An obstructing calculus, present in the distal left ureter at the level of S1, measures 10 mm in maximal dimension. There is severe left hydronephrosis and associated left perinephric fat stranding. In 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.)

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 [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.

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 euvoolemia. 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 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 shockwaves 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 nephrolithotomy 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, gastric bypass surgery and other malabsorptive conditions, 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. 25-Hydroxy vitamin D should be 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. 318-1), 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 renal-limited 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 less sensitive, renal ultrasound 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 and calculated urine supersaturation 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/d.

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 compared 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 only observational data to suggest 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). Second, 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 urine citrate. 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. Alkalizing 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 alkalization 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 typically annually, 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 the 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.

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319 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. Because 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 pyelocalveal system (*hydronephrosis*) occurs; lesions at or below the level of the bladder cause bilateral involvement.

Common forms of obstruction are listed in Table 319-1. 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, particularly follicular, and pelvic or colonic neoplasms with retroperitoneal involvement are causes of ureteral

TABLE 319-1 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
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 agonists	
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		

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 dynamic ureter, and vesicoureteral reflux. Reflux in children may result in severe unilateral or bilateral hydrourter and hydronephrosis. Overflow urinary incontinence combined with sudden-onset fecal incontinence, severe lower back pain, and saddle anesthesia, requires emergency evaluation for possible 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 319-2**. 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. 318**), 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 pre-renal 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

TABLE 319-2 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.

of transport proteins including the Na^+ , K^+ adenosine triphosphatase (ATPase), Na:K:2Cl cotransporter (NKCC2) 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 E₂ (PGE₂) (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. Nitric oxide synthases (NOS) in ureteral smooth muscle and urothelial tissues have been found to oppose the high ureteral pressure in unilateral obstruction.

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.

DIAGNOSIS

A history of difficulty in voiding, pain, infection, or change in urinary volume is common. Evidence for distention of the kidney or urinary bladder can often be obtained by palpation and percussion of the abdomen. A careful rectal and genital examination may reveal enlargement or nodularity of the prostate, abnormal rectal sphincter tone, or a rectal or pelvic mass.

Urinalysis may reveal hematuria, pyuria, and bacteriuria. The urine sediment is often normal, even when obstruction leads to marked azotemia and extensive structural damage. An abdominal scout film, although insensitive, may detect nephrocalcinosis or a radiopaque stone. As indicated in Fig. 319-1, if UTO is suspected, a bladder catheter should be inserted. Abdominal ultrasonography should be performed to evaluate renal and bladder size, as well as pyelocalveal 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 <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.

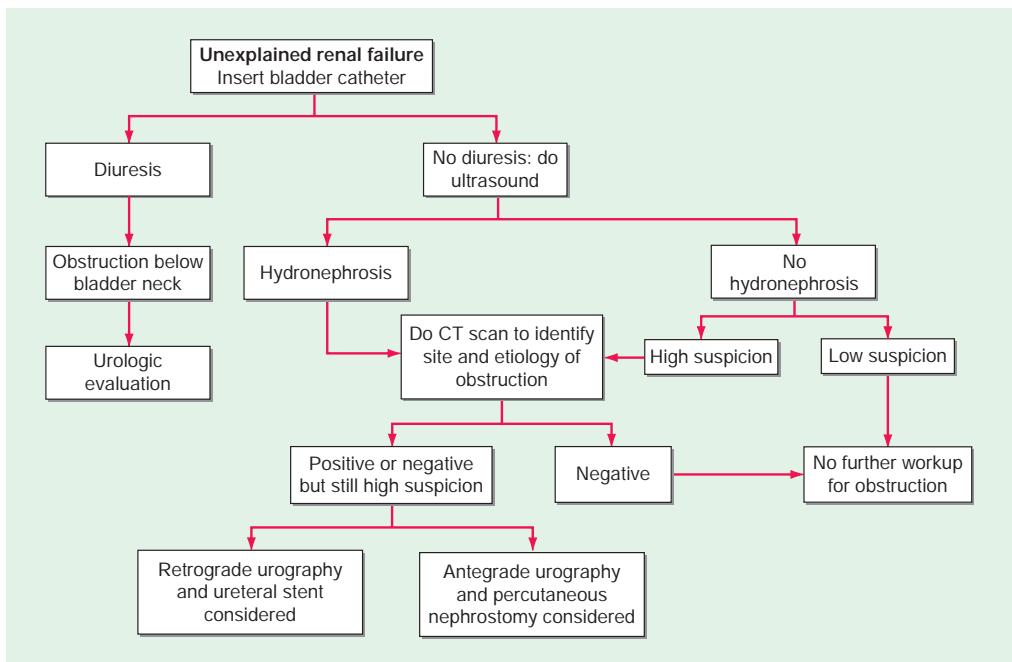


FIGURE 319-1 Diagnostic approach for urinary tract obstruction in unexplained renal failure. CT, computed tomography.

Recent advances in technology have led to alternatives and have replaced the once standard intravenous urogram in the further evaluation of UTO. The high-resolution multidetector row computed tomography (CT) scan in particular has the 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 not at this time superior to the CT scan and certain gadolinium agents carry a risk of systemic sclerosis in patients with renal insufficiency. Recently, promising alternatives to gadolinium have emerged. 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. Though radionuclide scans give less anatomic detail than CT scans, they are able to give differential renal function. In the case of asymmetric renal function, the clinician may decide on a preferable kidney to decompress in the case of bilateral obstruction. 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 5 α -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. The clinician should be aware of the risk of intraoperative floppy iris syndrome associated with cataract surgery in patients taking α -adrenergic blockers. Use of nonsteroidal anti-inflammatory medication must take into account the potential for renal harm, and 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 that increases the urine volume of electrolyte-free water. Electrolyte-free water excretion (hypotonic urine) is recognized as being present when the sum of the urinary concentrations of sodium and potassium, is lower than the serum sodium concentration. Causes include suppression of antidiuretic hormone at arterial baroreceptor sites or elevation of atrial peptides, and nephrogenic diabetes insipidus due to obstructive tubular injury. 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.

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Interventional nephrology is a procedure-oriented subspecialty with a focus on dialysis access for peritoneal and hemodialysis, typically performed under fluoroscopy. Ultrasound (US) evaluation of dialysis access is common and some practitioners perform renal and renal artery US evaluation as well as renal biopsies. Endovascular creation of arteriovenous fistulas (AVFs) is a recent addition to the procedural spectrum; (open) surgical access creation by nephrologists is limited to very few centers in the United States, while common in China, Germany, India, and Italy.

Interventional nephrologists (INs) usually provide patient care in multidisciplinary teams that include clinical nephrologists; access surgeons with vascular, transplant, or general surgery background; other interventionalists (with radiology or cardiology training); and dialysis unit access coordinators, nurses, and technicians involved in needle placement. Long-term preservation of venous and arterial vascular access options is one tenet of chronic kidney disease (CKD) care, leading INs to advocate for specific vascular access options (tunneled small-diameter catheters over peripherally inserted central catheters [PICCs] and cardiac devices (epicardial rather than endovascular lead passage).

HISTORY

The history of vascular access for hemodialysis is closely tied to the history of dialysis. The first hemodialysis treatments in humans were performed in 1924 using glass needles to access the radial artery and return blood into the cubital vein. In 1943 a “rotating drum kidney” was used to dialyze a 29-year-old housemaid with CKD by surgical exposure of different arteries until she ran out of access sites after 12 treatments. The challenge of repetitive vascular access prevented dialysis from becoming a routine method for the treatment of CKD until the development of an arteriovenous Teflon shunt and then the development of an autogenous arterial-venous access (arteriovenous fistula, AVF) by side-to-side-anastomoses between the radial artery and the cephalic vein at the wrist (Cimino fistula). Catheter-based approaches for chronic renal replacement therapy (RRT) were designed initially in 1961 for hemodialysis and in 1968 for peritoneal dialysis, both using Dacron felt cuffs to protect against infection.

Material sciences have continued to evolve the development of grafts for use in hemodialysis. A modified bovine carotid artery biological graft was introduced in 1972, followed by the use of expanded polytetrafluoroethylene (ePTFE) grafts in 1976, and, most recently in 2016, tissue-engineered blood vessels from human fibroblasts and endothelial cells. Some ePTFE grafts are modified with a silicone layer to allow for early cannulation within days of insertion. Ultra-high-pressure (up to 40 atm) angioplasty balloons are a mainstay of peripheral and central venous therapy, and Nitinol self-expanding stents and stent grafts serve as rescue tools for unsuccessful angioplasty as well as vessel rupture with extravasation.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF DIALYSIS ACCESS

Peritoneal Dialysis Peritoneal dialysis (PD) catheters can be placed fluoroscopically, peritoneoscopically, laparoscopically, and open surgically. Procedural success is typically linked to provider experience and procedural planning to optimize positioning of the PD catheter coil as this improves function and decreases drain pain and other complications. The internal cuff is placed within the rectus sheath just laterally to the linea alba, while the external PD catheter cuff should be located 2–4 cm from the skin exit site. Ingrowth of both cuffs ensures secure positioning of the catheter and allows water emersion. Over time the peritoneal catheter can become encased in a fibrous sheath, which, if limiting fluid flow during exchanges, can be disrupted by

guidewire manipulation. Omental entrapment of the catheter often requires laparoscopic intervention; omentopexy at the time of PD catheter placement can prevent later entrapment. Repeated infections affect the permeability of the peritoneal membrane, as does long-term exposure to glucose-containing exchange solutions. Encapsulating peritoneal sclerosis is a late-stage complication of PD thought to be triggered by repeated peritonitis.

Hemodialysis Catheters Dialysis catheters are typically made of polyurethane that softens at body temperature but is sufficiently strong to allow for blood flow rates of 400–500 mL/min in each of two channels inside a 14.5–16 French design without collapse of the catheter lumen. Tunneled catheters have a cuff that creates a barrier between skin flora at the exit site and the sterile catheter tunnel leading into the fibrous sheath covering the catheter from the vessel insertion point to its tip. The fibrous sheath can extend too far, impeding catheter flow and necessitating exchange of the catheter with disruption of the sheath by balloon angioplasty. Catheter-related bacteremia is best treated with exchange of the catheter and disruption of any fibrous sheath, although removal of the catheter and delayed reinsertion after several days is also successful. Thrombotic occlusion and later sclerotic scarring of the vein at catheter insertion sites is common, however, and removal of a catheter may lead to loss of this access site. Catheter wall contact points are thought to lead to central vein stenosis, which is more commonly observed in patients with catheter contact times of longer duration (>3 months). Catheter tip position in the large central veins instead of the right atrium causes additional injury from dynamic blood movement during dialysis treatments and should be corrected. A thrombus is commonly found attached to the catheter, often tethering the catheter to the vessel wall and right atrium. While some thrombi are mobile and dissolve with anticoagulation, a wall-tethered thrombus is often well organized with cellular components and quite resistant to pharmacologic lysis. Clinically significant pulmonary embolism from catheter-associated thrombus is rare, and it may be that only intra-atrial thrombus >2 cm in diameter deserves active intervention.

ARTERIOVENOUS GRAFTS AND FISTULAS

During the first decades of hemodialysis for loss of renal function, US patients were relatively young and without long-term systemic vascular disease. Creation of forearm Cimino AVFs was common, and access failure usually led to creation of a second AVF slightly higher up on the arm. As diabetes and hypertension with associated systemic arterial and venous vascular disease became more prevalent in the CKD population, placement of nonautogenous accesses (arteriovenous grafts [AVGs]) increased. In the mid-1990s, 65% of prevalent dialysis patients used an AVG for access. The US was an international outlier in this regard, and studies associated increased mortality in US dialysis patients with lower AVF prevalence. In the context of “Fistula First” and then “Fistula First, Catheter Last” campaigns, AVG prevalence decreased to its current value of less than 20%, while AVFs increased to near 65% prevalence. However, most centers still struggle with the challenging conditions of arteries and veins in these patients requiring that 75% of AVFs are now created in the upper arm, where the veins a priori are larger in diameter, and arteries can deliver higher blood flow rates due to large vessel diameter (see Fig. 320-1).

To provide successful dialysis, an AVF or AVG has to provide at least the desired blood pump speed (see Chap. 312) plus 100–200 mL/min to minimize recirculation and prevent collapse of the access. In the United States, this usually means flow in the 600–800 mL/min range. After creation of the arterial-venous anastomosis (or insertion of the AVG), blood flow increases significantly: brachial artery flow at rest is typically <50 mL/min, but after access creation flow volume in AVFs increases within weeks to 800 mL/min, while flow volume in AVGs increases within minutes to 1000 mL/min. The increased flow changes the arterial shear stress profile and leads to enlargement of the artery over time. In AVGs, this process is limited by the graft itself, which typically is 6 mm in diameter and 35–40 cm long, and access flows are 1200–1800 mL/min. The access vein in AVFs in the right shear stress environment enlarges over time, often to >10 mm in diameter in the

**A****C****B****D**

FIGURE 320-1 Dialysis access health depends on intra-access pressures and needle insertions. **A.** A right upper arm brachial-cephalic arteriovenous fistula (AVF) with two recurrences of clinically relevant inflow stenosis in 4 years has low-normal intra-access pressure before and after angioplasty; there is only minimal needle insertion site enlargement. **B.** In contrast, a right upper arm brachial-cephalic AVF with seven recurrences of cephalic arch outflow stenosis in 4-year cycles between states of high-normal to high intra-access pressures with notable needle insertion site enlargement. **C.** Focal needle insertions despite available graft segments led to penetrating skin ulcers over 3 years. **D.** Segmental needle rotation preserves skin integrity even after 7 years of arteriovenous graft (AVG) use.

upper arm such that the artery continues to enlarge until a narrow segment in the venous conduit becomes flow limiting. Flow volumes in these mature upper arm AVFs are usually 1400–1800 mL/min, but after a few years can be as high as 2000–4000 mL/min. Forearm AVFs usually have lower flow volumes (600–800 mL/min) as the feeding radial artery is of smaller diameter, and in the context of systemic vascular disease in the United States, only increases in diameter over many years.

Increased flows and pressure in the venous segment of the access circuit combine to lead to “chronic dialysis access disease” that manifests differently for each type of the common long-term accesses in predetermined segments particularly prone to shear stress and needle insertion-related injury. AVGs develop venous anastomotic stenoses that recur with very short periodicity in the 3- to 4-month range. Stent grafts can effectively be deployed to extend patency for usually 1 year at the site, after which the buildup of pauci-cellular fibrous depositions at the stent edges requires re-angioplasty one to three times per year. Forearm radial-cephalic autogenous accesses are most prone to low flow due to juxta-anastomotic stenoses. Over time, these stenoses can stabilize, and with enlargement of the inflow artery, they effectively provide protection against excessive flows and their sequelae. Upper arm brachial-cephalic autogenous accesses typically develop stenoses in the cephalic arch, which recur in accelerated fashion after each angioplasty. Flexible stent grafts in the cephalic arch extend intraprocedural intervals usually to 9–12 months. Upper arm transposed brachial-basilic autogenous accesses develop stenoses in the swing point where the basilic vein is curved to provide a location more lateral and closer to the skin to facilitate ready cannulation. Angioplasty and stent graft placement approaches extend patency. In both types of upper arm accesses, there are often prolonged periods with increased intra-access pressures due to outflow stenoses, which lead to enlargement of needle insertion site aneurysm as the skin heals in a pressurized, stretched state. Continued use of pressurized accesses leads to enlargement of needle sites, then thinning of the skin, scab formation, and, finally, full thickness ulceration with often significant bleeding events. Recognizing the occurrence of outflow stenoses early is an important skill for nurses and technologists working in dialysis units to learn in order to avoid irreversible loss of skin coverage, which can result in loss of the access.

High-access flow can lead to systemic complications, such as heart failure and pulmonary hypertension. Fistula inflow higher than outflow capacity leads to accelerated aneurysm formation and breakdown of skin coverage as intra-access pressures are increased over the ideal pressure of 20–35 mmHg. High-access flows are also associated with steal syndrome, typically ischemia of the hand. A variety of procedures have been described to reduce access flows, the most common being “banding,” where a 2-0 Prolene suture is guided around the inflow and a 3- or 4-mm spacer once or twice and is tied snugly over the spacer.

APPROACH TO THE PATIENT

Physical Examination of Dialysis Access

The 2019 KDOQI vascular access guidelines were developed under the tenet, “[t]he right access for the right patient at the right time.” Progression of CKD is highly variable, many patients die from other causes before reaching end-stage renal disease (ESRD), and some AVFs require 6–12 months to mature to usability in patients with HTN and diabetes leading to uncertainty as to when to create AVFs. The more common need of upper arm accesses for interventions to maintain patency favors the creation of forearm accesses during the pre-ESRD period. The processes of care from vein mapping, surgery, follow-up visits after access creation, to availability and timing of open surgical or endovascular interventions have profound effects on the overall success rate needed to achieve mature and usable accesses, and appear to be key factor with highly variable outcomes across the United States.

A central skill in dialysis access evaluation is the physical examination. Five aspects capture all aspects of possible pathology: Pulsatility reflects the force of access expansion during systole and the degree of softening during diastole. Very high blood pressures will suggest increased pulsatility, but the access softens remarkably during diastole. An outflow stenosis will lead to increased pulsatility and reduced softening during diastole. An inflow stenosis will blunt with the systolic component and create the impression of an “empty” access during diastole unless there is a coexisting outflow stenosis. The audible flow murmur can be characterized by pitch

and continuity ([Video 320-1](#)). A change in pitch toward higher frequency is typical at the site of a stenosis due to accelerated flow velocity at this site. A discontinuous flow murmur indicates that during diastole flow is so low that no audible shear force is created; this is the sign of a severe inflow or outflow stenosis. Typically, the stenotic inflow murmur is faint (like a whistle), whereas the stenotic outflow murmur can be coarse and loud (akin to a handsaw) ([Video 320-2](#)). A **thrill** is palpable through the skin when the vessel is close enough to the surface and the flow high enough in relation to the diameter of the vessel to create vibration of the vessel wall. A continuous thrill can be a sign of a well-developed access, usually in the inflow segment, dissipating as the access vessel branches and takes a deeper course. In contrast, a discontinuous thrill is found with severe stenosis. An isolated thrill is also found focally immediately after a stenosis. The differentiation from a “healthy” thrill can be made by documenting a change in pulsatility at the site of the focal thrill, increased retrograde (inflow) and decreased antegrade (outflow). **Augmentation** is the engorgement of the body of the access (where needles are inserted) with occlusion of the outflow necessary for safe and successful needle insertions. An inflow stenosis will impair augmentation as will side-branches and collaterals between the occluding finger/tourniquet and the inflow. The location of side-branches can be elucidated by moving the occluding finger closer toward the anastomosis until augmentation is achieved. With several collaterals, this may be a staged phenomenon. **Collapse of the access** with arm elevation (against gravity) is a measure of inflow and outflow capacity match or mismatch. A forearm access typically displays complete collapse while upper arm accesses typically show only partial collapse. An outflow stenosis or very high inflow will decrease the degree of collapse; banding of an upper arm access or a natural flow limiting stenosis may lead to complete collapse of an upper arm access.

Enlarged needle insertion sites (and any sites of suspected skin thinning) are best examined while occluding inflow: the completely empty access allows palpation of a firm, layered thrombus inside aneurysms as well as a better appreciation of the thickness of the overlying skin by rolling it between thumb and index finger. The chest wall and neck should be inspected for the presence of skin veins and venous distention, which are associated with central venous stenosis or occlusion, as is ipsilateral arm edema.

PRESERVATION OF VENOUS “REAL ESTATE”

Preserving access is a key care component for the patient with advancing CKD. Approximately 8–10% of this population has the need for cardiac rhythm management devices (CRMDs) that can

lead to loss of the upper arm cephalic vein as well as central venous stenoses and occlusions around device leads. Planning for which side a future autogenous access is to be placed and where a CRMD is located is recommended in all cases. CKD patients also have an increased frequency of hospitalizations, some of which require intravenous access beyond the hospital stay for antibiotics, nutritional support, or hydration. Avoiding PICCs in a patient with CKD stage 3 or 3b, and, instead, using internal (or external) jugular vein tunneled small-diameter catheters preserves arm veins for long-term access creation. Arterial access points for cardiac procedures should be chosen with AVF creation in mind.

Approach to the dialysis access of patients with a kidney transplant depends on the function of the transplanted kidney, the risk of recurrence of kidney disease in the transplant, the ability to limit access flow over time while maintaining patency, as well as the potential benefit of the AVF for blood pressure control.

FURTHER READING

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- Lok CK et al: KDOQI clinical practice guideline for vascular access: 2019 update. *Am J Kidney Dis* 75 (4 Suppl 2):S1, 2020.
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VIDEO 320-1 Flow murmur of an upper arm brachial-cephalic autogenous access (AVF) with a juxta-anastomotic stenosis. The sound is discontinuous as the stenosis is severe enough that only during systole is the flow volume high enough to create audible turbulence. There also is a high-pitch component of the murmur due to the high flow velocity during the peak of the flow cycle.

VIDEO 320-2 Flow murmur of an upper arm brachial-cephalic autogenous access (AVF) with a juxta-anastomotic stenosis after angioplasty. The sound is now continuous with systolic-diastolic modulation. There is an even pitch, overall lower than the pitch associated with peak flow in the setting of an untreated stenosis.