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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 recipi ents increase. More than 30% of kidney transplant recipient mortality 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) rejec tion 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. Calcium channel blockers are shown to improve long-term mortality. Ameliora tion 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 hyper plastic parathyroid glands to regress. Aseptic necrosis of the head of the femur when it occurs is probably due to preexisting hyperparathy roidism, 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 eryth ropoietin 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. Gastroin testinal 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 persis tently 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 sig nificantly toward the goals of longer patient survival and better qual ity 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. ■ ■FURTHER READING Allen PJ et al: Recurrent glomerulonephritis after kidney transplanta tion: Risk factors and allograft outcomes. Kidney Int 92:461, 2017. Chadban SJ et al: Summary of the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on the evaluation and management of candidates for kidney transplantation. Transplanta tion 104:708, 2020. Chapman JR et al: Cancer in the transplant recipient. Cold Spring Harb Perspect Med 3:pii:a015677, 2013. Euvrard S et al: Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Engl J Med 367:329, 2012. Grams ME et al: Kidney-failure risk projection for the living kidneydonor candidate. N Engl J Med 374:411, 2016. Hariharan S et al: Long-term survival after kidney transplantation. N Eng J Med 385:729, 2021. Hirsh HH et al: BK polyomavirus in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 33:e13528, 2019.

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Glomerular Diseases Two human kidneys harbor nearly 1.8 million glomerular capillary tufts. Each glomerular tuft resides within Bowman’s space. The cap sule 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 capil lary bed embedded in mesangial matrix (Fig. 326-1). 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. CHAPTER 326 Glomerular Diseases The glomerular capillaries filter 120–180 L/d of plasma water con taining 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 elec trostatic charge. The mechanics of filtration and reclamation are quite complicated for many solutes (Chap. 320). For example, in the case of serum albumin, the glomerulus is an imperfect barrier. Although albu min 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 dis eases into a smaller number of clinical syndromes. PATHOGENESIS OF GLOMERULAR DISEASE There are many forms of glomerular disease with pathogenesis variably linked to the presence of genetic mutations, infection, toxin exposure, autoimmunity, atherosclerosis, hypertension, emboli, thrombosis, or diabetes mellitus. Even after careful study, however, the cause often remains unknown, and the lesion is called idiopathic. Specific or unique features of pathogenesis are mentioned with the description of each of the glomerular diseases later in this chapter. Some glomerular diseases result from genetic mutations producing familial disease or a founder effect: congenital nephrotic syndrome from mutations in NPHS1 (nephrin) and NPHS2 (podocin) affects the slit-pore membrane at birth, and TRPC6 cation channel muta tions produce focal segmental glomerulosclerosis (FSGS) in adulthood;

A B C PART 9 Disorders of the Kidney and Urinary Tract D FIGURE 326-1 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.) polymorphisms in the gene encoding apolipoprotein L1, APOL1, are a major risk for nearly 70% of African Americans with nondiabetic end-stage kidney disease (ESKD), 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 membranoprolif erative 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 PPARγ causes a metabolic syndrome associated with MPGN; IgG3 subclass antibodies to antigens expressed on podocytes encoded by PLAR2gc indicate a poor prognosis in membranous nephropathy; Alport’s syndrome, from mutations in the genes encoding for the α3, α4, or α5 chains of type IV collagen, produces split basement membranes with glomerulosclerosis; and lysosomal storage diseases, such as α-galactosidase A deficiency causing Fabry’s disease and N-acetylneuraminic acid hydrolase deficiency causing nephrosialido sis, 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 microangi opathy, and acute kidney 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 glomerulone phritis. Most glomerular or mesangial antigens involved in immunemediated glomerulonephritis are unknown (Fig. 326-2). 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 second ary glomerular injury. Antiglomerular basement membrane disease producing Goodpasture's syndrome primarily injures both the lung and kidney because of the narrow distribution of the α3 NC1 domain of type IV collagen that is the target antigen. Local activation of Toll-like receptors on glomerular cells, deposi tion of immune complexes, or complement injury to glomerular struc tures 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 mol ecules engage the CD4/8 T-cell repertoire. Mononuclear cells by themselves can injure the kidney, but auto immune 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 pro duce the linear binding of anti-GBM disease. Preformed circulating immune complexes can precipitate along the subendothelial side of the GBM, while other immune deposits form in situ on the subepithelial side. These latter deposits accumulate when circulating autoantibodies find their antigen trapped along the subepithelial edge of the GBM. Immune deposits in the glomerular mesangium may result from the deposition of preformed circulating complexes or in situ antigenantibody 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. Overlap ping etiologies or pathophysiologic mechanisms can produce similar

Basement membrane Subepithelial deposit Endothelia Podocytes Subendothelial deposit Linear IgG staining IgG Lumpy-bumpy staining C B A TH1/2 Immune deposits Cytokines Chemokines Basement membrane damage Extracapillary proliferation Endocapillary proliferation Oxidants Proteases C3/C5-9MAC D FIGURE 326-2 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 antiIgG 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. glomerular lesions, suggesting that downstream molecular and cellular responses often converge toward common patterns of injury. PROGRESSION OF GLOMERULAR DISEASE Persistent glomerulonephritis that worsens kidney function is always accompanied by interstitial nephritis, renal fibrosis, and tubular atrophy. What is

not so obvious, however, is that kidney failure in glomerulonephritis best correlates histologically with the appearance of tubulointerstitial nephritis rather than with the type of inciting glomerular injury. Loss of kidney 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 neph rons. A second mechanism suggests that interstitial changes, including interstitial edema or fibrosis, alter tubular and vascular architecture

Mθ N Cytokines Chemokines CHAPTER 326 Glomerular Diseases 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 isosthenu ria 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. Con sequently, 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 capillar ies. The cross-sectional volume of these capillaries is decreased by interstitial inflammation, edema, or fibrosis. These structural altera tions in vascular resistance affect kidney function through two mecha nisms. First, tubular cells are very metabolically active, and as a result, decreased perfusion leads to tubular ischemic injury. Second, impair ment of glomerular arteriolar outflow leads to increased intravascular hypertension in less-involved glomeruli; this selective intraglomerular

hypertension aggravates and extends mesangial sclerosis and glomerulo sclerosis to less-involved glomeruli. Regardless of the exact mechanism, early acute tubulointerstitial nephritis (see Fig. A4-31) suggests poten tially recoverable kidney function, whereas the development of chronic interstitial fibrosis prognosticates permanent loss (see Fig. A4-25).

Persistent damage to glomerular capillaries spreads to the tubu lointerstitium in association with proteinuria. There is a hypothesis that efferent arterioles leading from inflamed glomeruli carry for ward inflammatory mediators, which induces downstream interstitial nephritis, resulting in fibrosis. Glomerular filtrate from injured glo merular capillaries adherent to Bowman’s capsule may also be misdi rected 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 devel opment 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 fibro blasts increase through several mechanisms: epithelial or endothelialmesenchymal transitions (15%), bone marrow–derived fibrocytes (35%), and the proliferation of resident fibroblasts (50%). Most renal myofibroblasts are formed from bone marrow fibrocytes or prolifer ating fibroblasts. Transforming growth factor β (TGF-β), fibroblast growth factor 2 (FGF-2), hypoxemia-inducible factor 1α (HIF-1α),

and platelet-derived growth factor (PDGF) are particularly active in this transition. With persistent nephritis, fibroblasts multiply and lay down tenascin and a fibronectin scaffold for the polymerization of new interstitial collagen types I/III. These events form scar tissue through a process called fibrogenesis. In experimental studies, bone morphogenetic protein 7 and hepatocyte growth factor can reverse early fibrogenesis and preserve tubular architecture. When fibroblasts outdistance their survival factors, apoptosis occurs, and the permanent renal scar becomes acellular, leading to irreversible kidney failure. PART 9 Disorders of the Kidney and Urinary Tract 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 work ing 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 necro sis, hypercalciuria, kidney stones, cystic kidney diseases, or renal vascular injury. However, when red blood cell casts (see Fig. A4-38) TABLE 326-1 Urine Assays for Albuminuria/Proteinuria 24-h ALBUMINa (mg/24 h) ALBUMINa/CREATININE RATIO (mg/g) DIPSTICK PROTEINURIA 24-h URINE PROTEINb (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.

or dysmorphic red blood cells are found in the sediment, glomerulo nephritis 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 kid ney disease. Screening spot urine albumin/creatinine ratio (UACR) of >30 mg/g suggests a need for further investigation. Greater than 300 mg/24 h of albuminuria represents frank proteinuria and more advanced kidney disease (Table 326-1). 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 popu lation. (Table 326-1). 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 pro teinuria 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 leuko cytes. This

latter finding has to be distinguished from urine infected with bacteria. CLINICAL SYNDROMES Various forms of glomerular injury can also be parsed into sev eral distinct syndromes on clinical grounds (Table 326-2). 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 reduc tion in glomerular filtration. If glomerular inflammation devel ops 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 progres sive glomerulonephritis (RPGN); the histopathologic term crescen tic 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 diag nosed as having a pulmonary-renal syndrome. Nephrotic syndrome describes the onset of heavy proteinuria (>3.0 g/24 h), hyperten sion, hypercholesterolemia, hypoalbuminemia, edema/anasarca, and microscopic hematuria; if only large amounts of proteinuria are present without clinical manifestations, the condition is sometimes called nephrotic-range proteinuria. The glomerular filtration rate (GFR) in these patients may initially be normal or, rarely, higher than normal, but with persistent hyperfiltration and continued nephron loss, it typically declines over months to years. Patients with a basement membrane syndrome either have genetically abnor mal basement membranes (Alport's syndrome) or an autoimmune

TABLE 326-2 Patterns of Clinical Glomerulonephritis GLOMERULAR SYNDROMES PROTEINURIA HEMATURIA VASCULAR INJURY Acute Nephritic Syndromes Poststreptococcal glomerulonephritisa +/++ ++/+++ – Subacute bacterial endocarditisa +/++ ++ – Lupus nephritisa +/++ ++/+++ + Antiglomerular basement membrane diseasea ++ ++/+++ – IgA nephropathya +/++ +++c – ANCA small-vessel vasculitisa Granulomatosis with polyangiitis (Wegener's) +/++ ++/+++ ++++ Microscopic polyangiitis +/++ ++/+++ ++++ Churg-Strauss syndrome +/++ ++/+++ ++++ Henoch-Schönlein purpuraa +/++ ++/+++c ++++ Cryoglobulinemiaa +/++ ++/+++ ++++ Membranoproliferative glomerulonephritisa ++ ++/+++ – C3 glomerulopathies ++ ++/+++ – Mesangioproliferative glomerulonephritis + +/++ – Pulmonary-Renal Syndromes Goodpasture's syndromea ++ ++/+++ – ANCA small-vessel vasculitisa Granulomatosis with polyangiitis (Wegener's) +/++ ++/+++ ++++ Microscopic polyangiitis +/++ ++/+++ ++++ Churg-Strauss syndrome +/++ ++/+++ ++++ Henoch-Schönlein purpuraa +/++ ++/+++c ++++ Cryoglobulinemiaa +/++ ++/+++ ++++ 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 diseasea ++ ++/+++ – Alport's syndrome ++ ++ – Thin basement membrane disease + ++ – Nail-patella syndrome ++/+++ ++ – Glomerular Vascular Syndromes Atherosclerotic nephropathy + + +++ Hypertensive nephropathyb +/++ +/++ ++ Cholesterol emboli +/++ ++ +++ Sickle cell disease +/++ +++c +++ Thrombotic microangiopathies ++ ++ +++ Antiphospholipid syndrome ++ ++ +++ ANCA small-vessel vasculitisa Granulomatosis with polyangiitis (Wegener's) +/++ ++/+++ ++++ Microscopic polyangiitis +/++ ++/+++ ++++ Churg-Strauss syndrome +++ ++/+++ ++++ Henoch-Schönlein purpuraa +/++ ++/+++c ++++ Cryoglobulinemiaa +/++ ++/+++ ++++ AL and AA amyloidosis +++/++++ + +/++ Infectious Disease–Associated Syndromes Poststreptococcal

glomerulonephritisa +/++ ++/+++ – Subacute bacterial endocarditisa +/++ ++ – HIV +++ +/++ –

CHAPTER 326 Glomerular Diseases (Continued)

TABLE 326-2 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. response to basement membrane collagen IV (Goodpasture's syn drome) 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 microangi opathy, 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. PART 9 Disorders of the Kidney and Urinary Tract These six general categories of syndromes are usually determined at the bedside with the help of a history and physical examination, blood chemistries, kidney 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, antiphospho lipid, 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 com ponents (C3 and C4). 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 fail ure, 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 ultrasound examination, and how the patient feels at presentation. Chronic glomerular disease often presents with decreased kidney size. Patients who quickly develop kidney failure are fatigued and weak and often have uremic symptoms associated with nausea, vomiting, fluid retention, and somnolence. Primary glomerulonephritis presenting with kidney failure that has progressed slowly, however, can be remarkably asymptomatic, as are patients with acute glomerulonephritis with out much loss in kidney 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 treat ment are encouraged to have a kidney biopsy. ■ ■KIDNEY PATHOLOGY A kidney 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 hematoxy lin 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 base ment membrane structure, Congo red for amyloid deposits, and Mas son'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 (C3 and C4), or specific antibod ies against a relevant antigen (PLA2R, THSD7A, and DNAJB9). Highresolution electron microscopy can clarify the principal location of immune deposits and the status of the basement membrane. Each region of a kidney biopsy is assessed separately. By light microscopy, glomeruli (ideally 20) are reviewed individually for dis crete 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 glom eruli show acellular, amorphous accumulations of proteinaceous mate rial 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 subepithe lial, 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 angiopa thy, 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 intersti tial fibrosis. Interstitial fibrosis is an ominous sign of irreversibility and progression to kidney failure. ACUTE NEPHRITIC SYNDROMES Acute nephritic syndromes classically present with hypertension, hema turia, 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 endo capillary proliferative glomerulonephritis. The incidence of poststrep tococcal glomerulonephritis has dramatically decreased in developed countries, and in these locations is typically sporadic. Acute nephritis in developing 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 particu lar 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 skin

infection. The kidney biopsy in poststreptococcal glomerulonephritis demon strates 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 immunemediated disease involving putative streptococcal antigens, circulating immune complexes, and activation of the alternate complement path way in association with cell-mediated injury. Leading candidate anti gens 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 deposits. The classic presentation is an acute nephritic picture with hema turia, pyuria, red blood cell casts, edema, hypertension, and oliguric acute kidney injury (AKI), 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 (~25%) but the strep tozyme test is positive in 80–95% of patients and includes antibodies to ASO, anti-DNAse, Altase, ASKase, and anti-NAD. Consequently, the diagnosis of poststreptococcal glomerulonephritis rarely requires a kidney 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. Treatment is supportive, with control of hypertension, edema, and dialysis as needed. Antibiotic treatment for active streptococcal infec tion should be given to patients and their cohabitants. There is no role for immunosuppressive therapy, even in the setting of crescents. Recur rent 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, non-nephrotic proteinuria, or hypertension. Overall, the prognosis is good, with ESKD being very uncommon in Glomerular schematic 1 Hump Poly Subendothelial deposits Mesangial deposits POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

children and adults. The prognosis in elderly patients is worse, with a high incidence of azotemia (up to 60%), nephrotic-range proteinuria, and ESKD.

■ ■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. Com mon 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 kidney biopsy reveals focal or diffuse proliferation with C3 (94%), IgG, and IgA staining, as well as mesangial, subendothelial, and subepithelial immune deposits. 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 deposi tion 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 kidney 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 kidney disease. Primary treatment is eradication of the infec tion with 4–6 weeks of antibiotics, and if accomplished expeditiously, the prognosis for kidney recovery is good. ANCA-associated vasculitis sometimes accompanies or is confused with SBE and should be ruled out, as the treatment is different. CHAPTER 326 Glomerular Diseases As variants of persistent bacterial infection in blood-associated glomerulonephritis, infection-associated glomerulonephritis can occur in patients with ventriculoatrial and ventriculoperitoneal shunts; pul monary, intraabdominal, pelvic, or cutaneous infections; and infected vascular prostheses. In developed countries, a significant proportion of cases afflict adults, especially the immunocompromised, and the pre dominant organism is Staphylococcus. The clinical presentation of these conditions is variable and includes proteinuria, microscopic hematuria, acute kidney injury, and hypertension. Serum complement levels are low, and there may be elevated levels of C-reactive proteins, rheuma toid factor, antinuclear antibodies, and cryoglobulins. Biopsy findings include membranoproliferative glomerulonephritis (MPGN), diffuse proliferative and exudative glomerulonephritis (DPGN), or mesangio proliferative glomerulonephritis, sometimes leading to RPGN. Treat ment 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 kidney disease are present in 30% of patients at the time of diagnosis, and the major ity will develop kidney abnormalities in the course of their disease. 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, leukocyte infiltration, activation of procoagulant factors, and release of various cytokines. In situ immune complex formation also plays a role in kidney 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 kidney pathology. The most common clinical sign of kidney disease is proteinuria, but hematu ria, hypertension, varying degrees of kidney injury, 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 kidney disease. Hypocomplementemia is common in patients with acute lupus nephritis (70–90%), and declining complement levels may

TABLE 326-3 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 hypercellularity with focal subendothelial immune deposits and mild mesangial

expansion ± fibrinoid necrosis Class IV Diffuse nephritis Diffuse endocapillary ± extracapillary hypercellularity with diffuse subendothelial immune deposits and mesangial alterations ± crescents ± fibrinoid necrosis 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. Recommendation for revision 2018. herald a flare. A kidney biopsy should be performed in most patients with kidney involvement to establish the histologic subtype, which guides therapy. PART 9 Disorders of the Kidney and Urinary Tract 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 version with ongoing refinement (Table 326-3) forms the basis for treatment recommen dations. Class I nephritis describes normal glomerular histology by normal light microscopy with minimal mesangial deposits on immu nofluorescent or electron microscopy. Class II designates mesangial immune complexes with mesangial proliferation. Both class I and II lesions are typically associated with minimal kidney manifestation and normal kidney function; nephrotic syndrome is rare. Patients with lesions limited to the renal mesangium have an excellent prognosis and need little or no 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 kidney diseases (see Figs. A4-14 and A4-15). Class III describes focal lesions involving <50% of the glomeruli with proliferation or scarring, often involving only a segment of the glomerulus. 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 kidney failure over 5 years. Patients with more severe proliferation involving a greater percentage of glomeruli or include fibrinoid necrosis 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, protein uria, hypertension, and decreased kidney function; 50% of patients have nephrotic-range proteinuria. Patients with crescents on biopsy often have a rapidly progressive decline in kidney function. Without treatment, this aggressive lesion has the worst kidney prognosis, with class IV-S worse than class IV-G. However, if a remission—defined as a return to near-normal kidney function and proteinuria ≤330 mg/dL per day—is achieved with treatment, kidney outcomes are excellent. 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. Voclosporin may also be used in combination with steroids and mycophenolate mofetil

in patients with focal or diffuse lupus nephritis. Belimumab can also be added to standard maintenance therapy. There is no consensus on use of high-dose intravenous methylprednisolone versus oral prednisone, monthly intravenous cyclophosphamide versus daily oral cyclophos phamide, or other immunosuppressants such as cyclosporine, tacroli mus, or rituximab. Prolonged use of cyclophosphamide is avoided in patients of childbearing age. The class V lesion describes subepithelial immune deposits produc ing 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. A4-14); this category of injury is treated like class IV glomerulonephritis. Sixty percent of patients pres ent with nephrotic syndrome or lesser amounts of proteinuria. Patients with lupus nephritis class V, like patients with primary membranous nephropathy, are predisposed to renal vein thrombosis and other thrombotic complications. A minority of patients with class V will present with hypertension and kidney dysfunction. There are conflict ing 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 immu nosuppressive agents. Therapy with inhibitors of the renin-angiotensin system also may attenuate the proteinuria. Antiphospholipid antibod ies present in lupus may result in glomerular microthromboses and a thrombotic microangiopathy. The kidney 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 kidney biopsy. Lupus patients with class VI lesions have >90% sclerotic glomeruli and ESKD 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. Kidney transplantation 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 anti-glomerular basement membrane (anti-GBM) disease. When they present with lung hemorrhage and glomerulonephritis, they have a pulmonary-renal syndrome called Goodpasture’s syndrome. The target epitopes for this autoimmune disease lie in the quaternary structure of α3 NC1 domain of collagen IV. Indeed, anti-GBM disease may be considered an autoimmune “conformeropathy” that involves the perturbation of quaternary structure of the α 345NC1 hexamer. MHCrestricted 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. Good pasture’s syndrome is rare and 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 hemoglo bin, fever, dyspnea, and hematuria, and older patients are more likely to present with isolated glomerulonephritis. Those who present with lung hemorrhage as a group do better than older populations who have prolonged, asymptomatic kidney 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 Goodpas ture’s syndrome to confirm the diagnosis and assess prognosis. Kidney 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. A4-17). As these lesions progress, there is concomitant interstitial nephritis with fibrosis and tubular atrophy.

The presence of anti-GBM antibodies and complement is recognized on biopsy by linear immunofluorescent staining for IgG (rarely IgA). In testing serum for anti-GBM antibodies, it is particularly important that the α3 NC1 domain of collagen IV alone be used as the target. This is because non-nephritic antibodies against the α1 NC1 domain are seen in paraneoplastic syndromes and cannot be discerned from assays that use whole basement membrane fragments as the binding target. Between 10 and 15% of sera from patients with Goodpasture’s syndrome also contain ANCA antibodies against myeloperoxidase. Prognosis at presentation is worse if there are >50% crescents on kid ney 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 hem orrhage, 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 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 nephrop athy. 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 30-45% prevalence along the Asian and Pacific Rim and 20% in southern Europe, compared to 10% 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 suscepti bility to it has been shown uncommonly to have a genetic component depending on geography and the existence of “founder effects.” No single causal gene has been identified. Clinical and laboratory evidence sug gests close similarities between IgA vasculitis (formerly called HenochSchonlein purpura) and IgA nephropathy. IgA vasculitis is distinguished clinically from IgA nephropathy by prominent systemic symptoms, a younger age (<20 years old), preceding infection, and abdominal com plaints. 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 kidney disease. IgA-dominant Staphylococcus-associated infectious glomerulo nephritis is associated with clinically significant kidney disease. The pathognomonic finding on kidney biopsy is dominant or codominant mesangial IgA deposits, either alone or with IgG, IgM, or complement. (See Glomerular Schematic 2.) IgA deposits are typically J-chain containing polymeric IgA1. Abnormalities in the O-glycosylation of the hinge region of primarily polymeric IgA1 seem to best account for the pathogenesis. Synthesis of poorly galactosyl ated 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 activating the complement system through the alternative and lectin pathways. Viral or other antigen exposure, or hereditary defects in alternative comple ment 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 kidney biopsy is necessary to confirm the diagnosis. Although the immunofluores cent pattern of IgA on kidney 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.

Glomerular schematic 2 Mesangial deposits plus more mesangial cells IgA NEPHROPATHY CHAPTER 326 The two most common presentations of IgA nephropathy are per sistent asymptomatic microscopic hematuria and recurrent episodes of macroscopic hematuria during or immediately following an upper respiratory infection, often accompanied by proteinuria. Nephrotic syndrome is uncommon. Proteinuria can also first appear late in the course of the disease. Rarely, patients present with acute kidney failure and a rapidly progressive clinical picture. IgA nephropathy can be a benign disease with some patients going into complete remis sion while others may have ongoing hematuria but well-preserved kidney function. Slow progression to ESKD is seen in only 25–30% of patients over 20–25 years. This risk varies considerably among populations. Cumulatively, risk factors for the loss of kidney func tion 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 hyper cellularity (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 kidney outcomes. Glomerular Diseases 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 kidney function. Steroid treatment or other immunosuppressives have demonstrated conflicting results. An oral targeted-release formulation of budesonide has been shown to reduce proteinuria and improve preserved kidney function in patients with risk of rapid progression. In preliminary studies the sodium-glucose transport-2 inhibitor (SGLT2i) dapagliflozin and the endothelin antagonist sparsentan have reduced adverse kidney outcomes. Tonsillectomy and fish oil have also been suggested in small studies to benefit select patients. When present ing 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 circu lating antineutrophil cytoplasmic autoantibodies (ANCAs); the most common antigen targets are proteinase 3 (PR3) and myeloperoxidase

(MPO) (Chap. 375). 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 (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), and renal-limited vasculitis belong to this group because they are associated with ANCAs and have a pauci-immune glomerulonephritis given the absence or paucity of immune complex deposition. Patients with any of these diseases can have any combi nation of the above serum antibodies, but anti-PR3 antibodies are more common in GPA, and anti-MPO antibodies are more common in MPA or EGPA. 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. Targeted determination of ANCA levels may be useful in monitoring response to therapy or if a relapse is clinically suspected. Since mortality is high without treatment, virtually all patients receive urgent treat ment. Induction therapy usually includes glucocorticoids and either cyclophosphamide or rituximab. Plasmapheresis remains controversial but is generally recommended in rapidly progressive kidney failure or pulmonary hemorrhage, or with concomitantly positive anti-GBM antibodies. Remission is induced in 75–90% of patients, but clinical relapse is common (25–50%). There is evidence to support a reduced dose corticosteroid regimen with discontinuation at 16 weeks recom mended. Additionally, novel complement antagonists may have a role as steroid sparing agents. Maintenance therapy is recommended for up to 1–2 years following remission and includes cyclophosphamide or rituximab, or in certain circumstances azathioprine or methotrexate.

PART 9 Disorders of the Kidney and Urinary Tract 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 kidney involvement, although most of these patients develop kidney 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. Kidney biopsies during active disease demonstrate segmental necrotizing glo merulonephritis without immune deposits and have been classified as focal, mixed, crescentic, or sclerotic (see Fig. A4-16). The disease is more common in patients exposed to silica dust and those with α1-antitrypsin deficiency, which is an inhibitor of PR3. Relapse after achieving remission is common and is more common in patients with GPA 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 is from adverse events often secondary to treatment rather than active vasculitis; this is particularly true in elderly patients in the first year of therapy. Patients should also be monitored long term for malignancy after immunosuppressive therapy. Microscopic Polyangiitis Clinically, these patients present simi larly to GPA, except they rarely have significant lung disease or destructive sinusitis. The distinction is made on biopsy, where the vasculitis in MPA is without granulomas. Some patients will also have injury limited to the capillaries and venules. Eosinophilic Granulomatosis with Polyangiitis When small-vessel vasculitis is associated with peripheral eosinophilia, cutaneous purpura, mononeuritis, asthma, and allergic rhinitis, a diagnosis of EGPA is considered. Hypergammaglobulinemia, ele vated levels of serum IgE, or the presence of rheumatoid factor some times 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 asso ciated with eosinophils. Small-vessel vasculitis and focal segmental necrotizing glomerulonephritis without immune deposits can be seen on kidney biopsy, usually absent of eosinophils or granulomas. The

cause of is thought to be abnormal immune function, 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). DDD is defined morphologically by dense deposits forming ribbons in the GBM. In the absence of this

specific morphology, the entity is catego rized as C3GN. Both are associated with the presence of a complement mutation believed to cause the kidney 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. Low serum C3 and a dense thickening of the GBM containing ribbons of dense despits and C3 characterize DDD (see Fig. A4-10). 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 ESKD. 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 com monly 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 thera pies remain undefined but include inhibition of the renin-angiotensin system, lipid lowering, steroids, and other immunosuppressants. Evi dence suggests a benefit of therapy with eculizumab, a monoclonal antibody directed at C5, which is activated by C3. ■ ■MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS MPGN has been previously identified as a disease with the classifica tion MPGN types I, II, and III; however, it is now considered a pattern of glomerular injury characterized by mesangial and subendothelial immune complexes, complement deposits and/or monoclonal protein deposits, or chronic endothelial cell injury. In addition to increased mesangial and endocapillary hypercellularity, there are thickened GBM’s with interposition of cellular elements between the endothelial cell and the GBM creating double contours, sometimes call “tramtracking” (see Fig. A4-9). (See Glomerular Schematic 3.) The MPGN pattern of injury can be seen with immune complex mediated diseases Glomerular schematic 3 Subendothelial deposits Widened mesangial Mesangial interposition Macrophage and mesangial cells MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

including cryoglobulinemia, infection associated GN, and hepatitis C and B; complement mediated diseases including inherited or acquired dysregulation of complement (see C3G Glomerulopathies); and mono clonal immunoglobulin mediated diseases including light and heavy chain deposition diseases. The MPGN pattern of injury can be seen with unusual deposits as well including fibrillary glomerulonephritis. Each of these diseases have distinct findings on biopsy, natural history and treatments. ■ ■MESANGIOPROLIFERATIVE GLOMERULONEPHRITIS Mesangioproliferative glomerulonephritis is characterized by expan sion of the mesangium, sometimes associated with mesangial hyper cellularity; 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 glomerulone phritis is made in <15% of kidney biopsies. NEPHROTIC SYNDROME Nephrotic syndrome classically presents with heavy proteinuria, mini mal hematuria, hypoalbuminemia, hypercholesterolemia, edema, and hypertension. If left undiagnosed or untreated, some of these syn dromes will progressively damage enough glomeruli to cause a fall in GFR, producing kidney 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 reten tion can be controlled with the use of diuretics, avoiding intravascular volume depletion. Venous complications secondary to the hyperco agulable 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 and SGLT2i can lower urinary protein excretion and preserve kidney func tion across a wide range of chonic kidney diseases. ■ ■MINIMAL CHANGE DISEASE MCD, sometimes known as nil lesion, causes 70–90% of nephrotic syn drome in childhood but only 10–15% of nephrotic syndrome in adults. MCD usually presents as a primary kidney disease but can be associ ated with several conditions, including Hodgkin's disease, allergies, use of nonsteroidal anti-inflammatory agents or lithium, infections, and other glomerular diseases. MCD on kidney biopsy shows no glomeru lar lesion by light microscopy and is negative for deposits by immuno fluorescent microscopy or occasionally shows small amounts of IgM in the mesangium (see Fig. A4-1). (See Glomerular Schematic 4.) Elec tron 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, although immune dysfunction is likely the initiating factor for MCD. Disturbances in T cell response may result in circulating glomerular permeability factors which directly affect the glomerular capillary wall, postulated to be T cell derived cytokines, such as IL13 and IL4. There is also evidence of increased CD80 on podocytes, promoting dysregu lated interactions with T cells via T lymphocyte antigen-4 (CLTA-4). Other evidence supporting cell-mediated immunity includes the presence of preceding allergies, altered cell-mediated immunity dur ing viral infections, and a high frequency of remissions with steroids. Evidence to suggest that there is a role for B cell dysfunction includes reports of patients with anti-nephrin antibodies and the successful treatment with the anti-CD20 monoclonal antibody, rituximab.

Glomerular schematic 4 MINIMAL CHANGE DISEASE 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 hyperten sion (30% in children, 20–50% in adults), microscopic hematuria (20% in children, 33% in adults), atopy or allergic symptoms (40% in chil dren, 30% in adults), and decreased kidney function (25–40%), which often returns to normal after remission of the nephrotic syndrome. The appearance of acute kidney 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 kidney 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 some times 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 steroidresistant 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 80–90% of adults will achieve complete remission, but the response is more delayed. Patients with steroid resistance may have FSGS on repeat biopsy. If the first kidney biopsy does not have a sample of deeper corticomedullary glomeruli, then the correct diagno sis of FSGS may be missed. CHAPTER 326 Glomerular Diseases 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. Relapses are less common in adults but are more resistant to subsequent therapy. Prednisone is first-line therapy. Other immuno suppressive drugs, such as cyclophosphamide, mycophenolate mofetil, calcineurin inhibitors (CNIs), and rituximab are reserved for frequent relapsers, steroid-dependent patients, or steroid-resistant patients. CNIs can induce remission, but relapse is also common when with drawn. The long-term prognosis in adults is less favorable when acute kidney failure or steroid resistance occurs. ■ ■FOCAL SEGMENTAL GLOMERULOSCLEROSIS FSGS refers to a pattern of kidney 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 326-4), the remaining patients are considered to have primary FSGS. FSGS

TABLE 326-4 Focal Segmental Glomerulosclerosis Primary focal segmental glomerulosclerosis Yet to be identified circulating permeable factor Secondary focal segmental glomerulosclerosis Adaptive response to hyperfiltration/reduced kidney mass, obesity Viruses: HIV/hepatitis B/parvovirus/SARS-CoV-2 Hypertensive nephropathy Reflux nephropathy Cholesterol emboli Drugs: Heroin/analgesics/bisphosphonates/ecstasy/interferon/anabolic steroids Oligomeganephronia Sickle cell disease Radiation nephritis Familial podocytopathies NPHS1 mutation/nephrin NPHS2 mutation/podocin PLCE1 mutation/phospholipase Cε1 INF2 mutation/inverted formin 2 WT1 mutation/Wilms tumor TRPC6 mutation/cation channel ACTN4 mutation/actinin α-Galactosidase A deficiency/Fabry’s disease N-Acetylneuraminic acid hydrolase deficiency/nephrosialidosis Uncertain cause PART 9 Disorders of the Kidney and Urinary Tract is now recognized as the most common cause of primary glomerular disease in patients with ESKD in the US. The pathogenesis of FSGS has multiple possible mechanisms including a circulating permeability fac tor (primary FSGS), an adaptive response to glomerular hypertrophy or hyperfiltration, and podocyte abnormalities associated with direct Glomerular schematic 5 Detachment of cell from GBM Collapsed capillary and scar Proliferation of subepithelial cells

toxic injury or genetic mutations. Risk polymorphisms at the APOL1 locus expressed in podocytes are thought to predispose patients to FSGS. The pathologic changes of FSGS are most prominent in glomeruli located at the corticomedullary junction (see Fig. A4-2), so if the kidney biopsy specimen is from superficial tissue, the lesions can be missed, which sometimes leads to a misdiagnosis of MCD. The most frequent variant is FSGS not otherwise specified (NOS), previously called classic FSGS, which may occur in primary or secondary FSGS. In addition to focal and segmental scarring, other variants have been described, including cellular lesions with endocapillary hypercellularity and heavy proteinuria; collapsing glomerulopathy (see Fig. A4-3) with segmental or global glomerular collapse and a rapid decline in kidney function; a perihilar lesion (see Fig. A4-4); or the glomerular tip lesion (see Fig. A4-5), which is usually steroid responsive and has a favorable prognosis. (See Glomerular Schematic 5.) FSGS can present with hematuria, hypertension, any

level of pro teinuria, and kidney injury. Nephrotic-range proteinuria and kidney injury are associated with a poor outcome, with 50% of patients reaching ESKD in 10 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 and SGLT2i. 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. CNIs have been used in patients requiring a steroid sparing regimen. Limited evidence suggests the use of cyclosporine in steroid-responsive patients helps ensure remissions. Relapse frequently occurs after cessation of cyclosporine therapy, and CNIs themselves can lead to a deterioration of kidney function due to their nephrotoxic effects. A role for other agents that suppress the immune system such as rituximab or mycophenolate mofetil has not FOCAL SCLEROSING GLOMERULONEPHRITIS Efferent arteriole Afferent arteriole

TABLE 326-5 Membranous Glomerulonephritis Primary/antigen-associated membranous glomerulonephritis PLA2R, NELL1, THSD7A, Sema3B, PCDH7, HTRA1, EXT1, EXT2, NCAM1 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, IgG4 disease Other systemic diseases: Fanconi’s syndrome, sickle cell anemia, diabetes, Crohn’s disease, sarcoidosis, Guillain-Barré syndrome, Weber-Christian disease, angiofollicular lymph node hyperplasia Abbreviations: PLA2R, phospholipase A2 receptor; EXT1 and EXT2, exostosin 1 and 2; NCAM1, neural cell adhesion molecule 1; NELL1, neural epidermal growth factorlike 1; PCDH7, protocadherin 7; Sema3B, semaphorin 3B; THSD7A, thrombospondin type-1 domain containing 7A. been established. FSGS recurs in 30% of kidney transplants, more com monly in primary FSGS, less commonly in secondary FSGS, and rarely in genetic FSGS. In recurrent posttransplant FSGS from presumed circulating factor, many patients will achieve a full or partial remis sion 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 or genetic FSGS. ■ ■MEMBRANOUS GLOMERULONEPHRITIS MGN, or membranous nephropathy as it is sometimes called, accounts for ~25% of cases of nephrotic syndrome in adults, with a peak inci dence between the ages of 30 and 50 years and a male-to-female ratio of 2:1. MGN is most often primary in the absence of an identifiable associated disease, but with the identification of novel associated anti gens (see Table 326-5), this nomenclature may change particularly in children in whom these antigens are increasingly found. 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 (see Table 326-5). Uniform thickening of the basement membrane along the periph eral capillary loops is seen by light microscopy on kidney biopsy (see Fig. A4-7); this thickening needs to be distinguished from that seen in diabetes and amyloidosis. (See Glomerular Schematic 6.) There may be characteristic “spikes” seen on silver stain due to the glomeru lar basement membrane reactivity to deposits. Immunofluorescence demonstrates diffuse granular deposits of IgG and C3, and electron Glomerular schematic 6 Foot

process fusion Subepithelial deposits MEMBRANOUS GLOMERULONEPHRITIS

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 70–80% of cases of primary MGN, IgG4 autoantibodies against the M-type phospholipase A2 receptor circulate and bind to a conformational epitope present in the PLA2R on human podocytes, producing characteristic in situ deposits. The diagnosis of MGN may no longer require a kidney biopsy in the setting of anti-PLA2R antibody positivity, normal creatinine, and no identifiable other causes of MGN. THSD7A is another antigen local ized on the podocyte surface that complexes with IgG4, while NELL1 is the most common non-PLA2R antigen accounting for up to 16% of primary MGN cases. These novel antigens (see Table 326-5) along with PLA2R account for over 90% of cases of primary MGN. In most cases of secondary membranous nephropathy, autoantibodies to these anti gens are absent, with rare reports of autoantibodies to PLA2R associ ated 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 primary MGN, and the response to therapy.

CHAPTER 326 Eighty percent of patients with MGN present with nephrotic syn drome and nonselective proteinuria. Microscopic hematuria is seen but less commonly than in IgA nephropathy or FSGS. Spontaneous remis sions occur in 20–33% of patients and often occur late in the course, making treatment decisions difficult. One-third of patients continue to have relapsing nephrotic syndrome but maintain normal kidney function, and approximately another third of patients develop kidney 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 in select patients with hypoalbuminemia. Glomerular Diseases The treatment of edema, dyslipidemia, hypertension, and inhibi tion of the renin-angiotensin system and the use of SGLT2i is recom mended. Therapy with immunosuppressive drugs is recommended for patients with primary MGN and persistent proteinuria. The choice of immunosuppressive drugs for therapy is controversial, however, patient risk stratification based on proteinuria, GFR, and serum albu min can help guide therapy choices with steroids and cyclophospha mide, CNIs or rituximab. Attaining remission is associated with a good long-term prognosis. ■ ■DIABETIC NEPHROPATHY Diabetic nephropathy is the single most common cause of chronic kidney disease 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; the vast majority of patients with diabetic nephropathy will have type 2 diabetes due to the higher prevalence compared to type 1 diabetes. 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 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. A4-24). This expansion in mesangial matrix is associated with the development of mesangial sclerosis. Some patients also develop eosinophilic, PAS+ nod ules called nodular glomerulosclerosis or Kimmelstiel-Wilson nodules.

Immunofluorescence microscopy often reveals the nonspecific depo sition 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 arterioscle rosis. This is associated with varying degrees of chronic glomerulo sclerosis and tubulointerstitial changes. Kidney 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 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 accu mulation of advanced glycosylation end products, circulating factors including growth hormone, connective tissue growth factor, TGF-β, and dyslipidemia. PART 9 Disorders of the Kidney and Urinary Tract The natural history of diabetic nephropathy has been historically well characterized in the ~40% of diabetics who develop it as a pro gression from glomerular hyperfiltration and renal hypertrophy to increasing albuminuria followed by declining GFR and ESKD. How ever, 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 ESKD. 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 per haps 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 326-1). Microalbuminuria appears 5–10 years after the onset of diabetes. It is currently recommended to test patients with type 1 disease for micro albuminuria 5 years after diagnosis of diabetes and yearly thereafter. Patients with type 2 diabetes should be tested for microalbuminuria at time of diagnosis followed by annual monitoring. Microalbuminuria classically progresses over 5–10 years to proteinuria and declining GFR, but in contemporary studies, greater heterogeneity is reported with regression to normoalbuminuria. 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 retinopa thy 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. 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 kidney biopsy. The risk of progression to ESKD 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. Kidney transplantation results in better survival. Good evidence supports the benefits of blood sugar and blood pres sure control, inhibitors of the renin-angiotensin-aldosterone system

(RAAS), and inhibitors of SGLT2 in slowing 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 con trol in patients with type 2 diabetes is less certain. Controlling systemic blood pressure decreases kidney and cardio vascular adverse events in this high-risk population. The vast majority of patients with diabetic nephropathy require three or more antihyper tensive drugs to achieve this goal. Drugs that inhibit the RAAS (ACE inhibitors, angiotensin receptor blockers [ARBs]) have been shown in large clinical trials to slow the progression of diabetic nephropa thy at early (microalbuminuria) and late (proteinuria with reduced glomerular filtration) stages, independent of their effects on systemic blood pressure. Finerenone, a nonsteroidal mineralocorticoid receptor antagonist, therapy in patients with diabetes and nephropathy on ACEi or ARB improved cardiovascular and kidney outcomes. In patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in those receiving SGLT2 inhibitors in addition to ACE inhibitors or ARBs. ■ ■GLOMERULAR DEPOSITION DISEASES Plasma cell dyscrasias producing excess light chain (80%), heavy chain (10%) or both immunoglobulins can lead to the formation of glo merular and tubular deposits. The same is true for the accumulation of serum amyloid A protein fragments and monoclonal gammopathy of renal significance (MGRS). This broad group of proteinuric patients has glomerular deposition disease. Light Chain Deposition Disease The biochemical characteris tics of nephrotoxic light chains produced in patients with light chain malignancies confer kidney injury; that of either cast nephropathy (see Fig. A4-21), which causes kidney injury but not heavy proteinuria or amyloidosis, or light chain deposition disease (LCDD) (see Fig. A4-20), which produces proteinuria with kidney injury. 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 prop erties at neutral pH, and abnormal metabolism probably contributes to the deposition. 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 syn drome may develop, and ~70% of patients progress to dialysis. Treat ment for LCDD is treatment of the primary disease. Less commonly, the deposits may be composed of heavy chains only (HCDD) or both ligh and heavy chains (LHCDD); both diseases have similar clinical characteristics to LCDD. Monoclonal Gammopathy of Renal Significance In MGRS, a

monoclonal immunoglobulin secreted by a nonmalignant or prema lignant B cell or plasma cell clone results in monoclonal deposits in the kidney which can manifest as proteinuria and ESKD. Treatment is controversial but may include chemotherapy. 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. 117). Hereditary amyloidosis is rare. Even though AA and AL amyloid occur for different reasons, their clinicopathophysiology is quite similar. Amyloid infiltrates the liver, heart, peripheral nerves, carpal tunnel, upper pharynx, and kidney, ultimately producing restrictive cardiomyopathy, hepatomegaly, mac roglossia, and heavy proteinuria sometimes associated with renal vein thrombosis. In contrast to LCDD, amyloid kidney deposits are fibrillar, stain with Congo red, and contain predominantly the variable region of lambda chains (see Fig. A4-19). In systemic AL amyloidosis, also

called primary amyloidosis, light chains produced in excess by clonal plasma cell dyscrasias are made into fragments by macrophages that aggregate into amyloid fibrils. Approximately 10% of patients have overt myeloma as defined by CRAB (hypercalcemia, renal insuffi ciency, anemia, or lytic bone lesions). Nephrotic syndrome is common and ~20% of patients progress to dialysis. AA amyloidosis is sometimes called secondary amyloidosis and is due to deposition of β-pleated sheets of serum amyloid A protein, an acute phase reactant. Fragments of serum amyloid A protein increase and self-aggregate by attaching to receptors for advanced glycation end products in the extracellular environment. Patients with AA amyloid have associated inflamma tory diseases including autoimmune diseases, chronic infections, and genetic autoinflammatory diseases. An increasing proportion of patients have unidentified chronic inflammation; this may reflect bet ter treatments for the previously associated diseases or a rise in chronic inflammation due to obesity. Nephrotic syndrome is common, and ~40–60% of patient’s progress to dialysis. Serum-free light chain analy sis 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 mesan gial regions of the kidney. The recommended treatment for primary amyloidosis is melphalan followed by autologous hematopoietic cell transplantation (HCT) which can achieve remission, however relapses are common. Patients who are not candidates for HCT often receive bortezomib-based regimens. Secondary amyloidosis is relentless unless the primary disease can be controlled. Drugs in development that dis rupt the formation of fibrils may be available in the future. Fibrillary and Immunotactoid Glomerulopathies Fibrillary and immunotactoid glomerulopathies are rare (<1.0% of kidney biop sies), morphologically defined diseases characterized by glomerular accumulation of nonbranching randomly arranged fibrils that are Congo red negative (see Fig. A4-18). Fibrillary glomerulopathy accounts for 85–90% of cases and is identified by the presence of the protein DnaJ heat shock protein family member B9 (DNAJB9) in the glomeruli, which is absent in the rarer immunotactoid glomerulopa thy. In both, glomerular and mesangial deposits contain oligoclonal or oligotypic immunoglobulins and complement, with 12- to 24-nm fibrils randomly arranged in fibrillary glomerulopathy and 16 to 52-nm fibrils organized into microtubules in immunotactoid glomeru lopathy. The cause of this “nonamyloid” glomerulopathy is mostly idio pathic; reports of fibrillary glomerulonephritis describe associations with malignancy, autoimmune disease, and monoclonal gammopathy. 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%), kidney injury (50%), a wide variety of histologic lesions, and ESKD within 2 to 6 years in 50% of patients. Most patients have disease limited to the kidney. Patients should be screened for associated disor ders. There is no consensus on treatment of this uncommon disorder, although rituximab has been reported to remit proteinuria. These diseases can recur in the kidney transplant. ■ ■FABRY'S DISEASE Fabry's disease is an X-linked inborn error of globotriaosylceramide metabolism secondary to deficient lysosomal α-galactosidase A (alpha-Gal A) activity, resulting in excessive intracellular storage of globotriaosylceramide. Affected organs include the vascular endothe lium, heart, brain, and kidneys. Classically, Fabry's disease presents in childhood in males with acroparesthesias, angiokeratomas commonly in groin and periumbilical areas, abdominal pain, cornea verticillate, and hypohidrosis. Over time, male patients develop cardiac involve ment, cerebrovascular disease, and kidney injury, with an average age of death around 50 years of age. Female heterozygotes with unfavor able X inactivation present with mild single-organ involvement or rarely severe manifestations including kidney failure but do so later in life than males. Kidney biopsy reveals enlarged glomerular visceral

epithelial cells packed with small clear vacuoles containing globotri aosylceramide; vacuoles may also be found in parietal and tubular epithelia (see Fig. A4-22). These vacuoles of electron-dense materials in parallel arrays (zebra bodies) are easily seen on electron microscopy. Ultimately, kidney 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 gly colipid globules under polarized light (Maltese cross). Measurement of alpha-Gal A activity and mutational analysis of the gene is diagnostic, with kidney biopsies sometimes helpful. Progression to ESKD occurs by the fourth or fifth decade. Treatment with inhibitors of the reninangiotensin system is recommended. Treatment with recombinant agalsidase alpha or beta or migalastat, a chaperone that facilitates traf ficking 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 kidney transplantation in patients with Fabry's disease are similar to those of other causes of ESKD.

CHAPTER 326 PULMONARY-RENAL SYNDROMES Several diseases can present with catastrophic hemoptysis and glo merulonephritis associated with varying degrees of kidney injury. 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 kidney injury may require dialysis. Diagnosis is difficult initially because biopsies and serologic testing take time. Treatment with plasmapheresis and methyl prednisolone is often empirical and temporizing until results of testing are available. Glomerular Diseases BASEMENT MEMBRANE SYNDROMES All kidney epithelia, including podocytes, rest on basement mem branes assembled into a planar surface through the interweaving of col lagen 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 develop ment. All epithelial basement membranes early in human development are composed of interconnected triple-helical protomers rich in α1.α1. α2(IV) collagen. Some specialized tissues undergo a developmental switch replacing α1.α1.α2(IV) protomers with an α3.α4.α5(IV) colla gen network; this switch occurs in the kidney (glomerular and tubular basement membrane), lung, testis, cochlea, and eye, while an α5.α5. α6(IV) network appears in skin, smooth muscle, and esophagus and along Bowman's capsule in the kidney. This switch probably occurs because the α3.α4.α5(IV) network is more resistant to proteases and ensures the structural longevity of critical tissues. When basement membranes are the target of glomerular disease, they produce moder ate proteinuria, some hematuria, and progressive kidney failure. ■ ■ANTI-GBM DISEASE Autoimmune disease where antibodies are directed against the α3 NC1 domain of collagen IV produces an anti-GBM disease often associated with RPGN and/or a pulmonary-renal syndrome called Goodpas ture's syndrome. Discussion of this disease is covered earlier in "Acute Nephritic Syndromes." ■ ■ALPORT'S SYNDROME Classically, patients with Alport's syndrome develop hematuria, and mild proteinuria (<1–2 g/24 h), which appears late in the course,

Glomerular schematic 7 PART 9 Disorders of the Kidney and Urinary Tract followed by chronic glomerulosclerosis leading to kidney failure in association with sensorineural deafness. Some patients develop lentico nus of the anterior lens capsule, "dot and fleck" retinopathy, and rarely, leiomyomatosis. Approximately 80–85% of patients with Alport's syndrome have an X-linked inheritance of mutations at the COL4A5 locus affecting in the α5(IV) collagen chain on chromosome Xq22–24. Female carriers have variable penetrance depending on the type of mutation or the degree of mosaicism created by X inactivation. Muta tions on chromosome 2q35-37 at the COL4A3 and COL4A4 loci of the α3(IV) and α4(IV) chains, respectively, are associated with autosomal recessive (AR) disease and less commonly autosomal dominant (AD) disease. With use of next generation sequencing, AD disease is now noted to likely occur more frequently than previously thought. Pedigrees with the X-linked syndrome are quite variable in their rate and frequency of tissue damage leading to organ failure. There is strong correlation between genotype and phenotype regarding risk of disease progression in males; truncating variants, including large dele tions and nonsense mutations, are associated with rapidly progressive disease with ESKD by age 30 in up to 90% of males. By contrast, those with missense or splice variants may not deteriorate until after the age of 30 with mild or late deafness. Early severe deafness, lenticonus, or proteinuria suggests a poorer prognosis. Usually females from X-linked pedigrees have only microhematuria, but up to 25% of carrier females have been reported to have more severe kidney manifestations. Pedi grees with the AR 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. Genetic testing can be used for the diagnosis of Alport's syndrome and the demonstration of the mode of inheri tance. In certain cases with high clinical suspicion or family history of Alport's, genetic testing alone may be sufficient for diagnosis. Since α5(IV) collagen is expressed in the skin, some X-linked Alport's patients can be diagnosed with a skin biopsy revealing the lack of the

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS α5(IV) collagen chain on immunofluorescent analysis. Patients with mutations in α3(IV) or α4(IV) require a kidney biopsy. Early in their disease, Alport's patients typically have thin basement membranes on kidney biopsy (see Fig. A4-23), which thicken over time into mul tilamellations 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, includ ing mothers of affected males. Primary treatment is control of systemic hypertension and use of ACE inhibitors and possibly SGLT2i to slow kidney disease progression. Although patients who receive kidney 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 dis order characterized by persistent or intermittent hematuria, which is usually microscopic hematuria and rarely macroscopic hematuria with flank pain. It is not typically associated with proteinuria, hyperten sion, or loss of kidney 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 has also been called benign familial hematuria. Many cases of TBMD have genetic defects in type IV collagen; in contrast to Alport's syndrome, the disease behaves as an autosomal dominant disorder that in ~40% of families segregates with the COL(IV) α3/COL(IV) α4 loci. Mutations in these loci can result in a spectrum of disease, ranging from TBMD to autosomal dominant or recessive Alport's. The GBM shows diffuse thinning compared to normal values for the patient's age in otherwise normal biopsies (see Fig. A4-23). 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 domi nant, with haploinsufficiency for the LIM homeodomain transcription factor LMX1B; pedigrees are extremely variable in the penetrance for all features of the disease. LMX1B regulates the expression of genes encoding α3 and α4 chains of collagen IV, interstitial type III collagen, podocin, and CD2AP that help form the slit-pore membranes connect ing podocytes. Mutations in the LIM domain region of LMX1B associ ate with glomerulopathy in 30–40% of patients and rarely progress to ESKD. Proteinuria or isolated hematuria is discovered throughout life but usually by the third decade. Genetic testing can confirm the diag nosis. Treatment is nonspecific, but renin-angiotensin system inhibi tion is recommended. Patients with ESKD 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 else where in the body. The group of diseases discussed here lead to vascu litis, renal endothelial injury, thrombosis, ischemia, and/or lipid-based occlusions. ■ ■ATHEROSCLEROTIC NEPHROPATHY Aging in the developed world is commonly associated with the occlu sion of coronary and systemic blood vessels. When the renal arterial circulation is involved, the glomerular microcirculation is damaged, leading to chronic nephrosclerosis. Several aggressive lipid disorders can accelerate this process, but most of the time, atherosclerotic progres sion to chronic nephrosclerosis is associated with poorly controlled hypertension. ■ ■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 ESKD have hypertension as a primary cause, and it is the second most common cause of ESKD after diabetic nephropathy in the US. Risk alleles associated with APOL1, a functional gene for apolipoprotein L1 expressed in podocytes are associated with an increased risk of ESKD. Other associated risk factors for progres sion to end-stage kidney disease include

increased age, male gender, smoking, hypercholesterolemia, duration of hypertension, low birth weight, and preexisting kidney 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. A4-25). 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 a study with self-identified African Americans with hypertensive neph rosclerosis that therapy initiated with an ACE inhibitor can slow the rate of decline in kidney 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. A4-28). The hemodynamic stress of malignant hypertension leads to fibrinoid necrosis of small blood vessels, thrombotic microangiography, a nephritic urinalysis, and AKI. In the setting of kidney injury, chest pain, or papilledema, the condi tion is treated as a hypertensive emergency. ■ ■CHOLESTEROL EMBOLI Aging patients with clinical complications from atherosclerosis some times shower cholesterol crystals into the circulation following an

endovascular procedure with manipulation of the aorta or with use of systemic anticoagulation. Less commonly, spontaneous emboli can occur and may shower acutely or shower subacutely which is 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 choles terol 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 capil lary injury leading to FSGS sometimes associated with hematuria, mild proteinuria, and loss of kidney function, which typically progresses over a few years. Occasional patients have fever, eosinophilia, or eosin ophiluria. 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. A4-26). There is no therapy to reverse embolic occlusions, and steroids do not help. Controlling blood pressure and lipids and cessation of smoking are usually recom mended for prevention.

■ ■SICKLE CELL DISEASE Sickle cell disease (SCD) is an autosomal recessive disease that occurs due to a mutation in the hemoglobin β-chain (HβS). Clinical dis ease occurs in homozygous patients (SS) or heterozygous patients in the presence of an abnormal or missing β-chain (SC, HbSβ). Under certain circumstances (i.e., hypoxia, hypovolemia, acidity, hyperos molality), HbS polymerizes which causes the red blood cell shape to distort. These cells attach to endothelia, causing obstruction as well as other changes to the vasculature that produce acute and chronic vasoocclusion disease in many organs, including the kidney. The major site of injury in the kidney is the renal medulla, an area supplied by the vasa recta capillaries that promotes sickling due to the relative hypoxic, acidotic, and hypertonic environment. Repeated injury overtime pro duces chronic organ damage leading to sickle cell nephropathy (SCN). Early changes of SCN include glomerular hyperfiltration, albuminuria, and both micro- and macro-hematuria. Nearly all SCD patients have concentrating defects which cause hyposthenuria and can lead to severe

dehydration. Later changes include papillary necrosis, renal infarction, interstitial nephritis, proteinuria, and FSGS. Rarely patients may present with MPGN. Several genetic risk factors have been identi fied that may increase risk for progression of CKD, including APOL1 gene variants. Treatment is directed at reducing the frequency of vaso-occlusive events and administering ACE inhibitors/ARBs and hydroxyurea in the hope of delaying a progressive decline in kidney function. Management of anemia in SCN patients is complex and may require high doses of erythropoiesis-stimulating agents. A number of patients will develop progressive CKD, and one study found that 20% of SCD patients develop ESKD before the age of 30. SCD patients with ESKD have poor prognosis on kidney replacement therapy (KRT), with a mean time to death of 4 years. Prognosis for ESKD patients improves after kidney transplant with 7 year survival of 67%. CHAPTER 326 Glomerular Diseases Sickle cell trait occurs in patients with one HbS and one normal hemoglobin. Although individuals usually do not experience vasoocclusive symptoms, most will gradually develop hyposthenuria due to subclinical infarction of the renal medulla and a consequent loss of concentrating ability. They may experience hematuria and are at higher risk for renal medullary carcinoma than SCD patients. ■ ■THROMBOTIC MICROANGIOPATHIES Thrombotic microangiopathy (TMA) refers to a pathologic lesion that causes thrombocytopenia and microangiopathic hemolytic anemia with schistocytes. Thrombotic thrombocytopenic purpura (TTP), Shiga toxin–mediated hemolytic-uremic syndrome (HUS), and complementmediated HUS represent a spectrum of primary TMAs that share these features and may have concurrent fever, kidney failure, and neurologic disturbances. HUS is suspected with patients have more severe kidney injury while TTP is suspected in adults with neurologic disease and more severe thrombocytopenia. 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

TABLE 326-6 Thrombotic Microangiopathies Primary thrombotic microangiopathy TTP Shiga-toxin HUS Complement-mediated HUS Secondary thrombotic microangiopathy Pregnancy related: preeclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelet count syndrome), postpartum (thought to be complement mediated) Drug induced: oral contraceptives or quinine, calcineurin inhibitors, antiplatelet agents (ticlopidine and clopidogrel), drugs of abuse (cocaine, IV use of oxycodone) Kidney transplant patients given OKT3 for rejection Malignant hypertension Autoimmune: antiphospholipid syndrome, lupus, scleroderma Infections: HIV, pneumococcal, CMV Cobalamin deficiency Abbreviations: CMV, cytomegalovirus; HUS, hemolytic-uremic syndrome; TTP, thrombotic thrombocytopenic purpura. material in and around glomeruli (see Fig. A4-27). These tissue find ings are similar to what is seen in secondary TMA, which includes a broad group of conditions known to be associated with TMA (see Table 326-6). PART 9 Disorders of the Kidney and Urinary Tract Shiga toxin–mediated HUS is caused by a toxin released by Esch erichia coli 0157:H7 and occasionally by Shigella dysenteriae. This Shiga toxin (verotoxin) directly injures endothelia, enterocytes, and kidney 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 fac tor (VWF). In the absence of 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 anti bodies to ADAMTS13 distinguishes the deficiency from the immune-

mediated disease. Complement-mediated HUS, previously referred to as atypical HUS, is thought to occur when there is a hereditary defi ciency or antibody to a regulatory protein in the alternative comple ment pathway leading to overactivation. 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, or longer for relapsing patients. There is an anec dotal role in relapsing patients for splenectomy. Refractory or relapsing patients may benefit from steroids, immunosuppressive drugs such as rituximab, or caplacizumab, a monoclonal antibody that blocks interaction between VWF and platelets. In the absence of ADAMTS13 antibodies, patients with a genetic deficiency of ADAMTS13 pro duction can be treated with fresh frozen plasma alone. Patients with Shiga toxin–mediated HUS are treated primarily with supportive care because antibiotics are thought to accelerate the release of the toxin and the diarrhea is usually self-limited. Patients with complementmediated HUS are treated with anticomplement therapy, such as ecu lizumab or ravulizumab. ■ ■ANTIPHOSPHOLIPID ANTIBODY SYNDROME

(SEE CHAP. 369) 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 kidney 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 kidney disease being the most common cause of glomerulonephritis in many parts of the world. Poststreptococcal Glomerulonephritis This form of glomeru lonephritis is one of the classic complications of streptococcal infec tion. The discussion of this disease can be found earlier, in the section “Acute Nephritic Syndromes.” Subacute Bacterial Endocarditis Kidney 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 Kidney disease is an impor tant complication of HIV disease. 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 is thought to be linked to APOL1 risk variants. 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 glo merulonephritis, 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 pro teinuria and hypoalbuminemia, but unlike patients with other etiologies for nephrotic syndrome, they do not commonly have hypertension, edema, or hyperlipidemia. Kidney ultrasound also reveals large, echo genic kidneys despite the finding that kidney function in some patients declines rapidly. Treatment with inhibitors of the renin-angiotensin sys tem 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 ESKD. 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

HIVinfected patient has improved dramatically. Kidney 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 micro scopic hematuria, nonnephrotic or nephrotic-range proteinuria, and hypertension. There is a close association between hepatitis B infec tion and polyarteritis nodosa, with vasculitis appearing generally in the first 6 months following infection. Kidney manifestations include renal artery aneurysms, renal infarction, and ischemic scars. Alterna tively, the hepatitis B carrier state can produce an MGN with predomi nant IgG1 deposition that is more common in children than adults or MPGN that is more common in adults than in children. Kidney histology is indistinguishable from idiopathic MGN or MPGN. Viral antigens, most commonly HBeAG, are found in the kidney deposits. Cryoglobulinemic glomerulonephritis has also been reported. Treat ment is with antiviral agents. Children have a better prognosis than adults. Up to 30% of patients with chronic hepatitis C infection have some kidney manifestations. Patients often present with type II mixed cryo globulinemia, nephrotic syndrome, microscopic hematuria, abnormal liver function tests, depressed C3 levels, anti–hepatitis C virus (HCV) antibodies, and viral RNA in the blood. The lesions most commonly seen, in order of decreasing frequency, are cryoglobulinemic glomeru lonephritis, 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. SARS-CoV-2 The novel coronavirus, SARS-CoV-2, is associ ated with several complications related to kidney disease including acute kidney injury, chronic kidney disease, and, rarely, glomerular diseases. The glomerular lesions reported in patients with COVID-19 include FSGS, minimal change disease, membranous nephropathy, ANCA-associated vasculitis, anti-GBM disease, IgA nephropathy and thrombotic microangiopathy. The glomerular disease most commonly associated with COVID-19 is collapsing glomerulopathy, a morpho logic variant of FSGS, also referred to as COVID-associated nephrop athy (COVAN). Patients may present with new onset nephrotic syndrome or nephrotic range proteinuria with AKI. There have been case reports of de novo glomerular disease and relapse of pre-existing glomerular disease following administration of COVID-19 mRNA vaccines, although evidence for causal link is not well established. The use of immunosuppression therapy may be considered in patients with severe nephrotic syndrome or persistent disease despite resolu tion of infection, however there is limited data to guide treatment recommendations. Other Viruses Other viral infections are occasionally associated with glomerular lesions, but cause and effect are not well estab lished. These viral infections and their respective glomerular lesions include cytomegalovirus producing MPGN or FSGS; influenza and anti-GBM disease; measles-associated endocapillary proliferative glo merulonephritis, with measles antigen in the capillary loops and mesangium; parvovirus causing mild proliferative or mesangioprolif erative glomerulonephritis or FSGS; mumps and mesangioprolifera tive 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 symp toms, 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. Neuron-derived neurotrophic factor has also been identified as an anti genic target. Other lesions have also rarely been described, including interstitial syphilitic nephritis. The diagnosis is confirmed with non treponemal and treponemal tests for Treponema pallidum. The kidney 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 infec tion with Mycobacterium leprae and can be classified by Ridley-Jopling criteria into various types: tuberculoid, borderline tuberculoid, midborderline and borderline lepromatous, and lepromatous. Kidney involvement in leprosy is related to the quantity of bacilli in the body, and the kidney is one of the target organs during splanchnic localiza tion. In some series, all cases with borderline lepromatous and lep romatous types of leprosy have various forms of kidney involvement including FSGS, mesangioproliferative glomerulonephritis, or renal amyloidosis; much less common are DPGN and MPGN. Treatment of the infection with multidrug therapy can reduce the incidence of kidney disease or produce remission of the kidney disease. Malaria There are 300–500 million incident cases of malaria each year worldwide, and the kidney is commonly involved. Glomerulo nephritis 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 Plas modium malariae, children are more commonly affected and kidney involvement is more severe. Transient proteinuria and microscopic hematuria can resolve with treatment of the infection. However, resis tant nephrotic syndrome with progression to ESKD 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 asso ciated with a sparse membranoproliferative lesion. The rare mesangio proliferative 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 kidney disease, and the glomerular lesions can be clas sified 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 associ ated with IgA immune deposits and progress despite antiparasitic and/ or immunosuppressive therapy. CHAPTER 326 Other Parasites Kidney involvement with toxoplasmosis infec tions 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 decreased GFR is rare. Acute DPGN, MGN, and mesan gioproliferative glomerulonephritis have all been observed on biopsy. Filariasis and trichinosis are caused by nematodes and are sometimes associated with glomerular injury presenting with proteinuria, hema turia, and a variety of histologic lesions that typically resolve with eradication of

the infection. Glomerular Diseases Acknowledgment The authors wish to thank Nicole Wyatt for her assistance with this chapter. ■ ■FURTHER READING De Vriese AS et al: Differentiating primary, genetic, and secondary FSGS in adults: A clinicopathologic approach. J Am Soc Nephrol 29:759, 2018. Kupin WL: Viral-associated GN: Hepatitis C and HIV. Clin J Am Soc Nephrol 12:1337, 2017. Hou J et al: C3 glomerulopathy: a review with emphasis on ultrastruc tural features. Glomerular Dis 2:107, 2022. Lebleu VS et al: Origin and functional heterogeneity of fibroblasts. FASEB J 34(3):3519-, 2020. Miller P, Caza T: The expanding spectrum and utility of antigens in membranous nephropathology. Curr Opin Nephrol Hypertens 32:232, 2023. Papazachariou L et al: Frequent COL4 mutations in familial micro heamaturia accompanied by later-onset/alport nephropathy due to focal segmental glomerulosclerosis. Clin Genet 92:517, 2017. Ronco P et al: Membranous nephropathy. Nat Rev Dis Primers 7:69, 2021. Sethi S et al: Mayo Clinic/Renal Pathology Society consensus report on pathologic classification, diagnosis, and reporting of GN. J Am Soc Nephrol 27:1278, 2016. Smith RJH et al: C3 glomerulopathy - understanding a rare complementdriven renal disease. Nat Rev Nephrol 15:129, 2019. Yau K et al: Prescribing SGLT2 inhibitors in patients with CKD: Expanding indications and practical considerations. Kidney Int Rep 7:1463, 2022.

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