advanced; severe tubulointerstitial disease is uncommon in patients with long-standing disease. Because sarcoidosis can cause kidney damage through other mechanisms, including direct ureteral involvement, retroperitoneal fibrosis, and hypercalcemia, hypercalciuria, nephrolithiasis, and nephrocalcinosis via excessive production of 1,25-dihydroxy vitamin D in granulomas, tubulointerstitial disease usually requires confirmation by kidney biopsy showing the presence of noncaseating granulomas and interstitial nephritis.

IgG4-Related Disease

IgG4-related disease is a group of diseases characterized by infiltration of different organs by lymphoplasmacytic infiltrates of IgG4-positive plasma cells with resultant fibrosis and is often associated with elevated serum IgG4 levels. There is often other organ involvement and occasionally associated glomerular lesions, including membranous and membranoproliferative glomerulonephritis.

Systemic Lupus Erythematosus

The tubulointerstitial disease of SLE typically occurs with concomitant glomerulonephritis. The degree of tubulointerstitial involvement in SLE is a poor prognostic sign with an associated increased risk for hypertension, progressive kidney dysfunction, and end-stage kidney disease.

Infections

Numerous infections, including those caused by bacteria, mycobacteria, viruses, parasites, and fungi, are associated with acute interstitial nephritis and chronic tubulointerstitial nephritis (see Acute Kidney Injury). The pathophysiology of infection-related interstitial nephritis may be direct infiltration of the kidney or an inflammatory response triggered by the infecting agent.

Malignancy

Kidney infiltration by lymphoma and leukemia may occur and present with non-nephrotic-range proteinuria, sterile pyuria, and enlarged kidneys on imaging studies. Diagnosis may be confirmed by biopsy. Gammopathies associated with lymphoproliferative disorders or multiple myeloma may also cause tubulointerstitial disease (see Kidney Manifestations of Gammopathies).

Numerous antineoplastic agents have been associated with tubulointerstitial disease, including carboplatin, cisplatin, cyclophosphamide, ifosfamide, nitrosoureas (such as carmustine, lomustine, semustine, and streptozocin), and panitumumab. Clinical features may include chronic kidney disease (CKD), mild proteinuria, and evidence of tubular dysfunction manifested as Fanconi syndrome and electrolyte abnormalities.

Medications

Analgesics

Long-term use of analgesic agents, particularly combinations of potentially nephrotoxic medications, is associated with chronic tubulointerstitial disease. However, the types and doses of medications leading to CKD have not been clearly defined. NSAIDs can cause AKI and may accelerate progression of underlying CKD, but it is controversial whether NSAIDs can cause de novo chronic disease. There is some evidence that acetaminophen may increase the risk of CKD with prolonged exposure. Clinical manifestations are nonspecific and may include slowly progressive CKD, varying degrees of usually mild proteinuria, hypertension, and anemia.

Calcineurin Inhibitors

The calcineurin inhibitors cyclosporine and tacrolimus can cause reversible AKI and a usually irreversible chronic tubulointerstitial disease. Duration of exposure and cumulative dose are risk factors, and laboratory features may include kidney dysfunction, hyperkalemia, hypomagnesemia, hypophosphatemia, hyperuricemia, and type 4 (hyperkalemic distal) RTA. Kidney biopsy shows patchy tubular atrophy and interstitial fibrosis. Therapy includes calcineurin dose reduction or non-calcineurin alternatives, if possible.

Lithium

Chronic lithium therapy can cause chronic tubulointerstitial disease, CKD, and nephrogenic diabetes insipidus. Prolonged duration of therapy and the cumulative dose are risk factors, but serum lithium levels do not correlate well with the risk of nephrotoxicity (patients can develop CKD with consistently therapeutic levels). Clinical features include polyuria and nocturia due to the loss of concentrating ability in the kidney (diabetes insipidus), and type 1 (hypokalemic distal) RTA can occur.

Diagnosis is often clinical based on history of lithium exposure, inappropriately dilute urine following water restriction, and variable degrees of CKD. Therapies include stopping lithium if possible to prevent further injury or concomitant use of amiloride to prevent entry of lithium into tubular cells if stopping lithium is not possible. Following lithium discontinuation, the prognosis of CKD is variable; mild improvement, stabilization, or progressive loss of kidney function can occur.

Lead

Prolonged lead exposure over years can cause lead nephropathy. Clinical features include CKD, bland urine sediment, subnephrotic proteinuria, and hyperuricemia. Kidney biopsy reveals a nonspecific chronic interstitial nephritis. The diagnosis should be considered in patients with current or past exposure to lead, extrarenal manifestations of lead toxicity, and elevated blood lead levels (although lead levels may have normalized if exposure has been reduced or stopped).

Hyperuricemia

Hyperuricemia is associated with chronic uric acid nephropathy due to deposition of sodium urate crystals in the interstitium. The inflammatory response causes interstitial fibrosis and CKD. Clinical features include hyperuricemia, CKD, bland urine sediment, subnephrotic proteinuria, and unremarkable kidney imaging. Kidney biopsy is required to make the diagnosis because clinical features are nonspecific.

Obstruction

Urinary obstruction can result in AKI and CKD. Clinical features may include hypertension, CKD, and changes in urinary habits such as incontinence, nocturia, and polyuria. Flank pain and renal or ureteral colic are usually not features of chronic obstruction given its insidious course. Imaging (typically ultrasonography) may reveal hydronephrosis and renal cortical thinning. Type 4 (hyperkalemic distal) RTA may occur, consistent with the tubular atrophy and injury on pathology. Treatment includes relief of the obstruction, and prognosis depends on the duration and severity of the obstruction. Recovery is usually diminished with obstruction of longer than 6 to 12 weeks.

KEY POINT

- Causes of chronic tubulointerstitial disease include various immunologic diseases, infections, malignancy, medications, lead exposure, hyperuricemia, and obstruction.

Management

Rapid determination and treatment of underlying causes of chronic tubulointerstitial disease may result in slower progression or slight reversal of kidney dysfunction, but significant improvement is unlikely with long-standing disease and chronic tubulointerstitial fibrosis. Practical steps include discontinuation of potentially offending drugs and toxins and treatment of underlying immunologic, infectious, obstructive, malignant, or other disease. Blood pressure control, use of ACE inhibitors or angiotensin receptor blockers when significant detectable proteinuria is present, and metabolic control of calcium and phosphate should be undertaken. Immunosuppressive therapy should be considered (in consultation with a nephrologist) in selected patients with an inflammatory cause and evidence of active disease.

KEY POINT

- Chronic tubulointerstitial diseases typically have limited improvement with therapy, even with rapid assessment and treatment of underlying causes.

Glomerular Diseases

Pathophysiology and Epidemiology

The glomerulus is the basic filtering unit of the kidney (**Figure 12**). Anatomically, each glomerulus consists of a tuft of capillaries formed by the branching of the afferent arteriole supported by a structural matrix (the mesangium) produced and maintained by specialized (mesangial) cells. Each kidney has approximately 1 million glomeruli providing 2 m^2 of glomerular capillary filtering surface. The glomerular basement membrane (GBM) provides both a size- and charge-selective barrier to the passage of circulating macromolecules. On the urinary side of the GBM lies a layer of podocytes, which are specialized epithelial cells that provide another barrier to plasma proteins via a specialized intercellular junction (the slit diaphragm). The glomerular capillary tufts are surrounded by Bowman's capsule, a single layer of parietal epithelial cells that form a cup-like sac that is continuous with the renal tubule and into which the filtrate from the glomerular capillaries is collected and passed to the renal tubule.

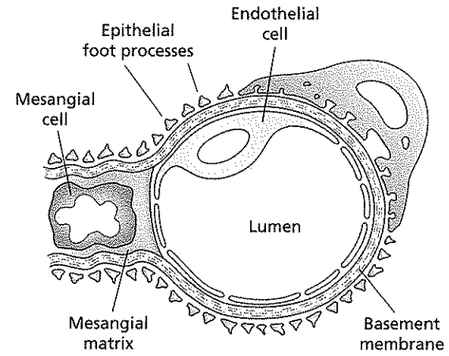

FIGURE 12. A normal glomerular capillary and surrounding structures. Each capillary consists of a layer of endothelial cells surrounded by a basement membrane on which sit specialized epithelial cells called *podocytes*. These layers constitute a barrier to plasma proteins and cells, which prevent their passage into the urine.

From a histologic standpoint, glomerular disease can be *diffuse* (all glomeruli are involved) or *focal* (only some glomeruli are involved). At the level of the individual glomerulus, a process is *global* if the whole glomerular tuft is involved or *segmental* if only a part is involved. To describe the pathologic process, the terms *proliferative* (an increase in the number of cells in the glomerulus), *sclerosing* (presence of scarring), and *necrotizing* (areas of cell death) are often used (for example, focal and segmental necrotizing glomerulonephritis; diffuse global proliferative lupus nephritis). Extracapillary proliferation or *crescentic* lesions are associated with accumulations of macrophages, fibroblasts, proliferating epithelial cells, and fibrin within Bowman's space; represent rupture of the glomerular membrane; and signify severe injury to the glomerular capillary wall. Interstitial fibrosis, which accompanies uncontrolled glomerular disease, is a poor prognostic sign.

Several mechanisms lead to glomerular dysfunction. Podocyte dysfunction can occur in genetic disease affecting key basement membrane proteins such as hereditary nephritis (also known as Alport syndrome). In diseases such as

minimal change glomerulopathy and focal segmental glomerulosclerosis (FSGS), circulating factors directly affect podocyte function and lead to proteinuria. In diabetes mellitus and amyloidosis, there is mechanical disruption of the glomerulus due to accumulation of normal or abnormal protein both in the capillary loops of the glomerulus and the mesangium. Immune mechanisms include in situ formation of immune complexes in membranous glomerulopathy or the localized effects of anti-GBM antibodies in Goodpasture syndrome; in conditions such as postinfectious glomerulonephritis and systemic lupus erythematosus, immune-mediated kidney injury is caused by deposition of circulating immune complexes.

Presently, more than 10% of the U.S. population has proteinuria or kidney dysfunction, often caused by glomerular disease. Diabetic kidney disease affects millions of people and is the major cause of end-stage kidney disease (ESKD) in the United States. Glomerular diseases associated with infections such as malaria, schistosomiasis, HIV, and hepatitis B and C are major worldwide health issues.

Clinical Manifestations of Glomerular Disease

Glomerular disease syndromes are typically classified by their characteristic features, including the pattern of abnormalities on urinalysis, any systemic features present, and the degree of kidney failure. The most common distinction is usually made between the nephrotic syndromes, in which leakage of plasma proteins is a predominant feature, and the nephritic syndromes (which reflect inflammation of the glomerulus and are also referred to as glomerulonephritis [GN]), in which there is passage of plasma proteins, erythrocytes, and leukocytes through the glomerulus into the renal tubule. These classifications, however, are not exclusive because some conditions may present with either or both patterns, and some disorders may progress from one pattern to the other. Therefore, kidney biopsy may be required to establish a diagnosis and guide appropriate therapy.

Glomerular disease may be limited primarily to the kidney but frequently occurs secondary to other systemic conditions, including infectious and autoimmune disorders. Infectious diseases linked to glomerular disease include poststreptococcal GN, HIV-associated glomerulopathy, and hepatitis C–associated cryoglobulinemic GN. Systemic lupus erythematosus is a classic example of a systemic immune complex disease associated with GN. IgA vasculitis and pauci-immune small-vessel vasculitis can also cause GN.

Glomerular disease should be suspected when proteinuria and/or hematuria are seen on urinalysis. The findings of nephrotic-range proteinuria or dysmorphic erythrocytes and erythrocyte casts in the urine sediment are also more specific for a glomerular origin. See Clinical Evaluation of Kidney Function for more details.

The Nephrotic Syndrome

The nephrotic syndrome is characterized by a urine protein excretion of >3500 mg/24 h or a urine protein-creatinine ratio of >3500 mg/g (termed *nephrotic-range proteinuria*) that may be accompanied by hypoalbuminemia, edema, and hyperlipidemia. However, many patients with high levels of proteinuria may not have the full syndrome.

The pathogenesis of the nephrotic syndrome is not completely understood. Hypoalbuminemia is thought to occur from urinary loss of albumin and increased catabolism (including uptake and catabolism of albumin by the proximal tubule). Edema results predominantly from increased sodium absorption by the distal nephron and increased capillary permeability. Elevated lipids occur from a combination of increased hepatic apolipoprotein synthesis in response to a low plasma oncotic pressure and decreased activity of key enzymes such as lipoprotein lipase and lecithin-cholesterol acyltransferase. Other complications include hypercoagulability, possibly related to loss of natural anticoagulants such as protein C and antithrombin III and upregulation of coagulation factors produced by the liver in response to a low oncotic pressure. Patients with untreated nephrotic syndrome also have a propensity for infection (possibly related to urinary loss of immunoglobulin). Urinary loss of binding proteins may be associated with deficiencies of vitamin D, thyroxine, and iron.

The nephrotic syndrome may be idiopathic (primary) or secondary to systemic diseases such as diabetes, infection, or autoimmune diseases. Although minimal change glomerulopathy is the most common cause of the nephrotic syndrome in children, membranous glomerulopathy and FSGS are the most common causes of idiopathic nephrotic syndrome in adults. Membranous glomerulopathy is the most common cause in white persons and FSGS in black persons. Diabetes is not only the most common secondary cause of the nephrotic syndrome but also the most common cause of the nephrotic syndrome in adults.

Initial evaluation begins by excluding secondary causes related to systemic disease, infection, malignancy, or medication. Screening includes testing for diabetes as well as antinuclear antibody and complement measurements for connective tissue disease. In some patients, cryoglobulins, hepatitis B and C serologies, HIV testing, serum protein and immunoelectrophoresis, and serum free light chains may be useful. Most adult patients with the nephrotic syndrome require a kidney biopsy to obtain a definitive diagnosis.

Treatment of the consequences of the nephrotic syndrome should occur simultaneously with treatment of the specific cause. Elevated lipid levels are typically treated with statin medications, with additional drugs added as needed for control of triglycerides. Anticoagulation may be needed if thrombotic complications occur. Prophylactic anticoagulation is not routinely provided to all patients with the nephrotic syndrome but is suggested in patients who have an additional risk factor for thrombosis. Prophylactic anticoagulation may also be considered in patients who are nephrotic with a serum albumin level ≤2.0 g/dL (20 g/L) with low bleeding risk regardless of cause. In patients with membranous glomerulopathy, the serum albumin threshold to anticoagulate in patients with low risk for bleeding has been suggested to be ≤2.8 g/dL (28 g/L). Edema is treated with a low salt diet and loop diuretics (alone or in combination with a thiazide and potassium-sparing diuretics).

The Nephritic Syndrome

The nephritic syndrome is associated with glomerular inflammation resulting in hematuria, proteinuria, and leukocytes in the urine sediment. The hallmark of hematuria in the nephritic syndrome is the presence of dysmorphic erythrocytes, with or without erythrocyte casts, that reflects a proliferative lesion in the glomeruli (which can be focal or diffuse). Proteinuria in the nephritic syndrome may be highly variable (from a few hundred milligrams to nephrotic levels). Systemic findings may include edema, hypertension, and kidney failure.

Three pathophysiologic mechanisms are associated with the nephritic syndrome: anti-GBM antibodies, pauci-immune GN (defined by necrotizing GN with few or no immune deposits), and immune complex deposition. Three different clinical syndromes may result from these mechanisms based on their time course: acute GN, rapidly progressive GN (RPGN), or chronic GN.

Serum complement levels may be useful in differentiating the underlying etiology of GN; levels are typically normal in anti-GBM antibody disease and pauci-immune GN but are low in immune complex GN (with the exception of IgA nephropathy). Additionally, crescentic lesions on pathologic examination of the kidney in a patient with the nephritic syndrome are associated with RPGN and a poor prognosis without treatment.

KEY POINTS

- The nephrotic syndrome is characterized by a urine protein excretion of >3500 mg/24 h or a urine protein-creatinine ratio of >3500 mg/g that may be accompanied by hypoalbuminemia, edema, and hyperlipidemia.
- Diabetes mellitus is the most common cause of the nephrotic syndrome in adults; membranous glomerulopathy and focal segmental glomerulosclerosis are the most common causes of idiopathic nephrotic syndrome in adults.
- The nephritic syndrome is associated with glomerular inflammation with evidence of hematuria, variable proteinuria, and sometimes leukocytes in the urine sediment; it may be associated with edema, hypertension, and kidney failure.
- Serum complement levels help differentiate the underlying etiology of glomerulonephritis (GN); levels are typically normal in anti–glomerular basement membrane antibody disease and pauci-immune GN but are low in immune-complex GN (with the exception of IgA nephropathy).

Conditions Associated With the Nephrotic Syndrome

See **Table 27** for details on nondiabetic conditions associated with the nephrotic syndrome.

Focal Segmental Glomerulosclerosis

Epidemiology and Pathophysiology

Approximately 25% of adults with idiopathic nephrotic syndrome have focal segmental glomerulosclerosis (FSGS) on biopsy. Incidence is increasing in all races, but it is especially common in black persons.

FSGS may result from genetic mutations to podocyte proteins, may be idiopathic, or may be secondary to another process. Some cases of idiopathic FSGS are thought to be related to a circulating plasma factor because a significant number of patients show recurrence after kidney transplantation. Secondary causes of FSGS include hyperfiltration injury to the glomerulus as in chronic hypertension, diabetes, and instances when kidney mass is reduced (progressive kidney disease, obesity, sickle cell disease, reflux nephropathy, congenital small kidneys, and after nephrectomy). Finally, direct podocyte injury can cause FSGS as seen in infections (HIV) and drugs (pamidronate, interferon).

Clinical Manifestations

Patients with idiopathic FSGS present with either asymptomatic proteinuria or edema. More than two thirds of patients are fully nephrotic at presentation; subnephrotic proteinuria may occur, especially with secondary FSGS from hyperfiltration injury. Hypertension, microscopic hematuria, and varying degrees of kidney failure are common. Serologic tests for systemic disease are typically negative, and complement activation is normal.

Diagnosis

The hallmark of FSGS is the presence of segmental scars in some glomeruli. Electron microscopy shows visceral epithelial cell foot process effacement but no immune deposits. There are several variants of FSGS, but the "collapsing" form is diagnosed when there is severe podocyte hyperplasia leading to collapse of the glomerular tuft. HIV infection is typically associated with collapsing FSGS.

Treatment and Prognosis

In idiopathic FSGS, only a minority of patients experience a spontaneous remission. Therefore, treatment is indicated in most patients. Therapy is usually with glucocorticoids or calcineurin inhibitors, both at the time of initial presentation and for relapsing disease. A complete or partial remission may be seen in up to 40% to 60% of patients using these treatments. Patients who enter remission (even partial) have a good prognosis compared with patients who have refractory disease. FSGS recurs in the transplanted kidney in 30% or more of cases.

TABLE 27. Nondiabetic Conditions Associated With the Nephrotic Syndrome

Condition	Frequency as a Cause of the Nephrotic Syndrome	Comments
Focal segmental glomerulosclerosis	36%-80%	Most common cause of primary nephrotic syndrome in the United States
		Predilection for black persons
		Five subtypes: not otherwise specified; perihilar variant; tip variant; cellular variant; collapsing variant (may be associated with HIV infection, heroin use, parvovirus infection, or pamidronate exposure)
		May be associated with or secondary to:
		Genetic mutations of podocyte proteins
		Direct podocyte injury (e.g., permeability factor), viral infections (e.g., HIV), drugs (e.g., pamidronate)
		Hyperfiltration (e.g., morbid obesity) and decreased kidney mass (congenital kidney dysplasia, reflux nephropathy)
Membranous glomerulopathy	18%-41%	Primary form (most common worldwide): antiphospholipase A_2 receptor autoantibodies can be found in 75% of cases
		May be associated with or secondary to:
		Systemic lupus erythematosus
		Infections: hepatitis B and C virus infections; syphilis; malaria
		Medication exposure: penicillamine; NSAIDs; TNF-α inhibitors; tiopronin
		Mercury or gold exposure
		Malignancies: bladder, breast, colon, lung, pancreas, prostate, stomach carcinoma; carcinoid; sarcomas; lymphomas; leukemias
		Thyroid disease
		Highest predilection for renal vein thrombosis among all causes of the nephrotic syndrome
Minimal change glomerulopathy	9%-16%	Most common cause of primary nephrotic syndrome in children
		May be associated with or secondary to:
		Atopic diseases
		Mononucleosis
		Malignancies: Hodgkin lymphoma and carcinomas
		Medication exposure: NSAIDs; interferon; pamidronate; lithium; rifampin

TNF = tumor necrosis factor.

In secondary FSGS caused by infection or drugs, treatment of the infection or removal of the offending agent may halt progression of the disease and improve symptoms. In obese patients with likely secondary FSGS, weight loss is sometimes associated with a drop in proteinuria, as is the use of ACE inhibitors or angiotensin receptor blockers (ARBs), and is the preferred initial therapy.

Membranous Glomerulopathy

Epidemiology and Pathophysiology

Membranous glomerulopathy (MG) is the most common cause of idiopathic nephrotic syndrome in adult white persons. MG may also be associated with infections (hepatitis B and C, malaria, syphilis), systemic lupus erythematosus, medications (gold salts, NSAIDs), and malignancies (solid tumors, lymphomas). In most patients with idiopathic MG, circulating antibodies directed to podocyte surface antigens (phospholipase A_2 receptor [PLA_2R]) activate complement and damage the GBM.

Clinical Manifestations

Pathological changes of MG may precede clinical manifestations by months. The clinical presentation of MG is indistinguishable from other causes of the nephrotic syndrome (edema, hypertension, microhematuria), but the propensity to thromboembolic events (particularly renal vein thrombosis) is much higher. Secondary causes should be sought, particularly occult malignancy in older patients.

Diagnosis

Diagnosis of MG is made by kidney biopsy. Light microscopy shows glomerular capillary loops that often appear thickened without any proliferative lesions. Immunofluorescence and electron microscopy show subepithelial immune dense

deposits. Where available, PLA_2R antibodies should be measured.

Treatment and Prognosis

Up to one third of patients with idiopathic MG remit spontaneously in 6 to 12 months. Conservative management is appropriate during this period. In patients with idiopathic MG who have persistent disease after 6 to 12 months or who have worsening kidney function or a thromboembolic event, regimens containing alternating glucocorticoids with cyclophosphamide or calcineurin inhibitors (cyclosporine or tacrolimus) may be employed. Other options for relapsing or refractory disease include mycophenolate mofetil, adrenocorticotropic hormone, and the anti-B-cell antibody rituximab. Renal survival is excellent if patients enter remission. In general, older patients, men, and those with heavy, persistent proteinuria and kidney dysfunction are at risk of progression.

Among the secondary causes of MG, treatment of hepatitis B virus infection with antiviral agents has been associated with improvement of proteinuria; glucocorticoids are not of benefit. Similarly, remission of proteinuria may occur with treatment of an associated malignancy or withdrawal of drugs, without needing immunosuppression. Treatment of lupus MG employs immunosuppressive regimens similar to primary MG.

Minimal Change Glomerulopathy

Epidemiology and Pathophysiology

Minimal change glomerulopathy (MCG; also known as minimal change disease) is the most common cause of idiopathic nephrotic syndrome in children and accounts for approximately 10% of cases in adults. Secondary causes of MCG include medications (such as NSAIDs, lithium, pamidronate, and the interferons) and malignancies (such as Hodgkin lymphoma and thymoma). A history of viral respiratory infection, atopy, or immunization preceding the onset of edema may be present. The pathogenesis of MCG is not fully understood but is thought to be related to production of cytokines by immune cells that lead to podocyte dysfunction.

Clinical Manifestations

Patients with MCG typically present with acute onset of edema and weight gain due to fluid retention. Urine protein levels tend to be significantly elevated (urine protein-creatinine ratio typically 5000-10,000 mg/g). Azotemia may occur, especially in older adults. The urine sediment is typically benign with few erythrocytes or erythrocyte casts. Complement levels are normal and serologic test results for systemic disease are negative.

Diagnosis

Diagnosis of MCG is confirmed with kidney biopsy, which shows normal glomeruli on both light and immunofluorescence microscopy. The tubules may show lipid accumulation. On electron microscopy, the GBM is normal with extensive effacement of visceral epithelial foot processes.

Treatment and Prognosis

Patients typically respond to glucocorticoids within 8 to 16 weeks. However, relapse is common, and in up to 40% of patients, the course of MCG is one of remission followed by relapse. For frequently relapsing or glucocorticoid-dependent disease, treatment options include cyclophosphamide, calcineurin inhibitors (tacrolimus or cyclosporine), mycophenolate mofetil, and rituximab. Although uncommon, progressive kidney failure may occur.

Diabetic Nephropathy

Epidemiology and Pathophysiology

Diabetic nephropathy (DN) is the leading cause of ESKD in the United States, accounting for approximately 40% of new patients presenting with kidney failure. Risk factors for developing DN include older age, race (American Indian, Mexican American, and black), poor glycemic control, hypertension, cigarette smoking, and a family history of kidney disease. The strongest clinical indicator for progressive kidney disease is the level of urine albumin. The pathogenesis of DN involves an early phase of hyperfiltration, which is mediated by hyperglycemia-associated elevation of angiotensin levels. This (reversible) phase is followed by a general activation of inflammatory and profibrotic pathways, resulting in laying down of extracellular matrix in all compartments of the kidney, followed by fibrosis and, eventually, ESKD.

From a pathologic standpoint, DN affects every compartment of the kidney. In the glomerulus, there is expansion of the mesangium and thickening of the basement membrane, followed by focal (nodular) sclerosis (the Kimmelstiel-Wilson lesion) then global sclerosis of the glomerulus. Interstitial fibrosis, tubular atrophy with thickened tubular basement membranes, and arteriolosclerosis are also seen.

Clinical Manifestations

Moderately increased albuminuria (formerly known as microalbuminuria), defined as a urine albumin-creatinine ratio of 30 to 300 mg/g, is typically the first abnormality seen in patients with type 1 and type 2 diabetes. It occurs in approximately 30% of patients after a mean of 5 to 15 years from diagnosis in type 1 and at less predictable intervals in type 2. Overt nephropathy (urine protein-creatinine ratio >300 mg/g) occurs around 10 to 15 years from disease onset in approximately 50% of patients with moderately increased albuminuria and progresses to ESKD in most patients.

Diagnosis

Annual testing for moderately increased albuminuria should begin at the time of diagnosis in type 2 diabetes and 5 years after diagnosis in type 1 diabetes. Kidney biopsy is not indicated unless there is a suspicion of another glomerular disease. However, the presence of findings of another systemic disease, abnormal serologies, acute onset of the nephrotic syndrome or short duration from onset of diabetes to onset of proteinuria, and rapid rate of progression of kidney

dysfunction suggest an alternative diagnosis and are indications for kidney biopsy.

Treatment and Prognosis

Achieving targets of glycemic control (hemoglobin A_{1c} <7%) and blood pressure (<140/90 mm Hg, according to the eighth report of the Joint National Committee) has been shown to prevent or delay progression of DN. The use of tighter glycemic (hemoglobin A_{1c} <6.5%) and blood pressure (<130/80 mm Hg) targets is controversial.

In patients who have diabetes with moderately increased albuminuria or severely increased albuminuria (formerly known as macroalbuminuria or overt proteinuria), ACE inhibitors or ARBs have been shown to slow progression. However, overly aggressive inhibition of the renin-angiotensin system, particularly with a combination of direct renin inhibitors/ACE inhibitors/ARBs, has not been shown to improve kidney outcomes and may be associated with hyperkalemia and episodes of acute kidney injury. Because of this, combination therapy is not recommended.

KEY POINTS

- Treatment of idiopathic focal segmental glomerulosclerosis includes glucocorticoids or calcineurin inhibitors, both at the time of initial presentation and for relapsing disease.
- Up to one third of patients with idiopathic membranous glomerulopathy remit spontaneously in 6 to 12 months; conservative management is appropriate during this period. *(Continued)*

KEY POINTS *(continued)*

- Patients with minimal change glomerulopathy typically respond to glucocorticoids; for frequently relapsing or glucocorticoid-dependent disease, treatment options include cyclophosphamide, calcineurin inhibitors, mycophenolate mofetil, and rituximab.
- Achieving targets of glycemic control (hemoglobin A_{1c} <7%) and blood pressure (<140/90 mm Hg) has been shown to prevent or delay progression of diabetic nephropathy.
- ACE inhibitors or angiotensin receptor blockers have been shown to slow progression of diabetic nephropathy.

Conditions Associated With the Nephritic Syndrome

See **Table 28** for details on conditions associated with the nephritic syndrome.

Rapidly Progressive Glomerulonephritis

Epidemiology and Pathophysiology

Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome characterized by evidence of GN with progression to kidney failure within weeks. It represents a clinical pattern of disease that may be associated with any etiology of GN or may be idiopathic. However, RPGN is particularly common with anti-GBM antibody disease (in younger patients) and pauci-immune small-vessel vasculitis (in older patients).

TABLE 28. Conditions Associated With the Nephritic Syndrome

Condition	Frequency as a Cause of the Nephritic Syndrome	Comments
Anti-glomerular basement membrane antibody disease	3%	Frequent cause of RPGN
Pauci-immune glomerulonephritis	15%-25%	Frequent cause of RPGN
Immune complex-mediated glomerulonephritis		
IgA nephropathy	25%-30%	Often asymptomatic; rarely causes RPGN
Henoch-Schönlein purpura	—	Often acute onset, occasionally with RPGN
Lupus nephritis[a]	20%	Variably associated with RPGN
Infection-related glomerulonephritis[a]	4%-8%	—
Membranoproliferative glomerulonephritis[a]	6%-10%	Rarely causes RPGN
Cryoglobulinemia[a]	—	Frequent cause of RPGN
Thin basement membrane disease	—	Asymptomatic microhematuria; good prognosis
Hereditary nephritis (also known as Alport syndrome)	—	Chronic and slowly progressive; extrarenal abnormalities involving the eye and cochlea

RPGN = rapidly progressive glomerulonephritis.

[a]Typically associated with low serum complement levels.

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Clinical Manifestations

Patients with RPGN typically present with the nephritic syndrome and may sometimes be in advanced kidney failure at the time of presentation. Other symptoms and clinical findings related to an underlying cause may also be present, such as systemic signs of vasculitis (arthritis, epistaxis, hemoptysis) or lung hemorrhage (Goodpasture syndrome). Kidney function usually deteriorates rapidly unless treatment is instituted.

Diagnosis

The diagnostic approach to RPGN is similar to that in patients with GN. Testing may indicate the underlying condition. For example, serologic tests may show positivity to ANCA in patients with systemic vasculitis or to anti-GBM antibodies in patients with anti-GBM antibody disease. Chest imaging may show diffuse infiltrates in a patient with pulmonary hemorrhage or nodules in the presence of granulomatosis with polyangiitis (formerly known as Wegener granulomatosis). Definitive diagnosis is made with kidney biopsy, which typically shows glomerular crescents associated with inflammation of glomerular capillaries. The specific diagnosis is made with immunofluorescence microscopy (immune complexes, linear anti-GBM antibody staining, or pauci-immune GN).

Treatment and Prognosis

All patients with RPGN (except those with infection-related GN who are actively infected) should be treated with high-dose intravenous (pulse) glucocorticoids, followed by oral glucocorticoid therapy. Most patients with RPGN also receive cyclophosphamide (oral or intravenous) or rituximab in cases of pauci-immune GN. Plasmapheresis is indicated in the presence of pulmonary hemorrhage or severe kidney failure to remove circulating antibody. Rapid diagnosis is critical; a delay may result in irreversible kidney failure or death from pulmonary hemorrhage. See Anti–Glomerular Basement Membrane Antibody Disease and Pauci-Immune Glomerulonephritis for further details. H

Anti-Glomerular Basement Membrane Antibody Disease

Epidemiology and Pathophysiology

Anti-GBM antibody disease is an autoimmune disease caused by antibodies directed against the noncollagenous domain of type IV collagen. These antibodies bind to the GBM, inciting an inflammatory response, damage to the GBM, and the formation of a proliferative and often crescentic glomerulonephritis. The same process can occur with the basement membrane of pulmonary capillaries, leading to pulmonary hemorrhage (known as *Goodpasture syndrome*). Anti-GBM antibody disease accounts for <15% of cases of RPGN.

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Clinical Manifestations

Patients with anti-GBM antibody disease present with a nephritic picture. Kidney function may rapidly deteriorate over days to weeks. Patients with pulmonary hemorrhage may have life-threatening respiratory failure with diffuse alveolar infiltrates on chest radiograph.

Diagnosis

In anti-GBM antibody disease, all of the classic features of the nephritic syndrome are usually present at the time of diagnosis. Serologies show normal complement levels and elevated anti-GBM antibody levels. On kidney biopsy, there is a proliferative GN, often with many crescents. There is linear deposition of immunoglobulin (usually IgG) along the GBM by immunofluorescence, but electron microscopy does not show electron-dense deposits.

Treatment and Prognosis

In patients with anti-GBM antibody disease, immunosuppressive therapy with cyclophosphamide and glucocorticoids, combined with daily plasmapheresis to remove circulating anti-GBM antibodies, leads to stabilization or improvement if treated early. The renal prognosis is poor in patients who require dialysis at the time of presentation. Relapses are rare. H

Pauci-Immune Glomerulonephritis

See Systemic Vasculitis in MKSAP 17 Rheumatology for more information.

Epidemiology and Pathophysiology

Pauci-immune GN is caused by microscopic vessel vasculitis affecting the kidney, resulting in necrotizing lesions in the glomeruli with few or no immune deposits. The renal lesion may occur with or without systemic vasculitis and is the most common cause of RPGN. Most patients have circulating ANCA directed against neutrophils. Three forms of systemic vasculitis are associated with pauci-immune GN: granulomatosis with polyangiitis (GPA; formerly known as Wegener granulomatosis), with granulomas associated with necrotizing vasculitis; microscopic polyangiitis (MPA), which is similar to GPA but without granulomas; and eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strauss syndrome).

Clinical Manifestations

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Kidney manifestations of pauci-immune GN may range from minimal disease with only hematuria to RPGN. Systemic symptoms may be nonspecific, including low-grade fever, myalgia, fatigue, and arthritis. Other clinical manifestations may include leukocytoclastic vasculitis resulting in palpable purpura, as well as pulmonary disease (the spectrum can vary from a nonresolving pulmonary infiltrate to fulminant pulmonary hemorrhage.) Compared with MPA, GPA may manifest with more prominent upper and lower respiratory tract involvement with granulomatous lesions on biopsy, often associated with tissue destruction (saddle nose, tracheal stenosis, hearing loss). Patients with EGPA usually have a history of asthma, pulmonary infiltrates, and eosinophilia.

Diagnosis

CONT.

More than 80% of patients with MPA or GPA are ANCA positive. GPA is closely associated with proteinase 3 (PR3)-ANCA, whereas MPA is primarily associated with myeloperoxidase (MPO)-ANCA. Up to 10% of patients with GPA and MPA are ANCA negative. Complement levels are normal. Tissue biopsy is required to make the diagnosis, but an empiric decision to begin treatment should be considered in rapidly deteriorating disease. Kidney biopsy shows absent or minimal staining with immunoglobulin (hence the term *pauci-immune*). The spectrum of abnormalities may range from mild focal and segmental GN to a diffuse necrotizing and crescentic GN. There is variable interstitial inflammation (granulomas imply a diagnosis of GPA) and vasculitis of arterioles and venules. Glomerular and interstitial fibrosis accompanies chronic disease.

Treatment and Prognosis

For induction, combination therapy with glucocorticoids and cyclophosphamide, with or without plasmapheresis, has markedly improved kidney and patient survival rates in those with ANCA vasculitis. The anti-B-cell antibody rituximab is equally effective and safer compared with cyclophosphamide in patients with mild-moderate disease. Maintenance regimens using azathioprine, mycophenolate mofetil, or methotrexate have been employed after patients have achieved remission.

Adverse prognostic signs include older age, severe pulmonary involvement, and severe kidney failure at time of presentation.

KEY POINTS

- Rapidly progressive glomerulonephritis is a clinical syndrome characterized by evidence of glomerulonephritis with progression to kidney failure within weeks.
- In patients with anti-glomerular basement membrane antibody disease, cyclophosphamide and glucocorticoids combined with daily plasmapheresis leads to stabilization or improvement if treated early.
- Kidney manifestations of pauci-immune glomerulonephritis may range from minimal disease with only hematuria to rapidly progressive glomerulonephritis; kidney biopsy shows absent or minimal staining with immunoglobulin.

Immune Complex-Mediated Glomerulonephritis

IgA Nephropathy

Epidemiology and Pathophysiology

IgA nephropathy (IgAN) is the most frequent cause of chronic GN, particularly in Asia and Northern Europe, and is rare in people of African descent. IgAN occurs more commonly in men, with a peak occurrence in the second to third decades of life. The pathogenesis of IgAN is thought to involve several sequential events beginning with genetic predisposition to the disease, the occurrence of IgA molecules that are galactose deficient at the hinge region of the immunoglobulin molecule, and the formation of autoantibodies against the abnormal IgA leading to immune complex formation. Immune complexes with associated inflammatory lesions are seen in the glomeruli in IgAN or in multiple extrarenal sites in IgA vasculitis (Henoch Schönlein purpura).

Clinical Manifestations

In adults, asymptomatic microscopic hematuria with or without proteinuria is the most common presentation of IgAN. Episodic gross hematuria following an upper respiratory tract infection (also known as *synpharyngitic nephritis*) is another classic presentation. Other features of nephritis such as hypertension, edema, and kidney failure with RPGN may occur in the acute phase or in patients with chronic disease.

Diagnosis

No serologic tests are diagnostic of IgAN. Serologic tests for systemic diseases and complement levels are usually normal. Kidney biopsy is required to make the diagnosis. On light microscopy, the most common finding is mesangial proliferation. Occasionally, endocapillary proliferation and crescents may be seen. The finding of IgA deposits as either the dominant or the codominant immunoglobulin on immunofluorescence is the diagnostic criterion for this condition.

Treatment and Prognosis

IgAN is a chronic condition, and many patients have a benign course with a 20-year kidney survival of approximately 75%. Low-risk patients are usually not actively treated and are followed with continued observation. Proteinuria >1000 mg/g, hypertension, kidney dysfunction, and mesangial and endothelial proliferation with tubulointerstitial damage are associated with a worse outcome. Patients with proteinuria and risk factors for progression may benefit from ACE inhibitors or ARBs. A 6-month course of glucocorticoids has also shown benefit in such patients.

IgA Vasculitis (Henoch-Schönlein Purpura)

Henoch-Schönlein purpura (HSP) is an IgA-associated small-vessel vasculitis seen predominantly in children but may occur in adults (see MKSAP 17 Rheumatology, Systemic Vasculitis). Kidney involvement is similar to IgAN, with the typical manifestations of the nephritic syndrome, often with acute kidney injury. Organ involvement may occur concurrently or sequentially. Recurrences, especially during the first year, are common. Diagnosis is confirmed either by finding an IgA-dominant leukocytoclastic vasculitis or by kidney biopsy, which shows lesions similar to IgAN. HSP is typically self-limiting. Some patients with severe abdominal findings are treated with short courses of high-dose glucocorticoids. Patients with severe GN are occasionally treated with immunosuppressive drugs; however, there are no reliable data to gauge efficacy.

Lupus Nephritis

See Systemic Lupus Erythematosus in MKSAP 17 Rheumatology for more information.

Epidemiology and Pathophysiology

Kidney involvement in systemic lupus erythematosus (SLE) is common, and lupus nephritis (LN) is a major source of morbidity. SLE/LN is the archetypal immune complex disease with immune deposits in all areas of the glomerulus. This leads to distinct patterns of histology, which are classified by the International Society of Nephrology into six classes (**Table 29**).

Clinical Manifestations

Patients typically present with extrarenal symptoms of SLE at the time of diagnosis of LN, with active lupus serologies and low complement levels. Occasionally, LN may be the initial manifestation. Patients with class I or II LN may have minimal or no renal findings, and those with classes III and IV present with varying degrees of the nephritic syndrome. Patients with class V LN present predominantly with proteinuria. Class VI is the end stage of long-standing LN. A kidney biopsy is indicated when clinically manifest kidney disease is present (typically proteinuria >500 mg/g and hematuria).

TABLE 29. Classification of Lupus Nephritis

Classification	Comments
I. Minimal mesangial LN	No renal findings
II. Mesangial proliferative LN	Mild clinical kidney disease; minimally active urine sediment; mild to moderate proteinuria (never nephrotic) but may have active serology
III. Focal proliferative LN, <50% glomeruli involved (active; active and chronic; or chronic)	More active urine sediment changes; often active serology; increased proteinuria (about 25% nephrotic); hypertension may be present; some evolve into class IV pattern; active lesions require treatment, chronic lesions do not
IV. Diffuse proliferative LN (>50% glomeruli involved); all may be with segmental or global involvement (active; active and chronic; or chronic)	Most severe kidney involvement with active urine sediment, hypertension, heavy proteinuria (frequent nephrotic syndrome), and often reduced GFR; serology very active; active lesions require treatment
V. Membranous LN glomerulonephritis	Significant proteinuria (often nephrotic) with less active serology
VI. Advanced sclerosing LN	More than 90% glomerulosclerosis; no treatment prevents kidney failure

GFR = glomerular filtration rate; LN = lupus nephritis.

Diagnosis

Serologic tests for SLE, including antinuclear antibodies and anti-double-stranded DNA antibodies, are typically positive. C3 and C4 complement levels are depressed, signifying activation of the classical complement pathway. Kidney biopsy is required to make the diagnosis and classify the lesions of LN (see Table 29). The histologic class and degree of activity and chronicity on biopsy are helpful in guiding therapy.

Treatment and Prognosis

Patients with class I and II lesions require no specific therapy directed at the kidney. Most patients with class III LN and all patients with class IV LN benefit from aggressive combination immunosuppressive therapy. In class V (membranous) LN, the clinical course is generally more benign, and therapy is similar to idiopathic membranous glomerulopathy. Induction therapy for severe proliferative LN (active class III or class IV) includes glucocorticoids with either cyclophosphamide or mycophenolate mofetil. The addition of plasmapheresis has not been shown to improve outcomes. Maintenance therapy with mycophenolate mofetil or azathioprine may be used after the 6-month induction period.

See **Table 30** for more information on the treatment of the specific LN classes.

Infection-Related Glomerulonephritis

Epidemiology and Pathophysiology

In the past, streptococcal infection with nephritogenic strains followed by GN led to the term *postinfectious* or *poststreptococcal GN* (PSGN) being employed. Over the past three decades, however, there has been a shift in the epidemiology of this group of diseases, especially in developed countries. Older adults and immunocompromised patients now constitute a significant proportion of such patients. The sites of infection can be widespread (not just the upper respiratory tract and skin as in PSGN). Nonstreptococcal infection, particularly with *Staphylococcus*, is as or more common than streptococcal infection. Finally, GN can be present at the time of infection (rather than a delay of at least a week after the infection, as in PSGN). The term *infection-related glomerulonephritis* (IRGN), therefore, is more appropriate. Diabetes is a major risk factor for staphylococcal-associated GN, with methicillin-resistant strains more common in such patients. Rarely, coagulase-negative *Staphylococcus* and gram-negative organisms (*Escherichia coli* being the most common) may be associated with GN.

IRGN is an immune complex–mediated disease. The antigen in the immune complex is derived from the infectious agent. After depositing in the subepithelial area (either within preformed immune complexes or as in-situ immune complex formation), complement activation and subsequent recruitment of inflammatory cells occur, leading to a proliferative GN.

Clinical Manifestations

Patients with IRGN clinically present with acute nephritic syndrome. In PSGN, the clinical manifestations typically occur

TABLE 30. Treatment of Lupus Nephritis

Class/Group	Treatment Recommendation
Class I	Treat as dictated by the extrarenal clinical manifestations of lupus
Class II	Proteinuria <1000 mg/24 h: as dictated by the extrarenal clinical manifestations of lupus
	Proteinuria >3000 mg/24 h with glucocorticoids or calcineurin inhibitors (CNIs)
Class III and IV	For remission induction:
	Initial therapy with glucocorticoids, combined with either cyclophosphamide or mycophenolate mofetil (MMF)
	For maintenance therapy:
	Azathioprine or MMF and low-dose oral glucocorticoids
	CNI with low-dose glucocorticoids in patients who are intolerant of MMF and azathioprine
Class V	For normal kidney function and non-nephrotic-range proteinuria: treat with antiproteinuric and antihypertensive medications, and only treat with glucocorticoids and immunosuppressives as dictated by the extrarenal manifestations of lupus
	For persistent nephrotic proteinuria, glucocorticoids plus an additional immunosuppressive agent: cyclophosphamide, or CNI, or MMF, or azathioprine
Class VI	Glucocorticoids and immunosuppressives only as dictated by the extrarenal manifestations of lupus
Pregnant patients with active disease	Hydroxychloroquine and prednisone are first-line therapy; azathioprine for more serious disease (azathioprine is inactivated by the placenta)

Recommendations from Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Inter Suppl. 2012;2:139-274. Copyright, 2012. With permission from Macmillan Publishers, Ltd.

CONT. after a latent period of 1 to 6 weeks. Staphylococcal GN typically is associated with ongoing infection at the time of development of nephritis. New-onset heart failure can occur in 25% of older patients.

Diagnosis

The diagnosis of IRGN is made on clinical grounds in patients who are nephritic and have an ongoing or preceding infection. A search for infection using microbiologic cultures usually shows the inciting organism in nonstreptococcal GN.

Most patients (especially those with PSGN) show depressed complement levels (usually C3, signifying activation of the alternative complement pathway). In PSGN, antibodies to streptococcal antigens (antistreptolysin-O, anti-DNAse B) are detected in almost all cases.

Adults may need a kidney biopsy to differentiate IRGN from other causes of kidney failure, notably acute interstitial nephritis from antibiotics or toxic acute kidney injury. Kidney biopsy typically shows a diffuse endocapillary proliferative and exudative glomerulonephritis, and, rarely, crescents on light microscopy. Immunofluorescence microscopy reveals C3-dominant or C3-codominant (with IgA or IgG) glomerular staining, which shows large "humps" of immune deposits in a predominant subepithelial distribution on electron microscopy.

Treatment and Prognosis

Treatment of the underlying infection is usually all that is necessary. There are no data to show that immunosuppressive therapy has a role in the treatment of IRGN. Up to 50% of adult patients (especially those with diabetes, older patients, and those with preexisting chronic kidney disease) may have persistent kidney dysfunction or even progress to ESKD.

Membranoproliferative Glomerulonephritis

Epidemiology and Pathophysiology

Membranoproliferative glomerulonephritis (MPGN) refers to the histologic findings of mesangial and endocapillary proliferation combined with the thickening of the GBM. There are two distinct pathophysiologic mechanisms: immune complex deposition (with or without complement staining) and activation of the alternative complement pathway with complement deposition (with minimal immunoglobulin staining) of the glomeruli. Immunoglobulin-mediated MPGN is associated with immune complex disease such as SLE, infections such as hepatitis C, and monoclonal gammopathy. Complement-mediated MPGN includes dense deposit disease (DDD) and C3 glomerulonephritis (C3GN); DDD and C3GN are rare diseases associated with uncontrolled activation of the alternative complement pathway.

Clinical Manifestations

Most patients with idiopathic MPGN are children or young adults who present with proteinuria or the nephrotic syndrome; they may also present with chronic nephritis.

Diagnosis

MPGN is a descriptive diagnosis of the kidney biopsy findings. Unless obvious, a search for the underlying cause should be undertaken. The findings of immunoglobulin (with or without complement staining) on biopsy should prompt a search for infections, autoimmune disease, or monoclonal gammopathy. Serologic tests may show evidence of an underlying infection (such as hepatitis C) or autoimmune disease (such as SLE). Complement levels may be depressed in MPGN, with an intermittently low serum complement level in immunoglobulin-associated MPGN and a reduced C3 level in C3GN and DDD; MPGN with predominant complement staining on biopsy should lead to an investigation of alternative complement pathway disorders.

Treatment and Prognosis

Treatment of the causative infection, autoimmune disease, or monoclonal gammopathy is the primary therapy in patients with MPGN. There is no specific treatment available for the C3 glomerulopathies; immunosuppressive regimens, typically involving tapering doses of glucocorticoids, have been employed with varying results. There is a significant recurrence rate of MPGN in patients with kidney transplants.

Cryoglobulinemia

Cryoglobulins are immune-related proteins that precipitate at temperatures below 37.0 °C (98.6 °F) in vitro that may be associated with a systemic inflammatory syndrome involving small- to medium-vessel vasculitis. There is wide variation in the type of kidney disease associated with cryoglobulinemia depending on the underlying etiology, including glomerulonephritis. See Kidney Manifestations of Gammopathies for more information.

Collagen Type IV-Related Nephropathies

Type IV collagen is an essential component of the GBM. Two genetic diseases affecting type IV collagen, hereditary nephritis (Alport syndrome) and thin basement membrane disease, cause glomerular disease. See Genetic Disorders and Kidney Disease for more information.

KEY POINTS

- Kidney biopsy is required for diagnosis of IgA nephropathy, with the most common finding being mesangial proliferation on light microscopy.
- Kidney biopsy is required to make the diagnosis and classify the lesions of lupus nephritis.
- Most patients with class III lupus nephritis (LN) and all patients with class IV LN benefit from aggressive combination immunosuppressive therapy.
- The diagnosis of infection-related glomerulonephritis is made on clinical grounds in nephritic patients who have an ongoing or preceding infection.
- Immunoglobulin-mediated membranoproliferative glomerulonephritis (MPGN) is associated with immune complex disease; complement-mediated MPGN includes dense deposit disease and C3 glomerulonephritis.

Kidney Manifestations of Gammopathies

Overview

Monoclonal production of protein by lymphocytes or plasma cells is associated with specific kidney disorders that may predominantly involve the glomerular or tubular compartments. There is increasing recognition of kidney diseases associated with clonal disorders that do not fulfill criteria for lymphoma or overt myeloma; these conditions are known as *monoclonal disorders of renal significance*. Kidney manifestations of monoclonal gammopathies may include variable degrees of proteinuria (sometimes the full nephrotic syndrome), tubular dysfunction, hypertension, and kidney failure.

A monoclonal gammopathy is present when serum or urine electrophoresis shows a monoclonal band or if there are abnormalities in the serum free light chain ratio. Diagnosis of kidney involvement in monoclonal gammopathy usually requires biopsy, which shows evidence of immune deposits in glomeruli, the tubulointerstitial compartment, or blood vessels. The pattern of deposition on biopsy, either organized or non-organized, may be diagnostically helpful (**Table 31**).

Management of monoclonal gammopathies with kidney involvement is focused on treatment of the underlying monoclonal disorder to prevent further kidney injury. Therapy for the associated kidney disease is primarily supportive and based on the nature and degree of kidney involvement. Management of other potentially nephrotoxic complications associated with monoclonal gammopathies, including hypercalcemia, hyperuricemia, and volume contraction in patients with multiple myeloma, is an essential component of treatment.

See Multiple Myeloma and Related Disorders in MKSAP 17 Hematology and Oncology for more information.

Amyloidosis

Amyloid consists of randomly oriented fibrils composed of various proteins that form organized β-pleated sheets within the tissues; amyloid resulting from monoclonal lambda or kappa light chains is termed *AL amyloid* (*AA amyloid* results from AA protein, an acute phase reactant seen in chronic inflammatory diseases). In amyloidosis involving the kidney, glomerular lesions tend to be prominent and present with proteinuria, often in the nephrotic range. However, amyloid deposits may also be found in tubular basement membranes, interstitial space, and blood vessels. Findings on biopsy show deposits that stain apple green on Congo red staining under a polarizing microscope; these deposits are also visible on electron microscopy. Primary treatment depends on the type of

TABLE 31. Causes and Patterns of Immune Deposition in Monoclonal Gammopathy

Organized Deposits
AL amyloid
Immunotactoid glomerulonephritis
Fibrillary glomerulonephritis
Cryoglobulinemic glomerulonephritis
Non-Organized Deposits
Monoclonal deposition disease (light chain/heavy chain/both)