Chapter e66: Glomerular Diseases

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KEY CONCEPTS

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1. Glomerular diseases vary in causes, clinical symptoms, treatments, and outcomes, but are united because they all affect the glomerulus, which is the filter of the kidney.

2. The five principal clinical features of glomerular disease are hematuria, proteinuria, edema, hypertension, and progressive kidney failure. These features occur to varying degrees among different glomerular diseases and between individual patients.

3. Glomerular diseases can be classified with many different systems, each of which has advantages and disadvantages. A basic classification is whether a glomerular disease is nephritic (reflecting inflammatory injury) or nephrotic (reflecting noninflammatory injury).

4. For some glomerular diseases there are treatments that can induce a remission, which is often based on suppression of the immune system. If disease remission cannot be achieved, we use conservative measures to reduce proteinuria, edema, hypertension, hyperlipidemia, and hypercoagulability, with the aim of stabilizing the loss of kidney function.

5. Patients undergoing treatment for glomerular disease must be monitored closely to assess their therapeutic response and any treatment-induced toxicity.

6. Among all glomerular diseases, minimal-change nephropathy is the most responsive to treatment with steroids.

7. Focal segmental glomerulosclerosis (FSGS) is difficult to treat for two reasons: first, it is difficult to distinguish primary FSGS, which may respond to steroids or other immunosuppressants, from the many causes of secondary FSGS, which will not respond to these treatments; second, the response of primary FSGS to steroids, unlike minimal change disease, is not robust.

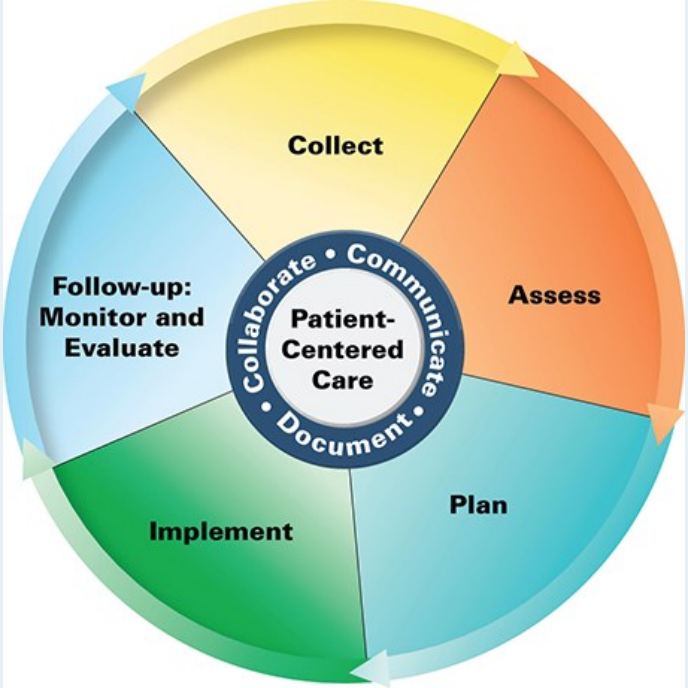
8. Systemic lupus erythematosus can cause many different types of kidney disease. The optimal treatment of lupus nephritis depends on the underlying lesion, the disease activity on biopsy, and the patient's symptoms in organs other than the kidney.

9. Post-streptococcal glomerulonephritis arises when the immune response to bacteria damages the glomerular filter. By definition, post-streptococcal glomerulonephritis occurs after the infection, so there is no role for antibiotic therapy. Symptoms are treated aggressively with conservative measures.

10. Membranous nephropathy can be either primary disease, or secondary to a long list of other causes. Within the last 10 years, the cause of primary membranous nephropathy has been identified as auto-antibodies to the phospholipase A2 receptor, resulting in significant improvements in diagnosis, treatment, and outcomes.

PATIENT CARE PROCESS

Patient Care Process for Managing Glomerular Disease



Collect

- Patient characteristics (eg, age, sex, ethnicity)
- History of present illness (eg, edema, gross hematuria, extra-renal symptoms such as hemoptysis and joint pains)
- Patient medical history (personal and family) (see Table e66-2)
- Social history (eg, tobacco use, history of drug use) and dietary habits including sodium intake
- Current medications including OTC NSAID use and blood pressure medications
- Objective data (see Table e66-2)
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
  - Labs including serum creatinine (SCr), serum albumin, complete blood count, urinalysis, random urine protein:creatinine ratio, and urine microscopy
  - May consider a limited serologic workup (eg, complement component C3 and C4 levels, anti-nuclear antibody, anti-phospholipase A2 receptor antibody)
  - Renal ultrasound

Assess

- Blood pressure (goal generally <130/80 mm Hg)
- Volume status for presence of peripheral edema, pulmonary edema, hypertension.
- Presence of life-threatening complications such as pulmonary hemorrhage and venous thromboembolism

- Ability to monitor weights and blood pressures at home
- Ability to tolerate immunosuppressive therapy such as corticosteroids (potential risk of steroid-induced diabetes, infections, weight gain, bone disease, and mania)
- Ability to pay for treatments

Plan*

- Blood pressure control with angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs)
- Volume control (edema +/− hypertension) with diuretics (see Table e66-3)
- Home monitoring of blood pressure and weight
- Immunosuppressive therapy if indicated
- Regular lab monitoring
- Patient education
- Referral to other providers, when applicable

Implement*

- Provide patient education regarding all elements of treatment and follow-up plan
- Schedule follow-up labs and clinic visits

Follow-up: Monitor and Evaluate

- Achievement of remission (definition depends on type of glomerular disease)
- Achievement of blood pressure and volume control (see Table e66-3)
- Taper/discontinue immunosuppressive medications when applicable
- Monitor for adverse events of treatment

Collaborate with patient, caregivers, and other healthcare professionals.

BEYOND THE BOOK

BEYOND THE BOOK

Visit the National Kidney Foundation website <https://www.kidney.org>. This website is useful to learn about kidney disease from the perspective of both patients and healthcare providers. Watch the video titled “New Insights Regarding Treatment of Membranous Nephropathy” at <https://www.kidney.org/content/new-insights-regarding-treatment>. This video provides an overview of the approach to treating membranous nephropathy, particularly with regards to immunosuppressive therapy, and is useful to enhance student understanding regarding the ASSESS and PLAN steps in the patient care process.

INTRODUCTION

Glomerular disease is one of the most common causes of end-stage kidney disease (ESKD). From the 2018 yearly report of all patients nationwide by US Renal Data Systems, the number of patients who started dialysis that year (incident patients) was 213,588, of whom 7% carried a diagnosis of primary glomerular disease.[1] This under-represents the total burden of glomerular disease because this figure of 7% does not include secondary glomerular diseases such as classic diabetic nephropathy, does not include patients starting dialysis due to undiagnosed glomerular disease that was erroneously labeled "hypertensive nephropathy,"[2] and does not include patients with "ESKD of unknown cause," who never had a biopsy, some of whom likely had glomerular disease. Altogether, if we combine primary, secondary, and undiagnosed glomerular diseases, we account for about 40% to 60% of new ESKD patients starting dialysis each year, which is roughly 100,000 people. A larger number of patients with glomerular disease are receiving treatment and trying to avoid progression of their disease to ESKD.

The aim of this chapter is to introduce clinicians to the general principles of glomerular disease, and then to highlight the characteristics of some of the most common glomerular disorders. Diabetic nephropathy is the most common glomerular disease in the United States and worldwide and is presented in Chapter 94. Nevertheless, the general principles of glomerular disease discussed in this chapter also apply to diabetic glomerular disease.

NORMAL GLOMERULAR ANATOMY AND FUNCTION

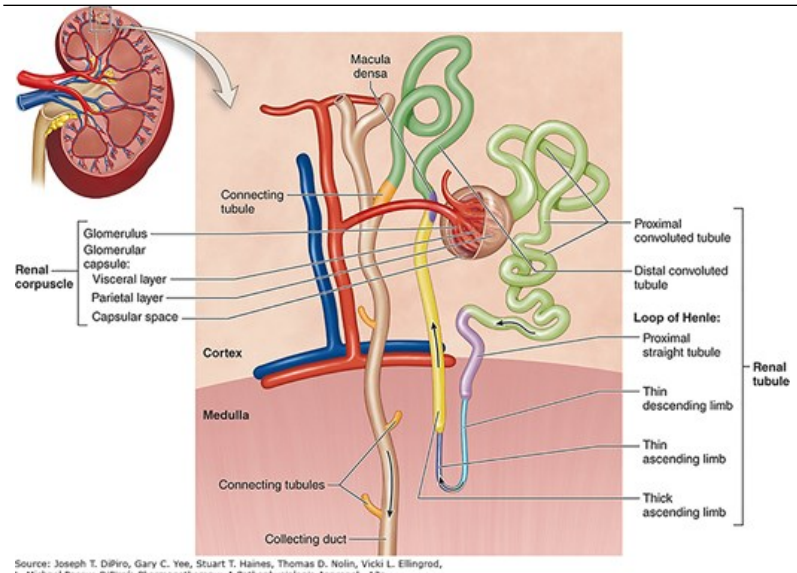
Evaluation, diagnosis, and treatment of glomerular disease is complex, because each glomerular disease differs from the next, and has such a wide variety with a given disease, including variations in cause, clinical severity, and histopathology on kidney biopsy, organ involvement and treatment, that the nuance and detail can become overwhelming. To simplify, there is a unifying feature to all glomerular diseases, which can be appreciated by considering the kidney as an organ that performs two basic functions: (1) the kidneys filter blood, making about 170 L of filtrate very day, which can be thought of a "raw urine," and (2) renal tubules reabsorb about 168 L of this filtrate, which includes valuable salt water and small molecules like glucose and amino acids. The renal tubules then fine tune the composition and amount of water to make our "final urine," which is ready for excretion. With these two basic functions in mind, the unifying feature of all glomerular diseases is that they disrupt the first of these, the filtration of blood.

As a starting point, consider the similarities between glomerular filtration and making a pot of coffee, with coffee grounds on top, then a coffee filter, and then water being forced from top to bottom by gravity to make a filtrate of coffee. With glomerular filtration, instead of coffee grounds on top, we have blood, which includes plasma, red and white blood cells, and serum proteins. Instead of a coffee filter preventing coffee grounds from entering the coffee pot, we have a glomerular filter preventing cells and serum proteins from passing through into the filtrate. And instead of a filtrate of coffee, the glomerular filtrate is about 170 L of "raw urine" as mentioned above. If we were to poke holes in a coffee filter with a pencil, coffee grounds would leak through into our filtrate of coffee. Similarly, if molecular holes are poked in the glomerular filter, red blood cells and serum proteins will leak through into the urinary filtrate. In this regard, blood cells and serum proteins that have leaked through the filter and into urine are the cardinal features of glomerular disease.

After this, the analogy breaks down. Instead of having one coffee filter, each kidney normally contains 500,000 to 600,000 glomerular filters, or just over 1 million glomeruli per person. Glomeruli are located within the outer shell of the kidney, which is called the cortex. There are no glomeruli within the inner shell of the kidney, which is called the medulla. Each glomerulus is a sphere, with a vascular pole on one side of the sphere. At this vascular pole, blood enters the glomerulus via an afferent arteriole, flows through a single tube called the glomerular capillary, which is bunched up inside the glomerulus into loops and then blood exits the glomerulus via an efferent arteriole (**Fig. e66-1**).

FIGURE e66-1

Components of the nephron. Each nephron originates in the cortex, at the renal corpuscle surrounding a small tuft of glomerular capillaries. Extending from the corpuscle is the proximal convoluted tubule, which leads to the proximal straight tubule that enters the outer medulla. This tubule continues as the thin descending limb and the thin ascending limb of the nephron's loop of Henle in the medulla. The loop of Henle ends with a thick ascending limb, a straight tubule that reenters the cortex and ends at its thickened macula densa area where it contacts the arterioles entering the glomerulus. Beyond the macula densa this tubule is the distal convoluted tubule, the end of which is the short connecting tubule. Connecting tubules from many nephrons merge into cortical collecting tubules and a collecting duct. (Reproduced, with permission, from Mescher AL. Junqueira's Basic Histology: Text & Atlas. 16th ed. New York: McGraw Hill; 2021.)



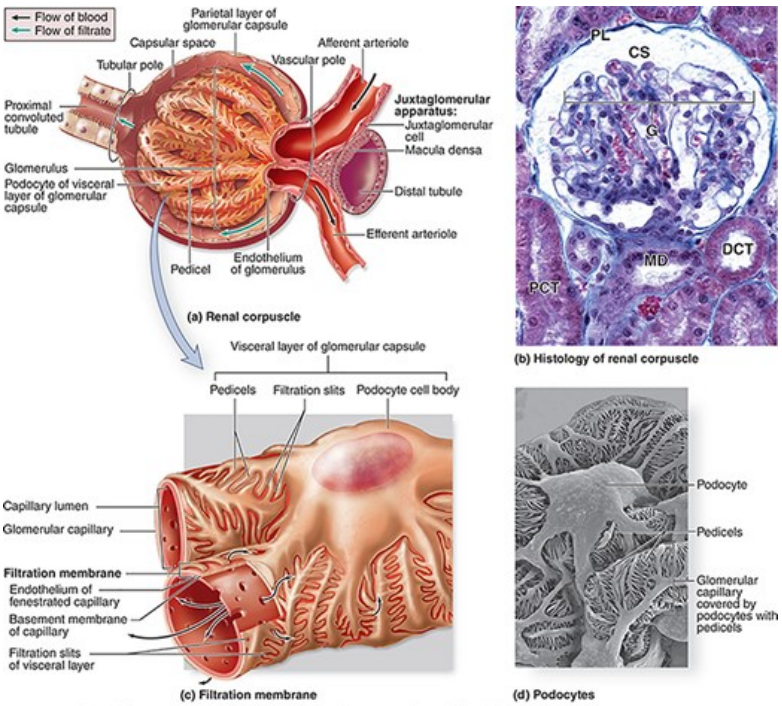
Within the glomerular capillary, blood plasma is filtered across a semi-permeable membrane by hydrostatic pressure of about 20 to 30 mm Hg, which is a uniquely high blood pressure compared to all other capillaries in our body. On the other side of the membrane, the filtrate that is formed within Bowman's space exits the glomerulus at the urinary pole and enters the first portion of the proximal tubule. Glomerular capillary loops are supported by a matrix of cells and interstitial tissue called the mesangium, which extends from the vascular pole into the center of the glomerular sphere, and which provides support to each of the glomerular capillary loops. Both the filtrate and blood that leave a particular glomerulus remain linked biologically. Filtrate from a particular glomerulus exits at the urinary pole and enters the first segment of the proximal tubule, while blood exits the glomerulus via the efferent arteriole and forms a network of capillaries to supply blood to the proximal tubule of the very same glomerulus. This linkage allows a single nephron to sense what it's glomerulus has filtered (by sampling sodium and chloride flow in the filtrate) and if a glomerulus is filtering excessively, to decrease blood supply to that glomerulus in a process called tubulo-glomerular feedback. Tubulo-glomerular feedback is an important part of the pathophysiology and treatment of several glomerular diseases.

As blood plasma crosses the glomerular filter to make a urinary filtrate, higher resolution reveals that the filter is composed of three layers (**Fig. e66-2**). The first layer is the endothelium, which has large pores called fenestrae that are lined with anionic polysaccharides. The pore size and negatively charged polysaccharides exclude blood cells and probably large lipoprotein complexes from crossing into Bowman's space, but the pores are too large to exclude plasma proteins. The second layer is the glomerular basement membrane (GBM), which is a gel of negative charged proteins that are excreted into the extracellular space by glomerular endothelial cells on one side and the glomerular visceral epithelial cells (or podocytes) on the other side. The major protein component of the GBM is type IV collagen, which forms trimeric strands (like weaving a bracelet from three threads) out of three different protein subunits (alpha-3, alpha-4, alpha-5), each encoded by a separate gene. Type IV collagen trimers are then crosslinked into a web by other anionic proteins, resulting in a tight, proteinaceous gel full of negative charges. The third layer of the glomerular filter is formed by podocytes, which cover the GBM except at narrow filtration pores, also called slit diaphragms, that permit water, electrolytes and small molecules through but exclude large molecules. Podocyte cover the outer surface of glomerular loops like an octopus family, but with hundreds of arms. These podocyte arms are called foot processes, which interdigitate with foot processes of a neighboring podocyte (**Fig. e66-2**).

FIGURE e66-2

(*A*) The renal corpuscle consists of a small mass of capillaries called the glomerulus, housed within a glomerular capsule. The visceral layer of the capsule is composed of complex epithelial cells called podocytes, which cover each capillary, forming slit-like spaces between interdigitating processes called pedicels. Blood enters and leaves the glomerulus through the afferent and efferent arterioles, respectively. (*B*) The micrograph shows the major histologic features of a renal corpuscle. The glomerulus (G) of capillaries is surrounded by the capsular space (CS) covered by the simple squamous parietal layer (PL) of Bowman capsule. Near the corpuscle is that nephron's macula densa (MD) and sections of proximal convoluted tubules (PCT) and distal convoluted tubules (DCT). (*C*) Filtrate is produced in the corpuscle when blood plasma is forced under pressure through the capillary fenestrations, across the filtration membrane or GBM surrounding the capillary, and through the filtration slit diaphragms located between the podocyte pedicels. (*D*) The scanning electron microscopy (SEM) shows the distinctive appearance of podocytes and their pedicel processes that cover

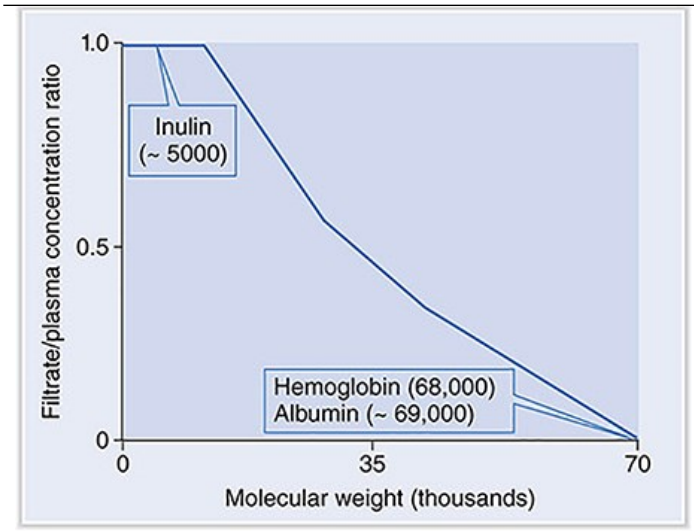
glomerular capillaries. (Reproduced, with permission, from Mescher AL. Junqueira's Basic Histology: Text & Atlas. 16th ed. New York: McGraw Hill; 2021.)



Working together, the three layers of the glomerular filter create a semi-permeable membrane with both size and charge selectivity: small molecules like sodium pass through the filter freely, while molecules of increasing size do not. In addition, molecules that are negatively charged (anionic) are prevented from filtration by negatively charged GBM, whereas molecules that are positively charged (cationic) can cross the filtration barrier more easily. **Figure e66-3** illustrates how the filtration fraction falls based on molecular size and charge. Filtration fraction is the concentration of a molecule on the far side of the filter within Bowman's space divided by the concentration on the near side of the filter within a glomerular capillary. Small molecules like sodium that easily pass through the glomerular filter have a filtration fraction of 1.0, whereas larger molecules have an increasingly small filtration fraction. Discussions of glomerular disease often focus on albumin, which is by far the predominant protein in blood serum. Albumin is a moderately large protein with many negative charges, so in normal circumstances its filtration fraction is very low.

FIGURE e66-3

(A) As molecular weight (and therefore size) increases, filterability declines, so that proteins with a molecular weight above 70,000 Da are minimally filtered. (B) For any given molecular size, negatively charged molecules are restricted more than neutral molecules, while positively charged molecules are restricted less. (Reproduced, with permission, from Kibble J, Halsey CR. The Big Picture: Medical Physiology. New York: McGraw Hill; 2009.)



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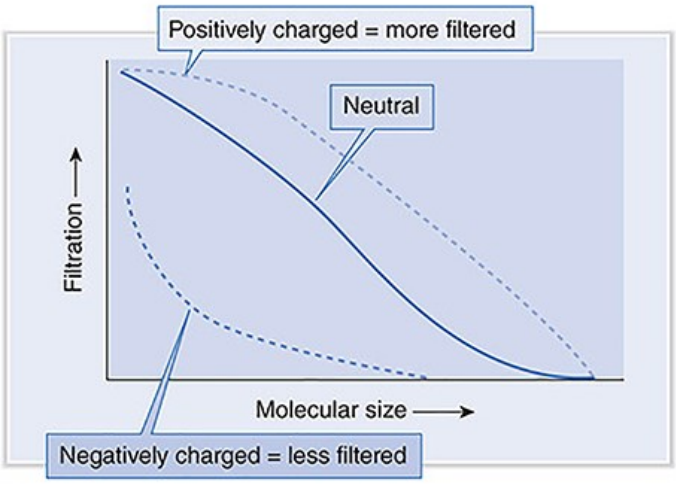

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Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

While the three layers of the glomerular filter work together, each layer can be a separate target for glomerular disease. For instance, the first layer of the glomerular filter is the target of damage with preeclampsia. The second layer of the filter is the target for both Alport's disease, which arises from hereditary mutations of type IV collagen, and also Goodpasture's disease (anti-GBM nephritis), in which autoantibodies attack subunits of type IV collagen. The third layer of the filter, the podocytes, is the direct target for glomerular diseases such as focal segmental glomerulosclerosis (FSGS) and membranous nephropathy. The mesangium, in addition to recirculating components of the GBM, provides structural support to glomerular capillary loops, and can synthesize and respond to various cytokines. Mesangial cells are a target for several glomerular diseases including immunoglobulin A (IgA) nephropathy and diabetic nephropathy.

GLOMERULAR DISEASE PATHOPHYSIOLOGY AND HISTOLOGY

Glomerular diseases are classified in many ways. Each classification scheme tells us something important about the disease. The classical division of glomerular disease is based on whether or not inflammation is present on kidney biopsy. If inflammation is present, a pathologist will describe the location, such as the mesangium (as seen with IgA nephritis) or inside the glomerular capillary wall (as seen with endocapillary proliferation from lupus nephritis), or within Bowman's space (as seen with crescentic glomerulonephritis from ANCA+ vasculitis). Noninflammatory injury is recognized by damage or alteration of the glomerulus in the absence of inflammation, such as the presence of fibrosis seen on light microscopy (also described as

sclerosis), or changes to the structure of the glomerular filter that are seen on electron microscopy, such as thickening of the glomerular basement membrane, or alternations of podocyte foot processes. With both inflammatory and noninflammatory glomerular injury, the appearance on kidney biopsy is divided into whether the disease appears "diffuse" (greater than 50% of all glomeruli in the biopsy are affected) or "focal" (less than 50% of glomeruli are affected), and for each glomerulus, whether the disease is "segmental" versus "global" (part of one glomerulus is affected vs the entire glomerulus). For both inflammatory and noninflammatory injury, fibrosis or sclerosis has good (but not perfect) prognostic value because for almost every glomerular disease, the percentage of tubulo-interstitial fibrosis correlates with the risk of progression to ESKD.

The glomerular capillary wall is susceptible to immune-mediated injury, most often from humoral immunity (meaning that antibodies bind an antigen and elicit an immune response).[3,4] The assumption is that the glomerulus is particularly prone to antibody attack because high blood flow and high capillary hydrostatic pressure expose the glomerular filter to more antibody than capillary beds elsewhere in the body. When antibodies attack the glomerulus, they can do so in many ways. Antibodies can be specific to glomerular antigens that are endogenous (proteins from our own body), such as Goodpasture's syndrome, in which auto-antibodies are formed against the alpha-3 subunit of type IV collagen. Antibodies can also arise from exogenous antigens, such as viral or bacterial proteins, leading to glomerular disease via several potential mechanisms. First, if antibodies to exogenous antigens cross-react with glomerular proteins (molecular mimicry), then mildly cross-reactive antibodies may reach the threshold for activating an immune response within the glomerulus. Second, circulating viral or bacterial antigens can be deposited on the glomerular filter by filtration pressure, and then attract an inflammatory response to foreign antigen, causing collateral damage to the glomerulus. This mechanism of injury is termed "in-situ immune complex formation" and is the primary pathophysiology underlying post-streptococcal glomerulonephritis. Third, antibody-antigen complexes can form within the circulation and then become passively entrapped in the glomerulus, which can attract an inflammatory response to the glomerulus. This mechanism of injury is termed "circulating immune complex formation" and it is the primary pathophysiology for hepatitis C–mixed-essential cryoglobulinemia. With each of these three mechanisms the severity of the inflammatory injury depends on several factors, the first being the relative rates at which antibody-antigen complexes are formed on the glomerular filter, versus how fast these antibody-antigen complexes are cleared away by podocyte endocytosis and mesangial recirculation of GBM proteins. An additional variable is that not all antibodies cause inflammation in the same manner.[4] In summary, antibodies are a common cause of glomerular disease, but the clinical features vary depending on which layer or cell or specific antigen within the glomerulus is targeted by the antibody, the rate at which antibody-antigen complexes are formed and removed, the type of inflammatory response elicited by a particular antibody-antigen complex, and more.

With respect to cellular immunity, neutrophils are a prominent feature of post-streptococcal glomerulonephritis, ANCA-vasculitis and proliferative lupus nephritis; monocytes and macrophages are components of cellular crescents in cases of rapidly progressive glomerulonephritis; and sensitized T-cells can also be detected in cellular crescents. In each case, however, these cells are not the primary cause of glomerulonephritis; they cause great damage but are responding to a cytokine alarm released by the initial cause. Experimentally, T-cells can attack the glomerulus in the absence of antibody deposition (similar to cellular-mediated rejection of a kidney transplant),[5] but it is very rare to see T-cell induced glomerular inflammation without antibody deposition in native kidneys (as opposed to transplant kidneys). The last circulating cell to mention is the diminutive platelet, which can cause glomerular disease in the absence of antibodies (such as with HUS/TTP) or in conjunction with antibodies (such as with lupus anti-coagulant). In combination, humoral and cellular immunity can activate an immune response within the glomerulus, and in conjunction with a host of molecular pathways including reactive oxygen species, proteinases, eicosanoids, and procoagulants, can alter the permeability, blood flow, and function of the glomeruli.[4] Vascular constriction and occlusion follow and result in the eventual destruction of glomeruli, which means that the entire nephron is lost.

CLINICAL PRESENTATION OF GENERALIZED GLOMERULAR DISEASE

It is easier to appreciate the differences between glomerular diseases by understanding the general symptoms, physical exam signs, and laboratory abnormalities of glomerular diseases in general. The five principal clinical features of glomerular disease are proteinuria, hematuria, hypertension, edema, and loss of kidney function, which are often categorized into one of two broad clinical phenotypes: nephritic syndrome or nephrotic syndrome. Nephritic syndromes are generally caused by inflammatory damage to the glomerulus, and use the suffix "itis," such as glomerulonephritis or renal vasculitis. Nephrotic syndromes are generally caused by noninflammatory damage and use the suffix "pathy" such as membranous glomerulopathy. When we discuss individual glomerular diseases, many of them are purely nephritic (such as anti-GBM nephritis) or nephrotic (such as minimal change disease), but others have an overlap of nephritic-nephrotic features (such as hepatitis C cryoglobulinemia). In addition, some glomerular diseases such as lupus nephritis are not a "single" disease and can present with pure nephritic syndrome in some patients (class III lupus) and pure nephrotic syndrome in other patients (class V lupus nephritis) (see **Table e66-1**). Lastly, in clinical practice, an individual with glomerular

disease may have some but not all the characteristics of nephritic or nephrotic syndrome. To meet criteria for nephritic syndrome, a patient should have glomerular hematuria along with proteinuria and hypertension. Similarly, a patient can have nephrotic-range proteinuria (greater than 3.5 g/day), but to meet criteria for the full nephrotic syndrome, one must also have a serum albumin less than 3.5 g/dL (35 g/L) and peripheral edema on physical exam.

CLINICAL PRESENTATION OF GLOMERULAR DISEASE	
NEPHRITIC SYNDROME • Hematuria, with dysmorphic red blood cells and red blood cell casts • Hypertension, sometimes severe • Edema, usually mild-moderate • Proteinuria, usually less than 3.5 g/day • Loss of kidney function (measured by rising serum creatinine or falling eGFR), sometimes progressing to ESKD in weeks • Sterile pyuria, with white cell casts	NEPHROTIC SYNDROME • Edema, which can be massive, with weight gain from fluid retention • Proteinuria of more than 3.5 g/day • Serum albumin less than 3.5 g/dL (35 g/L) • Loss of other serum proteins may cause hypercoagulability or immunodeficiency • Hyperlipidemia with lipiduria (lipid casts and oval fat bodies) • Kidney function can be normal or decreased, and if decreasing usually takes many years.
• Some glomerular diseases overlap nephritic and nephrotic features	

TABLE e66-1

Classification of Lupus Nephritis Based on World Health Organization Criteria

	Light Microscopy of Biopsy	Immuno-Fluorescence	Electron Microscopy	Typical clinical Symptoms
WHO Class I	Normal	Negative staining	Normal*	Mild proteinuria, ~ 500 mg/day*
WHO Class II "mesangial"	Increased number of mesangial cells +/− matrix. Glomerular loops appear normal	Mesangium stains with multiple antibodies	Electron dense deposits are within the mesangium, and sometimes in contiguous parts of the GBM.	Microscopic hematuria and mild proteinuria, ~ 500 mg/day*
WHO Class III "focal proliferative"	Less than 50% of glomeruli with either: 1. Increased number of glomerular cells (endothelial, mesangial, and infiltrating inflammatory cells). 2. Crescentic lesions in Bowman's space of parietal cells +/− macrophages, lymphocytes, fibroblasts.	Glomerular loops and the mesangium stain with nearly every antibody for "full house" staining.	Electron dense deposits are within mesangium and subendothelial GBM.	Mild-moderate nephritic syndrome +/− some extra-renal symptoms.
WHO Class IV	More than 50% of glomeruli with either:	Glomerular loops	Significant electron	Moderate-severe nephritic

"diffuse proliferative"	1. Increased number of glomerular cells (endothelial, mesangial, and infiltrating inflammatory cells). 2. Crescentic lesions in Bowman's space of parietal cells +/− macrophages, lymphocytes, fibroblasts.	and the mesangium have "full house" staining.	dense deposits within mesangium, subendothelial and intra-membranous GBM.	syndrome + several extra-renal symptoms
WHO Class V "membranous"	Class V can appear on its own (rarely) in which case the LM looks like membranous. "Spikes" are seen but might need silver stain or PAS to visualize the spikes. More often, class V appears in combination with class 3 or 4, in which case we say Class 3+5.	If membranous alone, the IF will have "full house" staining, distinguishing it from primary membranous. When seen with class 3+5 or class 4+5, the IF is already profoundly positive.	If membranous alone, deposits will be sub-epithelial. If class 3+5 or 4+5, then all of the mesangial, sub-endothelial and intra-membranous deposits from class 3 or 4 are joined by sub-epithelial GBM deposits from class 5.	Nephrotic syndrome if only class V, but this is rare. Class V is most often seen in combination with class III or class IV on biopsy, and the clinical situation for these patients will also be an overlap: mixed nephrotic-nephritic syndrome.
WHO Class VI "sclerosis"	No evidence of any cellular proliferation in the mesangium, glomerular loops or interstitium. Widespread fibrosis. Essentially, this is scar tissue from years of prior lupus nephritis.	Staining may be a mix of old granular staining with a high amount of background staining.	If there is very little normal kidney under light microscopy, then it is difficult to know "where" the deposits are. EM does not add much.	CKD stage 4/5.
Thrombotic microangiopathy with SLE - Not part of WHO classification	As with other causes of TMA, fibrin thrombi within glomerular capillary loops, leading to glomerular ischemia and GBM wrinkling and collapse of loops. Arterioles may show acute thrombi, chronic recanalization of thrombi, or reactive intimal hyperplasia of vessels. Thrombosis of larger arteries can infarct a wedge of renal cortex.	Thrombi should stain for fibrinogen	Platelets rich in granules may be seen within thrombi. Podocyte foot processes may be effaced, not due to proteinuria, but due to glomerular ischemia/loss of cellular architecture.	In pure form, a rising serum creatinine / falling kidney function, without hematuria or proteinuria. But can also be combined with proliferative lupus nephritis.

WHO, Word Health Organization; GBM, glomerular basement membrane; EM, electron microscopy; CKD, chronic kidney disease; LM, light microscopy; PAS, periodic acid–Schiff stain; SLE, systemic lupus erythematosus; TMA, thrombotic microangiopathy.

Proteinuria

Proteinuria is the most important feature of glomerular disease. In normal urine without glomerular disease, the most common protein (40%-50% of total urine protein) is uromodulin, also called Tamm-Horsfall protein, which renal tubules intentionally excrete into urine, and which forms hyaline casts when it crystalizes. The next most common proteins in normal urine are serum albumin and antibodies, which are lost in urine despite the best efforts of the glomerular filter. Since albumin and antibodies are the predominant proteins in blood, and such a large amount of blood undergoes filtration, the loss of a tiny percentage is not surprising. With respect to serum albumin, normal urine contains 15 to 30 mg/day, or about 20% of the total proteinuria. The remainder of protein in normal urine includes microscopic amounts of 1,000s other serum proteins that are lost through the filter, as well as other proteins that are secreted by tubules at much smaller amounts than uromodulin.

With this in mind the normal amount of protein in a 24-hour urine collection should be between 100 and 200 mg/day. A spot urine protein/creatinine ratio correlates with a 24-hour urine collection and should be 100 to 200 mg protein/gram of urine creatinine. Similarly, since the total amount of albumin per day should be 15 to 30 mg, a spot urine albumin/creatinine ratio should be less than 30 mg/g urine creatinine (3.4 mg/mmol creatinine). The spot urine albumin/creatinine ratio will always be less than the total protein/creatinine ratio, both in normal urine and with glomerular disease. Lastly, a urinalysis test strip primarily detects albumin (but for simplicity is inaccurately labeled as “protein”), so a urine dipstick should normally read “negative” or at most, “trace,” which is 15 mg/dL (150 mg/L) of albumin.

If proteinuria or albuminuria is greater than normal on any of these tests, then the patient might have glomerular disease. Whether the proteinuria is due to glomerular disease or not, the presence of excess proteinuria or albuminuria has prognostic value and is associated with increased all-cause mortality, increased risk of progression to ESKD, and increased fatal and nonfatal cardiovascular events.[6] But first, while proteinuria is the most important feature of glomerular disease, there are actually three basic causes of proteinuria, and a bit of detective work is needed to determine whether the problem is glomerular proteinuria, tubular proteinuria, or overflow proteinuria.

Glomerular Proteinuria

With glomerular proteinuria, excessive serum protein is leaking through the glomerular filter, as described above with the analogy of poking holes in a coffee filter with a pencil. The predominant protein in urine will be serum albumin, not because it leaks through the glomerular filter more easily than other serum proteins, but because it is the major protein in serum. Other notable serum proteins that are lost with glomerular proteinuria include coagulation factors, protein that normally keep material within the serum (like iron-binding transferrin, or vitamin-D binding protein), and serum antibodies. The magnitude of proteinuria with glomerular disease can be normal or only slightly above normal with mild disease and becomes clinically concerning at 500 to 1,000 mg/day. It is termed “sub-nephrotic” if the proteinuria is elevated but less than 3,500 mg/day, “nephrotic range proteinuria” if greater than 3,500 mg/day, and in rare cases can be as high as 20,000 to 30,000 mg/day.

Tubular Proteinuria

With tubular proteinuria, the problem is not excess serum protein leaking through the glomerular filter but incomplete reabsorption of protein by renal tubules. In clinical practice, distinguishing glomerular from tubular proteinuria is sometimes difficult, and some additional detail will help illustrate the difference between the two. Tubular proteinuria arises because the glomerular filter is very good but not perfect. Roughly 3,000 mg of albumin per day gets through the glomerular filter.[7] Since the normal albumin concentration in blood is 4 g/dL, which is 40 g/L, and our glomeruli filter 170 L/day, this translates to 6,800 g of albumin/day, or 6,800,000 mg of albumin/day through the glomerulus. If 3,000 mg/day of albumin is lost through the glomerular filter, the performance of the filter is remarkable, but even 3,000 mg of lost albumin is valuable. Accordingly, of this roughly 3,000 mg that makes it through the glomerular filter, our renal tubules reclaim all but about 15 to 30 mg/day, along with reclamation of other valuable molecules that make it through the filter, including smaller proteins, polypeptides, amino acids, glucose, and more. These details illustrate several points: (1) The final amount of albumin in normal urine (15-30 mg/day) arises from the combined efforts of a very good glomerular filter followed by very good tubular reuptake. (2) In patients who have 500 to 3,000 mg/day of proteinuria, without considering other features, both glomerular and tubular proteinuria should be considered, whereas in patients with more than 3,000 mg/day proteinuria, the cause is almost always glomerular disease. (3) The size of protein can help distinguish whether the proteinuria is caused by glomerular versus tubular disease. For instance, in a hypothetical patient with 2,000 mg proteinuria, if caused by pure glomerular disease, albumin will constitute more than 50% of the protein when separated by size using gel electrophoresis. By contrast, the same 2,000 mg/day in a patient with pure tubular proteinuria will have a lower percentage of albumin and a higher percentage of small and medium-size proteins, because the glomerular filter is still functioning as a size and charge barrier (see **Fig. e66-3** above). (4)

Patients with tubular proteinuria should not have microscopic hematuria, because the glomerular filter is still functioning. (5) Unlike glomerular disease, tubular proteinuria is often accompanied by urinary loss of other valuable molecules that are normally reabsorbed by renal tubules, such as excessive glucose in the urine in the absence of diabetes, or excessive phosphate in the urine causing low serum phosphate levels. Classic causes of tubular proteinuria include rare genetic conditions (Wilson's disease, hereditary fructose intolerance, Dent's disease), drugs with tubular toxicity (aminoglycosides, tenofovir, cisplatin, ifosfamide), heavy metals (lead and mercury), and a subset of patients with myeloma who have light-chain proximal tubulopathy.

Overflow Proteinuria

The third type of proteinuria is "overflow proteinuria" in which the serum has excessive amounts of a protein other than albumin, and this protein "overflows" the combined safeguards of the glomerular filter and tubular reuptake to end up in the urine. This nonalbumin serum protein is almost always an antibody, either a monoclonal gammopathy (a clone of one antibody, such as from multiple myeloma) or a polyclonal gammopathy (an excess of many thousands of antibodies, due to inflammation from a chronic infection such as viral hepatitis, or due to an autoimmune disease such as rheumatoid arthritis). Like tubular proteinuria, overflow proteinuria is important to distinguish from glomerular disease. If the cause is myeloma, then prompt chemotherapy is needed. If the cause is a polyclonal gammopathy, then additional tests are needed to diagnose the infection or autoimmune condition.

Hematuria

Hematuria is a major feature of nephritic glomerular disease and is also found to a lesser degree in some nephrotic glomerular diseases. To begin with, normal urine should test negative for blood on urinalysis, and under a microscope there should be 0 to 2 red blood cells per high power field (40× objective). If more blood than this is present in urine, then we use the term "gross hematuria" if the color of blood in urine is grossly visible to the naked eye, and we use the term "microscopic hematuria" if blood is visible only by microscope. Gross hematuria actually requires only a tiny amount of blood (about 50 µL/L of urine). A third possibility for blood on a urinalysis is a false positive due to rhabdomyolysis or hemolysis, which results in excessive myoglobin or hemoglobin in the urine, and it is these heme-pigments that are detected as "blood" by the chemistry of urinalysis test strips. In these cases, despite a positive test on urinalysis, the number of red blood cells on urine microscopy will be normal.

Hematuria, just like proteinuria, can be caused by both glomerular disease and non-glomerular disease, and the latter is actually more common. Non-glomerular hematuria arises most often when blood leaks from any capillary into the urine collecting system at a spot after the glomerular filter, which could be within renal tubules, collecting ducts, renal pelvis, ureters, bladder, or urethra. Accordingly, the common causes of non-glomerular hematuria are renal cancer, bladder cancer, kidney stones, trauma, or a urine infection causing enough inflammation that the bladder lining becomes friable. In addition, hematuria is sometimes difficult to distinguish from uterine bleeding with atypical menstrual flow, or in post-menopausal women. Lastly, non-glomerular hematuria can arise from rare cases of endometriosis within the ureters, microlithiasis in children without overt stones, or "benign hematuria" due to a non-kidney severe illness, in which case the hematuria should resolve on urinalysis when rechecked 4 to 6 weeks later.

In contrast, glomerular hematuria arises when red blood cells are pushed through the GBM. Under careful microscopic examination of urine, two features can reliably distinguish glomerular from nonglomerular hematuria. Red cells in urine due to a kidney stone, for example, will retain their normal shape as biconcave disks, or they will shrink or swell uniformly if the osmolality of urine is quite different from blood. Conversely, red cells in urine due to glomerular disease often appear "dysmorphic" meaning that the shape of the plasma membrane was disturbed as a consequence of being squeezed through the glomerular filter.[8] Dysmorphic red cells in urine are also termed "acanthocytes" (but their shape is NOT the same as acanthocytes on a peripheral blood smear) or more intuitively they are called "Mickey mouse cells" because the large blebs of red cell membrane resemble giant ears. The second finding on microscopy that distinguishes glomerular from nonglomerular hematuria is red blood cell casts. Red cell casts are highly specific for glomerular hematuria because the cells within any cellular cast must have been present within the early distal nephron when casts are formed. To elaborate, the shell of every cast is formed by uromodulin, which is intentionally secreted into the lumen of the nephron by renal tubule cells in the loop of Henle and ascending limb. As urine filtrate continues to flow into the distal convoluted tubule and collecting tubules, becoming more concentrated and acidic, the uromodulin precipitates into a more organized, lower-energy state, in a manner similar to how some proteins can organize into crystals, but in this case the preferred organization is to form a tube. If there are no cells within the distal nephron when uromodulin precipitates, then a hyaline cast is formed (which is why hyaline casts are a normal finding in urine). If there are any cells within the distal nephron when uromodulin precipitates into casts, then these cells become entrapped into the cast matrix and form a cellular cast. Hematuria from a kidney stone or bladder cancer cannot force red cells within the cast; the hematuria must be present much higher up within the distal nephron, and

hematuria at this location is overwhelmingly due to glomerular disease.

Hypertension

Hypertension is common among patients with glomerular diseases, as a result of increased renal sodium retention, and also increased release of vasoconstrictors within the kidney or systemically. Increased sodium retention causes hypertension due to plasma volume expansion, which is almost always present even if peripheral edema is clinically subtle. Increased vasoconstrictors include those released within the kidney, and also those released by vascular endothelium in patients with glomerular disease that is part of a systemic vasculitis. Specifically, both nephritic syndrome and nephrotic syndrome (especially the former) have increased renin activity, which leads to increased angiotensin II formation, a potent vasoconstrictor within both the systemic vessels and within glomerular efferent arterioles. Glomerular disease is also associated with variable increases in sympathetic activity and release of endothelin, which raises blood pressure. The first choice of medications to treat hypertension in glomerular disease is antagonists of the renin-angiotensin system, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), as described in detail below.

Edema

Edema is common among patients with moderate or severe glomerular disease. A differential of peripheral edema includes: acute or chronic congestive heart failure (which can be systolic or diastolic dysfunction, valvular disease, pulmonary hypertension, or right sided heart failure), decreased sodium excretion due to loss of kidney function (AKI or CKD, which leads to excess sodium balance and expansion of blood volume), lymphatic disease (usually surgical or traumatic damage, very rarely filariasis), or diseases that cause increased capillary leak (usually infectious or inflammatory disorders, very rarely congenital disorders). Edema follows gravity, with greatest severity in the lower legs after standing upright, followed by redistribution around the body after lying down with elevated legs. But some people clearly put more of their edema into ascites than their legs, and other patients are prone to pulmonary edema without legs or ascitic edema.

One explanation for edema in glomerular disease is excess sodium retention, similar to patients with AKI/CKD, but the sodium retention can occur even if kidney function is normal. Historically, there have been two competing hypotheses to explain the cause of edema in patients with nephrotic syndrome. The “overfill hypothesis” of edema contends that the ECF compartments are “overfilled” with salt water due to retention of sodium.[9] Conversely, the “underfill hypothesis” is based on the idea that, according to Starling’s law, hydrostatic pressure pushes fluid from pre-capillary arterioles into the extra-cellular space, while oncotic pressure draws fluid back from the extra-cellular space into the post-capillary venules. In short, the idea is that low serum albumin causes edema. It should be noted that a single explanation of edema does not fit all patients and clinical situations.

The third explanation for edema in nephrotic syndrome is leaky capillary membranes. This mechanism did not make it into the main debate of “underfill and overfill” historically, but nephrotic syndrome patients have demonstrated significantly higher capillary leak compared to normal patients.[10] The idea is that, similar to patients with septic shock who develop pulmonary and peripheral edema, the tight junctions between cells become “less tight” within the vasculature in patients with nephrotic syndrome. Research on the mechanisms of capillary leak with glomerular disease is ongoing.

Loss of Kidney Function

Loss of kidney function with glomerular disease is variable, and when it occurs, can manifest as either acute or chronic kidney disease. The most severe examples are patients with rapidly progressive glomerulonephritis (RPGN), which is defined as the nephritic syndrome with loss of 50% or more kidney function (or a doubling of serum creatinine) within 6 weeks. Patients with suspected RPGN should be admitted to the hospital, because every day without treatment can translate into irreversible loss of kidney function. The possible causes of RPGN are discussed at the end of this chapter.

More often, glomerular disease progresses chronically, over months to years. This is the case for hereditary glomerulonephritis from Alport’s syndrome, primary membranous glomerulopathy that is refractory to treatment, or severe IgA nephropathy, all of which can progress to ESKD over a few decades. In many cases, progressive CKD occurs even if the cause of glomerular injury has resolved. One reason for this is that, similar to neurons after a stroke, podocytes that die due to glomerular disease cannot be regrown. Neighboring podocytes attempt to stretch over the surface of the glomerulus to compensate, but there is a “point of no return” of approximately 70% podocyte loss within a single glomerulus after which the glomerulus will inevitably die due to glomerulosclerosis.[11] Second, if inflammation or acute kidney injury is severe enough to activate the molecular pathways that cause fibrosis of glomeruli and the tubulo-interstitium, these pathways take time to reverse.[12] Lastly, even in the best case scenario in

which kidney injury is halted prior to the "point of no return," full kidney function will not be restored. The healthy kidney tissue that remains can undergo hypertrophy and hyperfiltration, but similar to scar tissue elsewhere in the body, fibrosis is nearly impossible to repair. The percentage of tubulo-interstitial fibrosis is one of the most predictive findings from a kidney biopsy for chronic kidney disease.

Hyperlipidemia

In patients with the full nephrotic syndrome, serum cholesterol and triglycerides can be severely elevated, but can fully normalize if treatment for nephrotic syndrome results in remission. Hyperlipidemia arises because increased liver synthesis of albumin inadvertently also increases liver synthesis of lipoproteins, and at the same time, proteinuria results in loss of the serum protein lipoprotein lipase, which leads to decreased conversion of triglycerides into free fatty acids.[13]

Lipiduria

Fatty casts and oval fat bodies are frequently seen in the urine of patients with the nephrotic syndrome. Fatty casts resemble red cell casts (circles with no nucleus) but the circles are lipid droplets of various sizes instead of the uniform size seen with red cells. Under polarized light, the lipid droplets in fatty casts form an X or a "Maltese Cross."

Increased Risk of Deep Vein Thrombosis and Pulmonary Embolism

Nephrotic syndrome predisposes to clotting disorders. Blood is in constant balance, poised to form a clot in cooperation with platelets if bleeding arises, but also to prevent blood from clotting inappropriately, even if blood flow is sluggish. The liver synthesizes serum proteins on both sides of this see-saw, including anti-thrombin-III, protein C and protein S to prevent clotting, and to promote clotting, fibrinogen along with clotting factors II, V, VII, IX, X, XI, and XII. In patients with low serum albumin due to the nephrotic syndrome, liver synthesis is stimulated to make more serum albumin, and in the process the liver synthesizes other proteins, including those that promote and inhibit coagulation. At the same time, anti-thrombin III is small enough to be lost at high amounts in the urine when proteinuria is significant. The end result is increased risk of clotting, particular renal vein thrombosis (the renal veins are directly after anti-thrombin-III is lost from glomerular filtration into urine), as well as increased risk of deep vein thrombosis and pulmonary embolism.

Increased Risk for Infection

In addition to loss of serum albumin, nephrotic syndrome patients lose antibodies and complement proteins. Children with nephrotic syndrome are at particular risk for peritonitis and pneumococcus. Some patients with severe nephrotic syndrome receive infusion of antibodies (intravenous immune globulin) until they begin to enter clinical remission.

Sterile Pyuria, with White Cell Casts

In many causes of moderate or severe nephritic syndrome, white cells are often seen in the urine. Like other features of glomerular disease, white cells on urine microscopy are not specific for glomerular disease, and can also be seen with colonization from a poor quality clean catch (in which case squamous epithelia will also be present), or with lower urinary tract infections including cystitis. But if white cell casts are seen, then we know from the mechanism of cast formation that these white cells must have been within the distal nephron, so there are only three likely causes: an inflammatory glomerulonephritis, such as lupus nephritis, a pyelonephritis (which has very different clinical symptoms of flank pain, nausea, fever, and low blood pressure), or a tubulo-interstitial nephritis such as allergic interstitial nephritis or sarcoidosis (which should not have glomerular hematuria). In short, pyuria and white cell casts due to glomerular disease should be distinguishable from other causes by additional symptoms and urine findings.

TREATMENT OF GENERALIZED GLOMERULAR DISEASES

Kidney Disease: Improving Global Outcomes (KDIGO) is a global nonprofit foundation dedicated to improving the care and outcomes of kidney disease patients worldwide, and has promoted coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines for many kidney diseases. The KDIGO clinical practice guidelines for diagnosing and treating glomerular disease were published in 2012, and updated guidelines from 2020 are available.[14,15]

Treatment of glomerular disease can be broken down into three approaches: (1) treatments aimed at a specific diagnosis, often in the form chemotherapy or immunosuppression that aims to block immune-mediated glomerular disease. Some immunosuppressants are specific to one aspect of the immune system. Other immunosuppressants are very nonspecific and are chosen either because the molecular mechanism of a glomerular disease is not known, or because a glomerular disease dysregulates multiple aspects of immunity at the same time; (2) non-pharmacologic therapies that are generally applicable to all forms of glomerular disease, including various dietary recommendations; (3) pharmacologic therapies that are generally applicable to all forms of glomerular disease. In clinical practice, we refer to the combination of (2) and (3) as "conservative therapy" for glomerular disease.

Chemotherapy or Immunosuppression for Immune-Mediated Glomerular Disease

In this section, we will not describe dose or duration of these therapies, which vary between some glomerular diseases, and which vary between pediatric and adult populations. A modest amount of detail on medication dosing is included later in this chapter when individual glomerular diseases are described, but complete dosing details are beyond the scope of this chapter. Instead, the specific aim of the section below is to introduce the general mechanisms, risks, and benefits of chemotherapy and immunosuppression for patients with glomerular disease. Very often, immunosuppression of glomerular disease involves the use of 2 or 3 of the following medications, either at the same time, or sequentially. For non-inflammatory glomerular diseases, especially those with no known mechanism, it is possible that the benefit of these "immunosuppressant" medications may have nothing to do with the immune system, and may instead be helping by direct signaling to podocytes.[16] The overall risks and benefits of immunosuppression are generally straightforward: the benefit of immunosuppression is to hopefully stop immune-mediated injury, including loss of kidney function and death; the risk of immunosuppression is a predisposition to infection and cancer, and in patients receiving immunosuppression for glomerular disease, infections are the major cause of death. In summary, a delicate balance of immunosuppression is required: too little, and the glomerular disease remains active; too much, and the risk of infection and cancer becomes excessive.

Corticosteroids

Corticosteroids have a rapid anti-inflammatory effect in patients with glomerular disease by inhibiting the release of IL-1 and tumor necrosis factor by activated macrophages and inhibiting the release of interleukin-2 by activated T cells. In turn, production of many other inflammatory mediators is reduced, including prostaglandins, leukotrienes, platelet-activating factors, migration-inhibiting factor, and gamma-interferon. In addition to anti-inflammatory effects, corticosteroids also act through steroid-hormone binding receptors to alter transcription of multiple genes, which includes increasing podocyte expression of Nephrin (a key protein of the podocyte intercellular junction). Chronic steroid therapy can result in problematic side effects such as slowing bone growth in children, insomnia, avascular necrosis of long bones, acne, polyphagia, fluid retention, and mood disorders including mania and aggression. For patients on steroids for more than 10 to 14 days, the adrenal glands may stop making endogenous steroid, resulting in a state of secondary adrenal insufficiency if the corticosteroid dose is suddenly decreased below 5 to 10 mg/day. When stopping corticosteroid therapy, the dose should be lowered to 5 to 10 mg/day and then tapered gradually, monitoring for symptoms, while the adrenal glands restart endogenous steroid biosynthesis. The symptoms of abruptly stopping corticosteroids are those of adrenal insufficiency, and range from nausea/lack of appetite and weakness to hypotension, to full circulatory shock.

Cytotoxic Agents

Cytotoxic agents such as cyclophosphamide and chlorambucil create DNA-crosslinks, which prevent mitosis of dividing white cells (lymphocytes, monocytes, and neutrophils), and also induce apoptosis of white cells. Modest depletion of the number and activity of white cells is the goal of therapy for multiple inflammatory glomerular diseases. Cytotoxic therapy is also used with good response in several noninflammatory glomerular diseases, but usually as a second- or third-line therapy. To avoid excessive white cell depletion (leukopenia and neutropenia), which increases the risk of acquiring infections, complete blood counts are monitored weekly, and then monthly if the dose remains stable. Additional side effects of cytotoxic agents include sterility, hemorrhagic cystitis, alopecia, and the potential for lymphoma with long-term treatment.

Azathioprine

Azathioprine is a purine analog with multiple effects (the main mechanism of effect is uncertain) including misincorporation during DNA replication, which prevents mitosis of replicating immune cells, and suppression of purine synthesis, which prevents RNA synthesis in immune cells. Side effects include nausea and vomiting, leukopenia, megaloblastic anemia, and with long-term therapy, increased risk of nonmelanoma skin cancers.

Calcineurin Inhibitors

Cyclosporine and tacrolimus are calcineurin inhibitors, used to suppress the immune system in patients who receive organ transplant, and who suffer from various autoimmune diseases. Calcineurin inhibitors prevent T-cell activation and suppress IL-2 release. In addition, calcineurin inhibitors stabilize the cytoskeleton of podocytes, and for noninflammatory diseases such as FSGS this is a possible alternative mechanism of action (we do not know which mechanism is most important). Calcineurin inhibitor side effects include hypertension, hyperuricemia with risk of gout, hyperglycemia with risk of diabetes, neurotoxicity with risk of tremor, hyperkalemia, hypomagnesemia, and with long-term use, the risk of kidney toxicity. Cyclosporine has the additional side effects of gingival hyperplasia and hypertrichosis. Both drugs are metabolized by cytochrome P450 3A4/5 and have multiple drug-drug interactions that can affect therapeutic drug concentrations.

Mycophenolate

Mycophenolate is an analog of inosine and inhibits guanosine synthesis, especially the isoform that is present in activated B and T cells, resulting in suppression of lymphocyte proliferation (lymphopenia), and suppression of antibody production. Mycophenolic acid is the active drug, which can be administered as Mycophenolate mofetil (MMF) or sodium mycophenolate (SMP). For most glomerular diseases, MMF is administered at 1,500 to 3,000 mg/day in two divided doses, or SMP at 1,440 mg/day.[15] Overall, mycophenolate is well tolerated. Side effects that require dose reduction include leukopenia, nausea, diarrhea, or an excessive number of infections.

Rituximab

Rituximab is a monoclonal antibody against CD-20, which is present on pre-B cells and mature B cells but not on plasma cells. Rituximab binding to cells causes complement-mediated cytotoxicity and antibody-mediated cytotoxicity. CD-20 is also expressed on podocytes, so an alternative mechanism of action for some glomerular diseases is direct signaling to podocytes. Side effects of rituximab are generally mild and include infusion reactions (managed by premedication with anti-histamine and acetaminophen, with or without steroids) and increased risk of infection or reactivation of chronic infections (like hepatitis B or varicella viruses) due to B-cell depletion.

Plasmapheresis

Plasmapheresis or plasma exchange therapy can remove serum proteins that include auto-antibodies attacking the glomerulus, and then replace what is removed from the blood with either albumin or fresh-frozen plasma. Plasmapheresis also removes additional inflammatory mediators and has an immunosuppressive effect that is greater than simply the reduction of antibody levels. Plasmapheresis is usually reserved for only the most severe glomerular diseases. The best evidence for a clinical benefit with plasmapheresis is in patients with anti-GBM nephritis, which is discussed at the end of this chapter.[17] Plasmapheresis is sometimes used in patients with pulmonary-renal syndrome due to ANCA-vasculitis or mixed-essential cryoglobulinemia, but the clinical benefit in these patients is being questioned based on negative results from the randomized controlled Pexivas trial,[18] as well as negative results from a large retrospective review.[19]

Nonpharmacologic Therapies

Nonpharmacologic therapies for all glomerular diseases include sodium restriction to less than 100 mEq/day, which is important for the control of hypertension, edema, and proteinuria; low-fat diet for patients with nephrotic syndrome who have secondary hyperlipidemia; and possible dietary protein restriction. A common recommendation in CKD patients is to restriction protein intake to about 0.8 g/kg body weight/day. Protein restriction in glomerular disease is controversial. Protein restriction is not recommended for patients with the full nephrotic syndrome because intake of protein will be easily outpaced by urinary loss of protein, resulting in protein-calorie malnutrition. A simplified recommendation is for patients with glomerular disease to avoid fad diets with excessive protein intake. Moreover, in patients with severe edema, which can cause pain, skin blistering, skin ulceration, and acute stasis dermatitis, edema usually follows gravity. Edema can be treated without medications by elevating legs, and by using compression stockings each morning, placed when legs are least swollen. Smoking cessation is recommended for all patients with chronic kidney disease including glomerular disease, to decrease the risk of cardiovascular events.[20]

Pharmacologic Therapies

Pharmacologic therapies that are commonly utilized in the treatment of glomerular disease include diuretics, antihypertensive medications, lipid

lowering drugs, and others as described below.

Diuretics

Diuretics act to remove excess total body sodium. Sodium retention is common among patients with glomerular disease, leading to hypertension, edema, or both. Loop diuretics block the largest percentage of filtered sodium from being reabsorbed (~ 25%-30%), which is why they are the most effective class of diuretics. In patients with glomerular disease, increased "resistance" to loop diuretics is common and is due to several causes including:

- Decreased delivery of diuretic to the site of action in the lumen of the thick ascending limb of the loop of Henle. Loop diuretics are protein bound and only minimal amounts undergo glomerular filtration. Loop diuretics reach their site of action after transport through channels into proximal tubules and then from tubules into the lumen. Once inside the tubular lumen, the loop diuretic flows through the loop of Henle and then binds to the sodium-potassium-chloride cotransporter in the thick ascending limb from the luminal side of the channel. While loop diuretics are not filtered, the process of tubular uptake and tubular secretion of diuretic requires kidney "function" and correlates with glomerular filtration rate (GFR). As GFR decreases, higher doses of loop diuretic are required to achieve concentrations within the tubular lumen necessary for inhibiting sodium reabsorption.
- Binding of loop diuretics to albumin within the filtrate. Proteinuria results in excess albumin in the filtrate, which binds to diuretic within the lumen and decreases the amount of free (ie, nonprotein bound) diuretic available to bind the sodium-potassium-chloride cotransporter.
- The "braking" phenomenon, which refers to the gradual decrease (like applying the brakes of a car) of the clinical response to loop diuretics after daily use for weeks to months.[21] When loop diuretics successfully block sodium reuptake in the thick ascending limb, an increased amount of sodium is presented to the next segment of the nephron, which is the thin limb and distal convoluted tubule, containing the thiazide-sensitive sodium-chloride cotransporter. When loop diuretics are used chronically, the increased sodium load to the distal convolute tubule leads to adaptation, including hypertrophy (the cells become visibly larger), and greater density of sodium-chloride cotransporters per cell. In short, loop diuretic resistance develops over time because other parts of the nephron fight the diuretic effect. In these patients, the addition of a thiazide diuretic to block the overactive sodium-chloride cotransporters can overcome the resistance.[22]
- Reduced drug absorption due to bowel wall edema. This is a common explanation in clinical practice for loop diuretic resistance, but the effect is more likely from decreased blood flow during decompensated CHF, rather than the edema per se.[23] Another possibility is that gastrointestinal absorption may be decreased, but this effect should be confined to furosemide, which has a lower and more variable oral bioavailability than torsemide or bumetanide.[24]

Whether from changes in oral bioavailability or not, maximal diuretic effect depends on peak serum concentration of diuretic, which can be achieved by intravenous administration, either as a bolus or as a continuous infusion.[25] For patients with morbid edema, albumin (25%) infusions have been attempted to expand plasma volume and increase diuretic delivery to the renal tubules, but the effectiveness of combined albumin-diuretic therapy is minimal or negative.[26–28] Regardless of what dose or combination of diuretics is required, the goal of diuretic therapy in patients with glomerular disease and sodium overload is a slow and steady diuresis of 0.5 to 1.5 kg of weight daily until all excess salt water has been removed.

Antihypertensive Medications

According to Joint National Committee (JNC) 8 guidelines, the target blood pressure for patients with CKD is less than 130/80 mm Hg.[29] In patients with glomerular disease, many experts advocate gently pushing the blood pressure lower if tolerated, especially in patients with nephrotic range proteinuria, but this is not based on gold-standard data. The NIH-sponsored SPRINT trial showed that targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause.[30] An analysis of patients in the SPRINT trial with nondiabetic CKD found that the more intensive blood pressure goal (systolic blood pressure <120 mm Hg) was associated with lower rates of cardiovascular outcomes, renal outcomes, and death compared to the <140 mm Hg group.[31] There were some increased adverse events from blood pressures that were "too low" in the SPRINT trial, but it is anticipated that the next JNC guidelines will include lower blood pressure targets for at least a subset of patients with CKD.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are the first choice for all patients with glomerular disease who have hypertension and proteinuria. These medications delay the long-term loss of kidney function for patients with diabetic kidney disease, as well as some nondiabetic (primarily glomerulonephritis) kidney diseases. These medications, as well as antagonists to the mineralocorticoid receptor (spironolactone and eplerenone) also decrease proteinuria, which is independently associated with increased risk of kidney disease progression and major adverse cardiac events.[32] By indirectly or directly blocking the angiotensin receptor, ACEIs and ARBs reduce intraglomerular pressure. Additional mechanisms of action may include direct inhibition of RAAS signaling, and inhibition of pro-fibrotic pathways within the kidney. These beneficial effects on proteinuria are beyond what can be attributed by the drug's antihypertensive effects.

Combined use of ACEIs and ARBs can maximize blockade of the renin–angiotensin system by counteracting angiotensin II produced by non-ACE pathways,[33] which reduces proteinuria and slows the progression of CKD more than either treatment alone.[34] However, current recommendation are to avoid combination RAAS blockade due to increased adverse effects of hyperkalemia, acute kidney injury, and nonfatal stroke. Ongoing studies may help define the best balance between benefit and risk for dual or triple blockade of the RAAS system.[35]

If maximal doses of ACEIs or ARBs do not control blood pressure to goal, then a second medication must be added, which for glomerular disease is either a diuretic or a non-dihydropyridine calcium channel blocker. Diuretics are a better choice if both edema and hypertension are present, while non-dihydropyridine calcium channel blockers such as diltiazem or verapamil have modest anti-proteinuric effects and are a better choice if a patient needs to avoid hypokalemia from diuretics, or would benefit from reducing the heart rate by calcium channel blockade. Verapamil and diltiazem also serve as alternative first-line therapy in patients with angioedema or severe intolerance to ACEIs or ARBs.[36] Dihydropyridine calcium channel blockers such as amlodipine or extended-release nifedipine, on the other hand, are excellent at reducing systemic blood pressure but tend to increase intra-glomerular blood pressure, and if possible are avoided in patients with glomerular disease. If hypertension in glomerular disease is severe and requires three medications to reach goal, then like other forms of hypertension, one of the three medications should always be a diuretic (see Chapter 30).[29]

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) can cause CKD due to analgesic nephropathy, or AKI due to inhibition of prostaglandin-mediated compensation of afferent glomerular arteriole flow, or in rare instances allergic interstitial nephritis with significant proteinuria due to minimal change nephropathy (see Chapter 65). Nevertheless, it is formally true that NSAIDS have an anti-proteinuric effect. Indomethacin has a similar efficacy to ACEIs, and combined treatment with an ACEI results in additional proteinuria reduction.[37] However, the risks of AKI and CKD from NSAIDS outweigh the potential benefits.

Statins

Hyperlipidemia in patients with nephrotic syndrome can be severe, and there is a long-term association of nephrotic syndrome with atherosclerotic cardiovascular disease.[38] HMG-CoA reductase inhibitors, also known as "statins," such as pravastatin, simvastatin, atorvastatin, and rosuvastatin, are considered the treatment of choice.[39] They reduce total plasma cholesterol concentration, LDL cholesterol, and total plasma triglyceride concentrations (see Chapter 32). Aside from the lipid-lowering effects, statins can reduce cardiovascular risk independent of serum lipid concentrations. However, in contrast to the very clear clinical data showing benefit of statins in people with several cardiovascular conditions, currently there is not clinical data showing that statins prevent cardiovascular events in patients with glomerular disease.

Alirocumab and Evolocumab

Alirocumab and evolocumab are inhibitors of proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9). Inhibition of PCSK9 by these recently developed medications leads to increased recirculation of the LDL receptor to the hepatocyte surface and accelerated clearance of circulating LDL (see Chapter 32). These medications may be especially useful in treating hypercholesterolemia in patients who have nephrotic syndrome and those on peritoneal dialysis, since they tend to have high PCSK9 concentrations.[40] However, the benefit of these agents for kidney function and cardiovascular outcomes need to be demonstrated in large clinical trials.

Anticoagulation

Thromboembolic events including renal vein thrombosis, deep vein thrombosis, and pulmonary embolism are complications of severe nephrotic syndrome. Patients with documented thromboembolic events should be anticoagulated. Whether or not to start prophylactic anticoagulation in patients with the nephrotic syndrome is controversial, and the decision process balances the severity of nephrotic syndrome, additional risk factors for thrombosis such as immobility, risk for hypovolemia, timing of possibly surgery, fall risk, patient profession, and history of prior bleeding events.[41,42]

SGLT-2 Inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors block one of two classes of glucose re-uptake channels in the proximal tubule, leading to excess amounts of glucose in the urine. These new medications were originally intended to lower blood glucose in diabetic patients. However, they were also shown to reduce cardiovascular events among diabetics (the first medication to do so), and to slow the progression of kidney disease (see Chapter 94). In the kidneys, the SGLT-2 inhibitors appear to re-set the process of tubo-glomerular feedback and, similar to RAAS blockade, this decreases intra-glomerular pressure, decreases proteinuria, and prolongs long-term kidney function. The SGLT-2 inhibitors are a key, new medication for patients with diabetic nephropathy. The drugs also show a clinical benefit in patients without overt diabetic nephropathy, and it is possible that these medications may benefit patients with glomerular diseases other than diabetes.[43]

EVALUATION, DIAGNOSIS, AND ASSESSMENT OF THERAPEUTIC OUTCOMES

Evaluation and Diagnosis

If a patient is suspected of having glomerular disease based on hematuria, then microscopic examination of the urine can help distinguish non-glomerular hematuria from glomerular disease. If the suspicion of glomerular disease is based on proteinuria, then quantification of the amount and type of protein can distinguish glomerular proteinuria from tubular proteinuria and overflow proteinuria. The presence of hypertension and testing kidney function based on serum creatinine can determine the extent of kidney damage and stratify the initial approach to therapy. In the early stages of glomerular disease, serum creatinine can be deceptively normal because the remainder of the kidney will attempt to compensate by hyperfiltration and by increased tubular secretion of creatinine from remaining nephrons.

Patients with suspected glomerular disease should undergo an extensive medical history to identify potential systemic causes (see **Table e66-2**). Medication, environmental, and occupational histories may also help identify exposure to potentially nephrotoxic agents. A comprehensive physical examination and laboratory evaluation may reveal the presence of systemic diseases that may contribute to the development of glomerular disease. In addition, the patient's age, gender, and ethnic background may be helpful in pinpointing the specific type of glomerular disease. For example, lupus nephritis is more common in young women, whereas ANCA-associated vasculitis is dramatically higher in older patients.

TABLE e66-2

Evaluation of Patients Suspected of Having Glomerular Disease

Medical history

To identify symptoms of medical conditions that may cause glomerular disease

- Diabetes mellitus
- Amyloidosis
- Systemic lupus erythematosus
- Other familial conditions associated with kidney disease

To identify symptoms suggestive of nephrotic syndrome

- Reduced appetite
- Fatigue
- Weight gain
- Edema

Medication, environmental, and occupational histories

To identify possible exposure to potentially nephrotoxic drugs, toxins, or chemicals

Physical examination

To identify signs and symptoms associated with systemic diseases

- Hypertension
- Rash
- Arthritis
- Retinopathy
- Neuropathy
- Lymphadenopathy
- Hepatomegaly
- Malignancy

Laboratory evaluation

Urinalysis

- To determine nephrotic nature of glomerular disease
- Proteinuria, >3.5 g/day/1.73 m^2
- Lipiduria
- To determine nephritic nature of glomerular disease
- Hematuria
- Pyuria
- Cellular, granular casts

Glomerular filtration rate

- To determine extent of glomerular damage

Other tests

- To identify type and etiology of glomerular disease
- Serum complement concentration
- Antinuclear and anti-DNA antibodies
- Antistreptolysin antibodies
- Circulating antiglomerular basement membrane antibodies
- Cryoglobulins

Percutaneous kidney biopsy

- To provide definitive diagnosis of glomerular disease

In most cases of severe glomerular disease for which immunuosuppressive therapy is being considered, a kidney biopsy is needed to provide a definitive diagnosis. The main risk of kidney disease is bleeding, due to the fact that the kidneys receive ~ 20% of cardiac output. Safety measures for kidney biopsy include controlling the blood pressure to less than 150/90 before and after biopsy, stopping all reversible and irreversible platelet inhibitors (NSAIDs, aspirin, clopidogrel) and anticoagulants, ensuring stable and adequate hemoglobin and platelet counts beforehand (preferably a hemoglobin >10 g/dL [100 g/L; 6.21 mmol/L] and platelet count >100,000/μL [100 x 10^9/L]), the ability for the patient to position correctly and calmly (usually lying supine, and kidneys are accessed percutaneously through the mid-back), and the ability to provide informed consent.

Assessment of Therapeutic Outcomes

After a specific diagnosis of glomerular disease is made, a treatment plan with monitoring must be instituted. Some treatments require physical exam and lab monitoring for potential toxicity, and to decide whether the glomerular disease is responding to therapy (see **Table e66-3**). Serum creatinine concentration as well as creatinine clearance should be evaluated prior to and during treatment. For patients suspected of having significant proteinuria, the gold standard measurement is by 24-hour urine collection. Proteinuria may also be estimated from the ratio of urine total protein to

urine creatinine random urine collection, and overall there is good correlation of the random protein/creatinine ratio with 24-hour urine proteinuria.[44] Electrolytes are monitored for changes due either to the glomerular disease, or due to medications such as diuretics or RAAS inhibition. Home blood pressure monitoring should be performed regularly to assess the need for and/or the adequacy of antihypertensive therapy. Edema and fluid overload should be assessed regularly to gauge the need for diuretic initiation or dosage modification. For patients with nephrotic syndrome, serum lipid concentrations should be monitored at least quarterly. For patients with hematuria, urinalysis and a complete blood count should be obtained. The clinician should also be aware of the patient's appetite and energy level because these are indicators of a patient's overall well-being. After initial diagnosis, a repeat kidney biopsy may be needed in some cases to assess response to treatment and disease progression, to determine future treatment strategy, or to confirm the initial diagnosis. Patients receiving cytotoxic drug treatment should be evaluated to gauge their response and identify the presence of drug-related toxicities, with the frequency of monitoring varying from weekly to monthly to quarterly, depending on which drug is utilized.

TABLE e66-3

Monitoring Parameters to Assess Response to Glomerular Disease Treatment

- Kidney function
  - Serum creatinine concentration
  - 24-hour urine collection for creatinine clearance determination
  - 24-hour urine collection for urinary protein excretion
  - Urine protein-to-creatinine ratio
- Clinical signs and symptoms
  - Nephrotic syndrome
    - Proteinuria
    - Serum lipid concentrations
    - Edema
  - Nephritic presentations
    - Hematuria
    - Urinalysis
    - Complete blood count
  - Blood pressure
  - General well-being: appetite, energy level
- Kidney biopsy to assess disease progression and response to therapy
- Assessment of drug therapy adverse reactions and toxicities

The frequency of monitoring is dependent on the specific glomerulopathy and severity of the disease.

NONINFLAMMATORY GLOMERULAR DISEASES

Noninflammatory glomerular diseases often cause the nephrotic syndrome. The main causes of noninflammatory glomerular disease are minimal change disease, focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), and dysproteinemias including myeloma, light-chain deposition disease, and amyloidosis. While membranoproliferative glomerulonephritis (MPGN) often causes a mixed nephrotic-nephritic syndrome, it is discussed with inflammatory glomerulonephritis. Diabetic nephropathy is characterized by proteinuria that sometimes rises to nephrotic-level (see Chapter 94).

Minimal-Change Disease

Minimal-change nephropathy (also termed "nil disease" or "lipoid nephrosis") is the most common cause of nephrotic syndrome in children, accounting for 85% to 90% of nephrotic syndrome in children between 1 and 4 years of age. The percentage drops to less than 50% after age 10 and it

accounts for less than 20% of all primary nephrotic syndrome in adults. Minimal change is usually primary (idiopathic) for which a molecular mechanism still has not been identified. A minority of patients have "secondary" minimal change, meaning that the disease arose secondary (because of) something else, such as a medication side effect or an infection. Causes of secondary minimal change disease include: NSAIDs (usually seen in combination with NSAID-induced allergic interstitial nephritis), lithium, HIV infection, Epstein-Barr viral infection, or occasionally T-cell lymphomas/leukemias.

Clinical Presentation

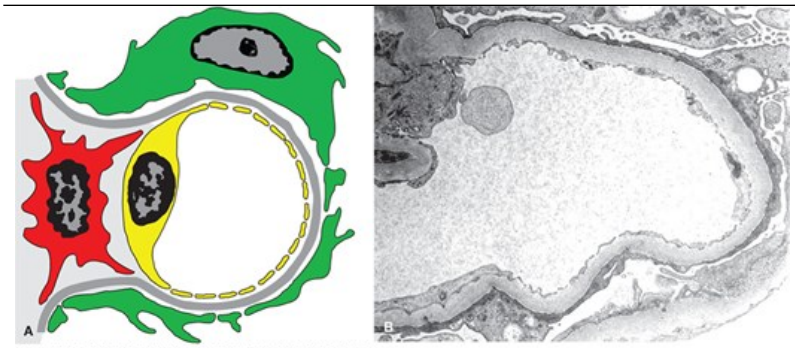
Minimal change disease usually presents with sudden onset edema and weight gain. Blood pressure is usually normal, as is kidney function, but patients have the full nephrotic syndrome, including nephrotic range proteinuria, hypoalbuminemia, edema, and hyperlipidemia. Under microscopy the urine sediment is negative for hematuria and cellular casts but can have oval fat bodies and fatty casts due to lipiduria. There are no serological tests, and the diagnosis can only be made on kidney biopsy. By light microscopy and immunofluorescence, the glomeruli appear normal, and electron microscopy is required to find an abnormality, hence the term "minimal change." Under electron microscopy there is spreading and fusion of podocyte foot processes along most of the glomerular filter. Although these foot process abnormalities are seen with most causes of nephrotic range proteinuria, with minimal change disease it is the principal or only abnormality on the kidney biopsy. Figures 66-4 and 66-5 depict a normal glomerulus and a glomerulus with minimal change disease, respectively.

FIGURE e66-4

Diagram (*A*) and electron micrograph (*B*) depicting a normal glomerular capillary. The diagram depicts a podocyte (green) with foot processes extending to the glomerular basement membrane (dark gray), an endothelial cell with fenestrations (yellow), and a mesangial cell (red) surrounded by mesangial matrix (light gray). (Reproduced, with permission, from Reisner H. Pathology: A Modern Case Study. 2nd ed. New York: McGraw Hill; 2020. https://accessmedicine.mhmedical.com/ Accessed September 12, 2022.)

FIGURE e66-5

Diagram (*A*) and electron micrograph (*B*) depicting minimal change disease. Electron microscopic features of minimal change disease include effacement of podocyte foot processes in the absence of ultrastructural features of other diseases. (Reproduced, with permission, from Reisner H. Pathology: A Modern Case Study. 2nd ed. New York: McGraw Hill; 2020. https://accessmedicine.mhmedical.com/ Accessed September 12, 2022.)



Treatment

Minimal change disease is treated with the general nonpharmacologic and pharmacologic measures for glomerular disease, especially sodium restriction, RAAS blockade, and diuretics. In addition, minimal-change disease is the most responsive glomerular disease to corticosteroids. In children, because steroid therapy leads to remission in more than 90% of patients, and because minimal change is the most common cause of the nephrotic syndrome, most children with nephrotic syndrome do not undergo kidney biopsy. Instead, they are empirically treated with steroids, and those that respond are diagnosed with "steroid-sensitive nephrotic syndrome," which is assumed to be due to minimal change disease. Children with nephrotic syndrome are empirically treated with prednisone 60 mg/m^2/day for 4 to 6 weeks.[14] Adults are administered prednisone 1 mg/kg/day (maximum 80 mg) or 2 mg/kg/every 2 days (maximum of 120 mg) for at least 4 weeks. The goal of treatment is complete remission, defined by negative proteinuria. In children the response rate is excellent, with complete remission in 50% of children after 1 week and >90% after 4 weeks of steroids.[45] In adults a complete remission takes longer, with 50% of adults responding to steroids by 8 weeks and an additional 10% to 25% responding by 16 weeks.[46] Patients who achieve complete remission carry the added diagnosis of "steroid-sensitive disease." Patients who achieve complete remission must remain on steroids but can begin to reduce the steroid dose 2 weeks later, tapering over 2 to 5 months in children, and tapering by 6 months in adults. Patients who do not respond to therapy by 16 weeks are considered "steroid-resistant," and steroids can be tapered off more rapidly.

Among patients who achieve complete remission, relapse is unfortunately common. More than 80% of "steroid sensitive" patients will experience a relapse of proteinuria within 6 to 12 months, requiring repeat steroid therapy, usually at a lower dose and shorter duration compared to the initial presentation. Some patients relapse infrequently, while others relapse frequently and can carry the diagnosis of "steroid-dependent" disease.

Chronic steroid therapy can result in problematic side effects such as growth retardation, insomnia, avascular necrosis of long bones, acne, polyphagia, and mood disorders. For patients developing side effects from chronic steroid therapy, or who decline initial steroid therapy, or who develop "steroid-resistant" disease, a second-line treatment for minimal change is required. Spontaneous remissions do occur, but often require years, and the risk of persistent nephrotic syndrome for years while hoping for a spontaneous remission is greater than the risks of medical treatment. Alternative medications to steroids include cytotoxic chemotherapy (cyclophosphamide or chlorambucil), calcineurin inhibitors (cyclosporine or tacrolimus), mycophenolic acid, or rituximab.[15] Based on limited data, these second-line therapies achieve remission in about 75% of patients, and none is clearly superior. One limitation of calcineurin inhibitors is that, if remission is achieved, then another recurrence is very common as the medications are tapered down.

Adults who initially have steroid-sensitive minimal change disease, and then become steroid-resistant on a subsequent relapse of disease, often have focal and segmental glomerulosclerosis (FSGS) on a second biopsy, which forms the basis for speculation that some forms of minimal change disease are part of a spectrum with FSGS.[47]

Focal Segmental Glomerulosclerosis

Focal segmental glomerular sclerosis (FSGS) is a histopathologic description on kidney biopsy, and the clinical difficulty is determining the cause. The most common causes of FSGS are primary (idiopathic), which appears to result from a circulating factor in blood that has not been identified, secondary FSGS due to large number of conditions, and heritable/genetic FSGS, most of which involves genes that control the podocyte cytoskeleton.[48–50]

In the case of primary FSGS, we presume the cause is a circulating factor because, when these patients have lost kidney function and undergo kidney transplantation, FSGS can recur within the new kidney within hours to days, and these patients sometimes respond just as rapidly to plasmapheresis. Although the rapid recurrence and rapid remission with pheresis argue for the existence of a circulating factor, the identity of this factor remains elusive.

Secondary FSGS can be caused by a few drugs, namely pamidronate (but only at very high doses) and heroin (but only in selected outbreaks, suggesting a contaminant within batches of drug but not the opioid itself), but drug-induced FSGS is fairly rare. Most secondary FSGS is caused by "adaptive" changes over many years in patients who have a mismatch between body size and the number of glomeruli (so either a person is too large, or the number of glomeruli are too few). This is sometimes called the "Brenner" hypothesis of FSGS, and is described using terms such as "maladaptation to reduced nephron mass." Clinical examples of adaptive FSGS include large body size due to morbid obesity or high-protein diets with anabolic steroids, or reduced glomerular number due to congenital hypoplasia, premature birth, sickle-cell disease, and nephrectomy. Not all patients with these clinical conditions will develop secondary FSGS over years-decades, but the risk is significantly increased. There is also an aggressive form of secondary FSGS seen among patients with untreated HIV infection due to podocyte damage, which we call HIV-associated nephropathy.

A third cause of FSGS to consider is genetic. Mutations in more than 20 genes have been identified from families with FSGS, and the unifying theme is that these genes all appear to regulate the podocyte cytoskeleton, consistent with the podocyte's unique shape, with protrusions that end in many hundreds of foot processes. The inheritance pattern of genetic FSGS varies with patient age and gene and can be recessive (especially in children), dominant (especially in adults), or maternal (such as mitochondrially inherited FSGS with seizures).

A special variant of genetic FSGS, the inheritance of G1/G2 risk alleles of *APOL1* among people of West African ancestry, may explain why FSGS is roughly 4× more common in Black adults compared to non-Black adults. Similar to sickle cell anemia, the GI and G2 "risk alleles" of the *APOL1* gene help resist a serious infection (African sleeping sickness due to trypanosomes) and these alleles are principally found among people of West African ancestry. Only one allele is needed to kill trypanosomes and resist sleeping sickness (much like the benefit of one sickle cell allele in resisting malaria), but people who inherit two copies of *APOL1* risk alleles are at increased risk for biopsy-proven focal and segmental glomerulosclerosis (much like the severe phenotype from two sickle cell alleles). When we look at the frequency of the G1 and G2 alleles among Black adults, and the magnitude of increased risk these alleles confer for FSGS, these alleles can mathematically account for all of why FSGS is 4× more common among Blacks than people of European descent. The mechanism by which these APOL1 risk alleles cause FSGS is still uncertain and a focus of research. Testing patients for these APOL1 risk alleles is of uncertain value and is not routine, because the lifetime risk of FSGS with two copies of G1 and/or G2 is only 4% to 5%,[51] which is much lower than nearly 100% penetrant Mendelian mutations, and with no mechanism for why these *APOL1* alleles cause disease, and no treatment thus far, a positive test will not change a patient's treatment.

FSGS is uncommon in children with nephrotic syndrome but precise statistics are uncertain because, as described in the section on minimal change disease, children who respond to steroids are presumed to have minimal change disease and do not undergo kidney biopsy. In adults, FSGS was historically the second most common cause of nephrotic syndrome after membranous, but the incidence of FSGS has been increasing, and for the last 20 years has been the most common cause of biopsy-proven nephrotic syndrome in US adults.[52]

Clinical Presentation

Patients with FSGS, whether primary, secondary, or genetic, present with proteinuria, which can be sub-nephrotic or nephrotic. Hypertension, microscopic hematuria, and impaired kidney function may be seen in up to half of all patients. If nephrotic range-proteinuria is present, some patients will have normal serum albumin and minimal to no edema, while others will have the full nephrotic syndrome. These clinical differences are the first step in making the clinically difficult decision of who may have primary FSGS and therefore should consider immunosuppressive therapy. Patients with primary FSGS are more likely to have the full nephrotic syndrome, while patients with secondary FSGS are most likely to have nephrotic-range proteinuria without nephrotic syndrome. Features on kidney biopsy can also help distinguish primary versus secondary disease. The gold-standard for primary FSGS is whether the disease recurs shortly after kidney transplantation and responds to plasmapheresis therapy.

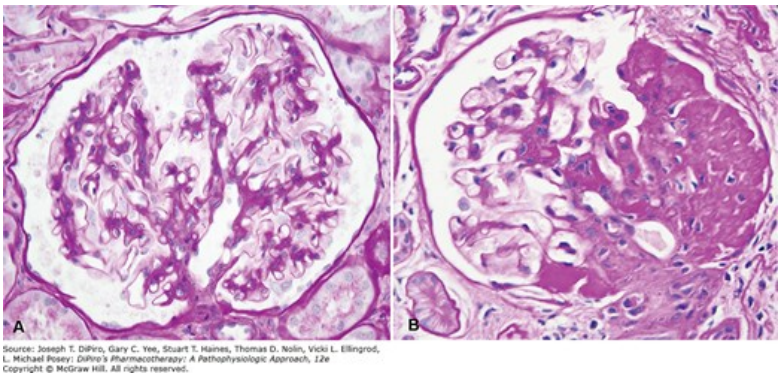
Histology

As the name would suggest, FSGS under light microscopy is defined by sclerosis of glomeruli that is focal (involving some, but not all of the glomeruli), and segmental (involving only a part of the glomerulus). Figure e66-6 depicts a normal glomerulus (A) compared to a glomerulus with focal segmental

glomerulosclerosis (B). There are histologic subtypes, including the tip lesion (in which sclerosis involves only the tip of the glomerulus furthest from the vascular pole), a cellular variant, and a collapsing variant (in which at least one capillary loop within a glomerulus appears to have collapsed inwards upon itself). Immunofluorescence in FSGS reveals focal and segmental deposition of IgM and C3 in areas of sclerosis, which is considered to be nonspecific trapping of proteins. Electron microscopy will show effacement of foot processes, similar to minimal change disease. Foot process effacement will be partial instead of diffusely complete in patients who have clinically milder disease, such as secondary causes of FSGS, or sub-nephrotic primary FSGS. Similar to the overlap on clinical presentation, it is difficult to definitively distinguish primary versus secondary FSGS based on histology, and the combined use of clinical features with histology is often needed for a final decision.

FIGURE e66-6

(*A*) Light microscopy of a normal glomerulus. The periodic acid–Schiff (PAS) stain accentuates collagen in glomerular basement membranes, mesangial matrix, Bowman capsule basement membrane, and tubule basement membranes. (*B*) Light microscopy of a glomerulus (PAS stain) depicting focal segmental glomerulosclerosis. (Reproduced, with permission, from Reisner H. Pathology: A Modern Case Study. 2nd ed. New York: McGraw Hill; 2020. https://accessmedicine.mhmedical.com/ Accessed September 12, 2022.)



By virtue of the fact that FSGS is focal, the histopathology can be completely missed on kidney biopsy if an inadequate number of glomeruli are sampled. For instance, if FSGS affects 20% of all glomeruli in a particular patient (which would likely be mild disease), then an inadequate biopsy with only one glomerulus would have an 80% chance of missing the diagnosis, a biopsy with two glomeruli would have a 64% chance of missing the diagnosis, and a biopsy with 20 glomeruli would have a $0.8\%^{20}$ chance, which is a 1.1% chance of missing the diagnosis. These figures apply to FSGS and other focal glomerular diseases, and help illuminate why the KDIGO guidelines recommend that an "adequate" kidney biopsy for patients with glomerular disease should have at least 20 glomeruli.[14]

Treatment

The treatment of FSGS is controversial because of a paucity of data from randomized, placebo-controlled trials, as well as the difficulty of distinguishing primary versus secondary FSGS. Patients who are diagnosed as primary FSGS and have the nephrotic syndrome are candidates for a trial of immunosuppression. Those with secondary FSGS have treatment directed at the underlying, secondary cause (eg, weight loss if secondary to morbid obesity). All patients with FSGS, whether primary or secondary, and whether nephrotic or subnephrotic, are treated with conservative measures as described above for general glomerular disease.[49]

If immunosuppression is undertaken for primary FSGS, the KDIGO recommendation is corticosteroid therapy with prednisone (or prednisolone) at the same dose and duration as used for minimal change disease.[14] The response rate to steroids is both slower and less frequent than with minimal change. The median time to complete remission is 3 to 4 months, although 5 to 9 months may be needed in some patients. By 16 weeks, if a patient has not achieved at least partial remission, defined by a 50% reduction in proteinuria, then steroids are tapered off and the patient is considered "steroid resistant." Based on large retrospective studies, 50% to 70% of patients will achieve at least a partial remission on steroids. Some of this response may include patients with spontaneous remission, which can occur, but we do not have definitive data from placebo-controlled trials to know the relative efficacy of corticosteroid therapy.

If a patient has "steroid resistant" FSGS, or has contraindications to corticosteroids due to diabetes, bone disease or mood disorders, then the preferred alternative to corticosteroids is calcineurin inhibitors. Cyclosporine with a therapeutic trough of 100 to 175 ng/mL (mcg/L; 83 to 146 nmol/L),

or tacrolimus with a therapeutic trough of 5 to 10 ng/mL (mcg/L; 6.2 to 12.4 nmol/L), for at least 6 months, achieves similar benefits, with a partial or complete response in about 70% of patients.[53,54] However, about 50% of patients who respond will relapse shortly after tapering the calcineurin inhibitor. Other steroid-sparing therapies, which are discussed above in the treatment of minimal change disease, include mycophenolate, rituximab, and cyclophosphamide, but for FSGS the data on these therapies are less robust than the data for calcineurin inhibitors.[15,55]

In patients who achieve complete remission the prognosis is good, with less than 10% progressing to ESKD within 10 years.[49] At the other end of the spectrum, among patients who are resistant to therapy, 50% progress to ESKD within 10 years, with a highly variable rate, sometimes within months, sometimes many years. Patients with severe proteinuria (more than 10-15 g/day), high serum creatinine at diagnosis, steroid resistance, and interstitial fibrosis on kidney biopsy are more likely to progress to ESKD rapidly. In patients who undergo kidney transplantation for ESKD, FSGS will recur in 40% of kidney allografts soon after transplantation.[49] Patients who had rapidly-progressing FSGS in their native kidneys are more likely to have recurrence in their transplant. Genetic FSGS should not recur after transplantation. Genetic FSGS is more common in children or adults from families with a clear pattern of inheritance, and among adults with primary FSGS who do not have a family history, the benefit of routine genetic testing has not been established.[15]

Membranous Nephropathy

Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults, with peak incidence between ages 30 and 50 years. Autoantibodies against a podocyte antigen, the M-type phospholipase A2 receptor (PLA2R), have been found in 70% to 80% of patients with primary membranous nephropathy.[56] Antibodies to PLA2R are sufficiently specific that many experts now recommend presumptive diagnosis of primary MN without the need for kidney biopsy. Autoantibodies against thrombospondin type-1 domain-containing 7A have been found in 3% to 5% of cases of MN,[57] but these autoantibodies are also found in secondary membranous due to cancer.[58] Autoantibodies against neutral endopeptidase (NEP) have been described in rare cases of neonatal membranous nephropathy.

About 25% of adults and 80% of children have secondary causes of membranous nephropathy. In the United States, the most common secondary causes are autoimmune diseases (lupus), chronic infections (hepatitis B, hepatitis C, or syphilis), neoplasms (large-sized adenocarcinomas such as lung, breast, stomach, colon, or prostate), and medications used historically for rheumatoid arthritis (gold or penicillamine). Malaria and schistosomiasis are common causes of secondary membranous in other parts of the world. A full list of other, rare secondary causes of MN is beyond the scope of this chapter. It is important to distinguish primary versus secondary MN with history, exam, serologies, and age-appropriate cancer screening, because primary MN is treated with aggressive immunosuppression, while some of the secondary causes of MN (cancer, infections) can dramatically worsen if immunosuppression is administered.

Clinical Presentation

Most patients with membranous nephropathy present with heavy proteinuria (exceeding 3.5 g/day) and the nephrotic syndrome with minimal to no nephritic features. Urine microscopy often reveals lipiduria and oval fat bodies, but microscopic hematuria is present in fewer than 25% of patients, and red cell casts are quite rare. The onset of nephrotic syndrome is usually insidious, in contrast to the fulminant onset of minimal change disease. If nephrotic syndrome is present, the presenting symptom can be deep vein thrombosis or pulmonary embolism due to hypercoagulable state. The incidence of renal vein thrombosis varies from 5% to 62% and can be asymptomatic (especially if unilateral) or may cause gross hematuria with loin pain.

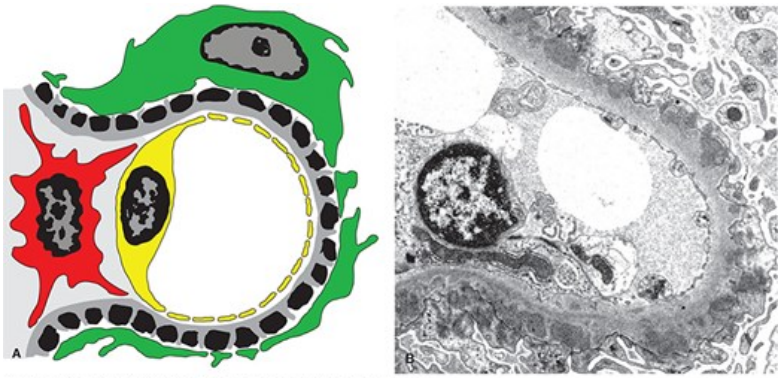
Histology

Kidney biopsy under light microscopy reveals glomeruli with normal mesangium and normal cellularity. The hallmark feature of membranous nephropathy is sub-epithelial deposits on light microscopy and electron microscopy (see **Fig. e66-7**), but in early stages of MN these deposits can be difficult to see, glomeruli may appear normal on light microscopy, and electron microscopy is required to be able to see the deposits and make the diagnosis. Over time, subepithelial deposits of MN become surrounded by newly synthesized glomerular basement membrane, and this extra basement membrane looks like “spikes” of the GBM under light microscopy, especially when visualized with special stains to enhance basement membrane components (either Periodic acid–Schiff [PAS] or Jones stains). The subepithelial deposits, which do not stain, eventually become large enough to look like “holes” within the GBM. In later stages of MN, the GBM becomes progressively thickened, and the mesangium becomes sclerotic. Immunofluoresence in primary MN will show granular deposits of IgG and C3 along the GBM, and if the GBM also stains positively for PLA-2R

antibodies, then primary MN is confirmed. If the GBM stains negatively for PLA-2R, or stains positively for thrombospondin type-1 domain-containing 7A, then secondary MN due to adenocarcinoma is likely. If the GBM stains positively for IgG, IgM, IgA, antibody light chains and more ("full house"), then the MN is secondary to class V lupus. Serologies for lupus are usually positive in these patients, but in some cases the serologies do not become positive until 1 to 3 years later.

FIGURE e66-7

Diagram (*A*) and electron micrograph (*B*) depicting membranous nephropathy. Electron microscopic features of membranous nephropathy include numerous subepithelial electron-dense deposits that correspond to the immune complexes seen by immunofluorescence microscopy, and effacement of podocyte foot processes. (Reproduced, with permission, from Reisner H. Pathology: A Modern Case Study. 2nd ed. New York: McGraw Hill; 2020. https://accessmedicine.mhmedical.com/ Accessed September 12, 2022.)



Treatment

All patients with primary and secondary MN should be treated with conservative measures. For secondary MN, additional treatment is directed at the underlying cause; if due to adenocarcinoma, then surgical resection can result in remission, and if due to a virus or parasite, then treating the infection is indicated. For primary MN, additional treatment involves the decision of whether to use immunosuppression. The risks and benefits of immunosuppression involve an assessment of the clinical severity of disease, for which treatment may be worth the risk, balanced with the likelihood that a spontaneous remission will occur, in which case immunosuppression is not worth the risk. Up to 30% of patients with spontaneous MN experience spontaneous remission, but this takes time, often 1 to 3 years after disease onset. The likelihood of spontaneous remission correlates with milder disease. Of patients who do not have a spontaneous remission within two years, half have persistent proteinuria with long-term preservation of kidney function, while the other half have gradual loss of kidney function to ESKD over 5 to 10 years, and these are the patients who will benefit most from immunosuppression. A predictive algorithm has been developed which incorporates the level of proteinuria, initial creatinine clearance, and the slope of kidney function decline over 6 months.[59] To simplify the decision tree somewhat for the purposes of this chapter: (1) if proteinuria is less than 4 g/day, then immunosuppression is not initiated, and spontaneous remission after 1 to 3 years is likely. (2) If proteinuria is between 4 and 8 g/day, wait six months and monitor to see if a spontaneous remission is beginning, and if not, then consider starting immunosuppression. (3) if proteinuria is more than 8 g/day with the full nephrotic syndrome, and GFR is greater than 30 mL/min/1.73 m^2, immunosuppression is recommended. The logic here is that a kidney with GFR above 30 mL/min/1.73 m^2 is still "worth saving," the nephrotic syndrome is severe enough that complications are likely, and the 10-year algorithm predicts progress toward ESKD if untreated. (4) if proteinuria and the nephrotic syndrome have already caused a complication such as life-threatening pulmonary embolism, then start immunosuppression. There are additional nuances to this decision tree, but this detail is beyond the scope of this chapter.

Immunosuppressive treatment for MN is different than minimal change and FSGS in that corticosteroid treatment by itself has no benefit. The three options for immunosuppression in primary MN are cytotoxic therapy, calcineurin inhibitors, and rituximab, each in conjunction with a small or moderate amount of corticosteroid. Cytotoxic therapy involves a modified "Ponticelli protocol" of alternating corticosteroids and oral cyclophosphamide for 6 months.[60] For the first month, KDIGO recommends starting with a very high dose of 1,000 mg/day intravenous methylprednisolone for 3 days followed by oral prednisone 0.5 mg/kg for 27 days. For the second month, patients receive oral cyclophosphamide at

2.5 mg/kg/day with prednisone 10 mg to avoid steroid withdrawal symptoms. This cycle is repeated on months 3 to 4 and months 5 to 6, followed by a steroid taper.[15] Calcineurin inhibitors for MN are administered twice daily for 6 months or longer, either cyclosporine 3.5 mg/kg/day aiming for a trough of 125 to 225 ng/mL (mcg/L; 104 to 187 nmol/L), or tacrolimus 0.05 to 0.075 mg/kg/day aiming for a trough of 3 to 10 ng/mL (mcg/L; 3.7 to 12.4 nmol/L). Rituximab for MN is most often infused at two doses of 1,000 mg IV, 2 weeks apart, and repeated at 6 months if there is no remission based on a combination of proteinuria and serologic monitoring.

Lastly, in addition to being an acceptable serologic test for the diagnosis of primary MN without need for kidney biopsy, the titre of anti-PLA-2R antibody can assist with decisions on immunosuppression.[61] Antibody titres tend to change several months before changes in proteinuria. For patients with intermediate proteinuria who are being monitored for 6 months in the hope of spontaneous remission, persistent nephrotic syndrome would argue to start immunosuppression, but if the anti-PLA-2R titre is clearly falling, then proteinuria should remit soon, and a few more months of monitoring may provide the proof to avoid unnecessary immunosuppression. Alternatively, in patients with severe disease who received immunosuppression but still have persistent nephrotic syndrome 6 months later, raising the question of treatment failure, a falling antibody titre provides reassurance that the treatment is working and remission of proteinuria will come soon. Lastly, in patients who achieve complete remission, the return of a positive anti-PLA2R titre occurs several months prior to a recurrence of proteinuria to help plan for repeat immunosuppressive therapy.

Dysproteinemias and Amyloidosis

Dysproteinemia is the general term for a monoclonal antibody in serum that is causing disease within an organ. Dysproteinemias can cause glomerular disease (nephrotic, nephritic or both), and dysproteinemias can also cause non-glomerular kidney disease. Instead of focusing on how dysproteinemias can cause MPGN, this section provides an overview of how dysproteinemias can affect the kidney in many ways. A dysproteinemia is suggested by finding an increased level of a monoclonal immunoglobulin in serum, but the diagnostic difficulty is that most monoclonal immunoglobulins in serum are not causing any harm to the kidney or any organ, leading to the term monoclonal gammopathy of unknown significance (MGUS). The incidence of MGUS increases with age, and in one seminal study from the Mayo clinic, MGUS was found on serum protein electrophoresis with immunofixation in 3.2% of patients older than 50, 5.3% of patients old than 70, and 7.5% of patients older than 85.[62] Based on these numbers, in many patients with kidney disease, finding a serum monoclonal antibody is less likely to explain the cause of kidney disease, and more likely to be a coincidental MGUS with a kidney disease caused by something else. A patient diagnosed with MGUS can, over years, progress to having smoldering multiple myeloma or overt myeloma, which frequently affect the kidney. Along the spectrum between MGUS and myeloma are patients who have a monoclonal antibody in serum with reassuring kidney biopsy, but they have new proteinuria or progressive kidney failure of unclear cause. On kidney biopsy, sometimes the monoclonal antibody is binding with high affinity to kidney tissues, in which case we use the term monoclonal gammopathy of renal significance (MGRS).[1] There are roughly 10^{15} different potential antibodies in the human repertoire, each with different amino acid sequence, polypeptide folding, and antigen-binding characteristics, and these differences determine how (and whether) the kidney will be attacked by a dysproteinemia. The severity of kidney disease also depends on the rate at which an antibody is being produced by a clone of B-cells. The most common patterns of kidney disease with dysproteinemias are myeloma cast nephropathy, light-chain deposition disease, and amyloidosis.

Myeloma Cast Nephropathy

Myeloma cast nephropathy tends to present with rapid loss of kidney function. Patients are often oliguric, and sometime anuric. Cast nephropathy occurs when a B-cell clone is synthesizing excess light chains, which are filtered across the glomerulus and reach high concentration in the urine as overflow proteinuria. If conditions are just right, then the light chains will precipitate within the tubules and form insoluble casts that plug up the nephron. Precipitation into casts depends on the biophysical properties of the antibody (some amino acid sequences will fold/organize into casts much more readily than others), and proteins tend to precipitate more often when concentrated, and under a certain salt concentration or acidity. Clinically, a patient will suddenly stop making urine, as if they have a urine obstruction, but the bladder will be empty. The obstruction is not within the urine collecting system, but is higher up, within every tubule of each nephron within the kidney.

Pathology

Kidney biopsy reveals intraluminal proteinaceous casts in the distal nephron. The casts are usually acellular, homogenous with multiple fracture lines. Persistence of casts produces giant cell inflammation and tubular atrophy. Immunofluorescence should confirm the casts stain with light chains, and the staining should be kappa or lambda but not both (confirming a monoclonal proteinuria).

Treatment

To reverse the process of precipitation of antibodies within the distal nephron, treatment includes (a) aggressive hydration to increase fluid flow with nephrons, which reduces the concentration of antibody within the nephron so cast formation is less likely; (b) immediate chemotherapy against plasma cells or mature B-cells, to reduce the amount of antibody that is being produced; (c) consideration of plasmapheresis, although the clinical data suggest that the only patients who might benefit from pheresis are those that respond to chemotherapy. It is not certain whether the pheresis itself confers significant benefit; (d) hemodialysis to replace kidney function until a patient responds to chemotherapy, and the intra-tubular casts have time to dissolve.

Light-Chain Deposition Disease

Light-chain deposition disease tends to present with significant proteinuria, and often the full nephrotic syndrome. Progressive renal failure is the rule. Response to traditional chemotherapy is poor. On kidney biopsy, LCDD involves deposition of light chains into glomeruli (mesangium and GBM) and tubular basement membranes but spares the kidney's blood vessels (in contrast to AL amyloidosis). The deposits appear pale on H&E stain, are PAS positive (like diabetes), and are Congo-red negative (unlike Amyloid). On immunofluorescence the GBM and tubular BM will have granular staining with either kappa or lambda light chain, but not both (because the disease is from a single cancer clone, with only one light chain), and may show granular, electron dense material on EM.

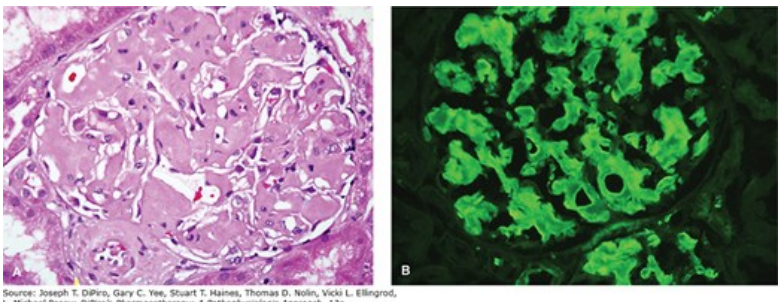
Amyloidosis

Amyloidosis occurs when proteins, because of a specific amino acid sequence, or a peptide cleavage event, fold abnormally into beta-pleated sheets that are insoluble and deposit between cells, producing atrophy and cell death. There are three general type of amyloidosis: AL amyloid, AA amyloid (which occurs in inflammatory states like rheumatoid arthritis or familial Mediterranean fever) and hereditary amyloid. AL amyloid is rare among dysproteinemias because only a small fraction of antibodies have amino acid sequences that favor folding into B-pleated sheets, but AL a common cause of systemic amyloidosis.

The clinical presentation of renal amyloidosis is nephrotic syndrome, often very severe, without nephritic features. Blood pressure may be low due to deposition of amyloid within the systemic vasculature. Ecchymoses are common because minimal pressure can induce the systemic blood vessels to bleed. Depending on the amino acid sequence, amyloid will have a proclivity to particular organs, which can include the heart, liver, peripheral nervous system, gastrointestinal tract, tongue, and gums. On kidney biopsy amyloid can form nodules (like diabetes) but the amyloid nodules will not stain well with PAS, whereas diabetic nodules stain strongly with PAS. Congo red stain shows green birefringence of amyloid under polarized light. On immunofluorescence, light chain amyloidosis (see **Fig. e66-8**) will stain with either kappa or lambda, but not both (because of the monoclonal nature of cancer). On EM amyloid may have small nonbranching fibrils 7.5 to 10.0 nm wide, of variable length and periodicity.

FIGURE e66-8

Light chain amyloidosis. (*A*) By light microscopy, amyloidosis causes replacement of normal glomerular architecture by amorphous acidophilic (eosinophilic) material (hematoxylin and eosin stain, H&E stain). (*B*) Immunofluorescence microscopy of amyloid demonstrates deposits of monoclonal immunoglobulin light chains (anti-lambda). (Reproduced, with permission, from Reisner H. Pathology: A Modern Case Study. 2nd ed. New York: McGraw Hill; 2020. https://accessmedicine.mhmedical.com/ Accessed September 12, 2022.)



INFLAMMATORY GLOMERULAR DISEASE

The basic presentation of inflammatory or proliferative glomerular diseases is usually nephritic, but the clinical findings can vary widely. A mild case of IgA, for example, may have only microscopic hematuria, with no proteinuria, no hypertension, and no loss of kidney function over 20 years. At the other end of the spectrum, rapidly progressive glomerulonephritis with Goodpasture's syndrome can progress from onset of disease to ESKD in weeks, and if untreated has a 90% chance of mortality. The most common specific diagnoses in inflammatory glomerular disease are discussed in detail below.

Immunoglobulin A Nephropathy

IgA nephropathy uses the suffix "pathy" of a noninflammatory disease but has the clinical symptoms of an inflammatory/proliferative glomerulonephritis in ~ 95% of patients. IgA is also known as Berger's disease, after the French physician who first described the disease. It is the most common primary glomerulonephritis in the world and accounts for 10% of patients with ESKD in many countries. The prevalence of IgA varies from a high of 45% of all glomerulonephritis in Asia to 30% to 40% in Europe and 10% to 15% in the United States. Within the United States, the diagnosis is rare among Black patients with glomerulonephritis, but as high as 35% among Native Americans in New Mexico.[63] These differences in IgA prevalence around the world are often ascribed to genetics, or possibly environment, but the differences in prevalence also reflect regional variations in who should undergo kidney biopsy. For example, if one region performs kidney biopsy only if patients who have glomerular hematuria and more than 1 g proteinuria, while another region performs kidney biopsy in all patients with glomerular hematuria regardless of proteinuria, the latter will have a "higher" prevalence of IgA. These types of differences in disease detection are known to confound data on disease prevalence throughout the Health Sciences. The true prevalence of IgA including mild disease is not known. One study from Japan suggested the prevalence of clinically silent IgA may be as high as 16% of the population.[63]

The diagnosis of IgA can only be made by kidney biopsy (detailed histology below) and is defined by dominant or co-dominant staining of IgA on immunofluorescence. There are no serologic tests for IgA, and the levels of serum immunoglobulins are unhelpful. Like many glomerular diseases the cause of IgA can be primary or secondary. Primary disease is caused by a multi-hit process that begins with errors in post-translational glycosylation of IgA heavy chains. Specifically, the hinge region (roughly in the middle of the IgA heavy chain) should have galactose residues added to O-glycans as part of post-translational modification of amino acids in that region of the protein. Patients with IgA fail to add galactose residues to a variable number of O-glycans in the region. These defects in glycosylation are hereditary, but are not sufficient to cause disease, and are only step 1 in the "multi-hit" process. In the next step, in most but not all patients, these aberrant, galactose-deficient O-glycans are perceived as "non-self" and result in IgG auto-antibodies directed against the hinge region of IgA. In the third step, if the levels of both galactose-deficient IgA and the IgG auto-antibody are high enough, and the binding affinity of IgG auto-antibodies is strong, then IgG-IgA immune complexes will form within the circulation. These can be detected in patients with IgA nephropathy but are still not sufficient to cause disease. In the last step, these circulating immune complexes bind to the GBM during glomerular filtration and in some but not all patients, these complexes become entrapped within the mesangium and elicit an antibody-mediated, inflammatory cascade.[64]

Clinical Presentation

Primary IgA nephropathy commonly presents in the second and third decades of life but can occur at any age. Clinical severity can vary tremendously. Most patients present with asymptomatic microscopic hematuria, with variable degrees of proteinuria, hypertension, and decreased kidney function. Ten years after diagnosis, approximately 10% to 20% will reach ESKD, and after 20 years this is true for 30% of patients. Predictors of eventual progression to ESKD are persistent hypertension, GFR that is already decreased, obesity, and especially the magnitude of proteinuria.[63] Instead of subtle microscopic hematuria, some patients present with synpharyngitic gross hematuria, in which a respiratory infection (or rarely gastrointestinal infection) results in a flare of hematuria.[63] Patients often seek medical care for their reddish-brown or "coca-cola" colored urine, and a workup of the many causes of gross hematuria eventually leads to a diagnosis of IgA. The timing of a flare of hematuria at the time of pharyngitis is different from the 2-week delay after pharyngitis that is characteristic of post-infectious glomerulonephritis. Rarely, patients with IgA nephropathy present with the nephrotic syndrome, or may present with rapidly-progressive glomerulonephritis (described later in this chapter), in which kidney function declines over weeks instead of years.

Secondary IgA nephropathy is caused by liver disease and several bowel diseases, and as with all secondary glomerular diseases, treatment should be directed at the underlying cause. Circulating IgA antibodies are normally cleared by the liver. Increased levels of circulating IgA in patients with liver

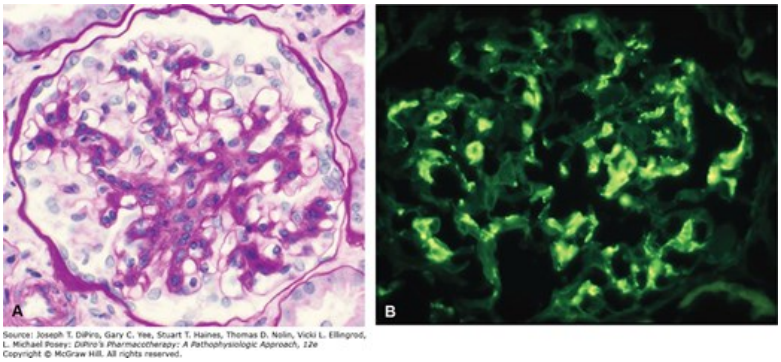
disease result in IgA nephropathy in some but not all patients, probably via a multi-hit process (but not identical to that of primary IgA). IgA secondary to liver disease usually causes hematuria without progressive CKD and disappears after liver transplantation or other treatment to improve liver function. Inflammatory bowel disease also increases the levels of circulating IgA because it is a secreted antibody from lymphoid tissue in the gastrointestinal tract. When IgA arises in patients with Crohn's disease, multiple case reports describe that remission of Crohn's leads to remission of IgA.[65] Similarly, in patients with celiac disease who develop IgA nephropathy, restriction to a gluten-free diet results in remission of disease.

Histology

As mentioned above, the diagnosis of IgA can only be made by kidney biopsy. Testing for auto-antibodies is not commercially available and, as described above, would not be sufficiently predictive due to the multi-hit process of pathophysiology. The Oxford histologic classification system provides a uniform approach to biopsy evaluation in primary IgA, and its predictive value has been demonstrated in multiple patient cohorts.[66] Light microscopy typically reveals mesangial cell proliferation (which means more than three mesangial cells in a glomerular capillary loop, in a biopsy section of typical thickness), but in mild disease, the glomeruli can appear normal (see **Fig. e66-9**). Rarely, in patients with the clinical syndrome of RPGN, glomerular crescents will be found (crescents and RPGN are discussed later in the chapter). On immunofluorescence, the glomerular capillary loops will stain brightly with IgA, most often more brightly than any other antibody, but in some cases the staining will be co-dominant. On electron microscopy, the mesangium will contain electron-dense deposits, which are sometimes seen in the sub-endothelial GBM, contiguous with these areas of mesangium.

FIGURE e66-9

(*A*) IgA nephropathy with mesangioproliferative glomerulonephritis with mesangial proliferation (PAS stain). (*B*) Immunofluorescence microscopy demonstrating intense mesangial staining for IgA, but no staining along the glomerular capillary loops. (Reproduced, with permission, from Reisner H. Pathology: A Modern Case Study. 2nd ed. New York: McGraw Hill; 2020. https://accessmedicine.mhmedical.com/ Accessed September 12, 2022.)



Treatment

Patients with mild IgA disease, defined as microscopic hematuria, normal proteinuria, normal blood pressure and normal kidney function, may be treated with the nonpharmacologic measures described above in the Treatment of Generalized Glomerular Diseases, and closely monitored over many years. Patients with proteinuria >0.5 g/day, regardless of blood pressure, are treated with full conservative measures including ACEIs or ARBs. The goal blood pressure is at least lower than 130/80 mm Hg and possibly lower, as described previously. For patients with proteinuria greater than 1 g/day despite 3 to 6 months of optimal care with ACEIs or ARBs, additional therapy is recommended. In the 2012 KDIGO guidelines, 6 months of daily corticosteroids were the preferred additional therapy, but studies have shown high rates of serious adverse events from steroids.[67] The current recommendation is that patients with persistent proteinuria >1 g/day undergo individual assessment of the risks and benefit of corticosteroids, and consider referral to a clinical trial site for one of many experimental treatments that are currently under evaluation.[64] A kidney biopsy showing crescents is not, by itself, sufficient to recommend use of steroids or other aggressive therapy.

IgA vasculitis, formerly known as Henoch-Schönlein Purpura (HSP), is a rare disease that most often presents in children or young adults. It is difficult to study rare diseases in children, but the current hypothesis is that the pathophysiology is very similar to primary IgA as described above. The symptoms of IgA vasculitis are the same as primary IgA, with glomerular hematuria and a variable degree of proteinuria, hypertension, and loss of

kidney function. In addition, IgA vasculitis causes a skin rash on the thighs, buttocks and low abdomen, with a variable degree of abdominal pain. The skin rash and abdominal pain lead to medical evaluation, and eventually to the diagnosis. The supposition is that the skin and GI symptoms are caused by deposition of the same circulating IgA-IgG antibody complexes that deposit in the mesangium. Skin biopsy, if performed, will show leukocytoclastic vasculitis that stains predominantly with IgA. On kidney biopsy, the histology under light microscopy, immunofluorescence, and electron microscopy resembles all the findings of primary IgA nephropathy. Treatment of IgA vasculitis should probably be the same as for IgA nephropathy, with a decision for systemic steroids based on whether proteinuria persists after maximal conservative therapy for 3 to 6 months.

Post-Infectious Glomerulonephritis

Post-infectious glomerulonephritis (PIGN) usually occurs in healthy children who are 5 to 15 years of age, and is uncommon in children under age 2, or in adults over the age of 50. Most often it is caused by a “nephritogenic” strain of streptococcus in patients with bacterial pharyngitis, or less commonly with a skin infection (impetigo). There are specific “nephritogenic” strains of Group A, beta-hemolytic Streptococci: types 1, 4, and 12 (for pharyngitis), and types 49 and 2 (for impetigo). About 14 days after the infection, the immune response to infection with a nephritogenic strain results in antibody-mediated glomerular damage. These antibodies may bind with streptococcal antigens that have already deposited on the glomerular filter to form immune complexes that activate an inflammatory response (in-situ immune complex formation), or immune complexes may form with streptococcal antigens within the circulation and then deposit on the glomerular filter (circulating immune complex formation), or the antibodies may be intended for bacterial antigens but are cross-reacting with the glomerular antigens in the absence of streptococci (molecular mimicry). The evidence is strongest for in-situ immune complex formation, but by any of these three mechanisms, antibody-antigen complexes will activate complement and recruit neutrophils and monocytes, leading to a brisk inflammatory glomerulonephritis.

Many other infections can cause infectious glomerulonephritis with a similar biopsy and similar features. Instead of occurring 2 weeks after streptococcal pharyngitis, these other infections are smoldering chronic diseases such that, when humoral immunity begins to kick in 2 to 6 weeks later, the infection is still present. As such, these are not strictly speaking, post-infectious, and we use the term “infectious glomerulonephritis” instead, but the basic mechanisms and clinical presentations are similar. Examples of smoldering infections that can cause infectious glomerulonephritis include sub-acute bacterial endocarditis, chronic Staphylococcus epidermidis infection of a ventriculo-peritoneal shunt, or chronic bacterial liver abscess.[68]

Clinical Presentation

With PIGN there is often enough hematuria for patients to see coca-cola colored urine, similar to patients presenting with synpharyngitic IgA nephropathy, but unlike IgA, all symptoms including the hematuria that changes urine color begin 2 weeks after the infection. All patients with PIGN will have microscopic hematuria, and there are varying degrees of other nephritic syndrome features. Urine microscopy will reveal dysmorphic red cells and often red cell casts, or mixed red and white cell casts. Hypertension is common and can be dramatically severe in children, including emergency room visits for hypertensive emergency with seizures. Proteinuria is usually less than 3 g/day but is sometimes nephrotic-range, and as such PIGN is one of the glomerular diseases that can sometimes have an overlap of nephritic with nephrotic features. Kidney function is usually decreased and falling at the time of presentation. Other laboratory tests include decreased serum C3 complement (because antibody-antigen complexes are activating complement, which uses up C3 in serum faster than it can be synthesized), increased anti-streptolysin O titers after a nephritogenic streptococcal pharyngitis, or increased anti-DNAse B titers after a nephritogenic bout of impetigo. The diagnosis can be made based on these clinical features and lab tests. Kidney biopsy is not indicated unless the patient has prolonged hematuria, proteinuria, or depressed C3 level, in which case the purpose of kidney biopsy is to rule out other types of glomerulonephritis such as lupus, RPGN, or MPGN.[68]

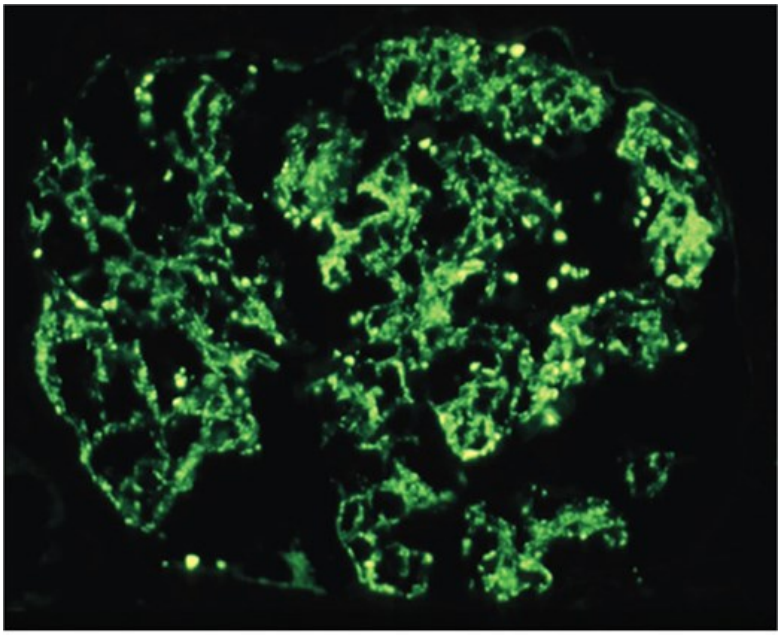
Overall, the long-term prognosis of PIGN is very good in children. Diuresis usually begins 7 to 10 days after acute onset. Kidney function returns to baseline within 3 to 6 weeks in more than 95% of patients. Gross hematuria lasts for 1 to 2 weeks, and proteinuria usually resolves within 6 months in more than 90%. Microscopic hematuria may persist for up to 2 years. Most children will have no detectable kidney disease in the long term. Adults, on the other hand, do not heal as well as children and are less fortunate. As many as 50% of adults will have persistent proteinuria, hypertension, and kidney insufficiency, with eventual progression to end-stage kidney failure. These adult patients are examples, as described in the discussions of general glomerular disease pathophysiology earlier in the chapter, of how an episode of acute glomerulonephritis can lead to an inflammatory cascade that persists, even after the initial cause has resolved.

Histology

If performed, kidney biopsy reveals hypercellular glomeruli with proliferation of mesangial and endothelial cells, and infiltration of neutrophils, monocytes, and eosinophils. The infiltrate will be prominent within glomerular capillary loops and the mesangium, consistent with where antibody-antigen complexes are depositing. Glomerular crescents may be seen and if more than 30% of glomeruli have crescents, along with a reduction of 50% in kidney function, then the PIGN is causing RPGN.[68] Immunofluorescence examination reveals diffuse granular deposits of IgG and C3 along the GBM and in the mesangium (**Fig. e66-10**).

FIGURE e66-10

Acute post-infectious glomerulonephritis. Immunofluorescence reveals diffuse granular deposits of IgG and C3 along the GBM and in the mesangium. (Reproduced, with permission, from Reisner H. Pathology: A Modern Case Study. 2nd ed. New York: McGraw Hill; 2020. https://accessmedicine.mhmedical.com/ Accessed September 12, 2022.)



Treatment

For a patient whose infection took place weeks ago, antibiotics are of no benefit and only create the risks of side effects. Treatment of post-infectious glomerulonephritis is supportive and is directed at hypertension from sodium retention due to the nephritic syndrome. Because the hypertension is due to low-renin sodium retention, ACEIs and β-blockers are less effective at controlling blood pressure, while diuretics and calcium channel blockers are more effective. In patients with crescentic disease on biopsy, steroids and/or immunosuppressive agents can be considered, but unlike other causes of RPGN, the efficacy and safety of these agents has not been established for post-infectious disease,[68] and for variants of infectious glomerulonephritis caused by smoldering, chronic infections, the benefit of immunosuppression must be carefully balanced against the risk of exacerbating the infection.

Membranoproliferative Glomerulonephritis

Historically, membranoproliferative glomerulonephritis (MPGN) has accounted for 7% to 10% of all cases of biopsy-confirmed glomerulonephritis and has been the third or fourth leading cause of ESKD among patients with glomerular diseases. MPGN is a "pattern of injury" based on histology, rather than a specific disease. In the last 10 years, the entire classification scheme for MPGN has changed, mainly due to advances in our understanding of the very complex pathophysiology of C3-related diseases, and of refinements in our appreciation of monoclonal disorders of renal significance. Formerly classified as MPGN type 1, or type 2 or type 3, the new classification scheme for MPGN is as follows:

(1) Immune complex MPGN, which is usually due to mixed essential cryoglobulinemia from chronic hepatitis C infection. Sometimes, the immune complex MPGN is caused by a monoclonal light or heavy chain gammopathy, in which case only one type of antibody will stain under immunofluorescence.

(2) Complement-mediated MPGN, which is usually a C3 glomerulopathy. These are rare diseases in which excess activation of the alternative complement pathway leads to deposition of C3 as the brightest stain on immunofluorescence of kidney biopsy. The alternative complement cascade can be overly activated by many different proteins and stimuli. Methods for diagnosing the cause of C3 glomerulopathy, and decisions for optimal treatment, are subjects of rare-disease clinical research and are beyond the scope of this chapter. In very rare cases, a distinct type of complement mediated MPGN is found on kidney biopsy. C3 dense deposit disease is diagnosed based on the pathognomonic finding of a dense, ribbon-like glomerular basement membrane on electron microscopy. Dense deposit disease, unfortunately, responds poorly to current treatments, and frequently recurs after kidney transplantation.

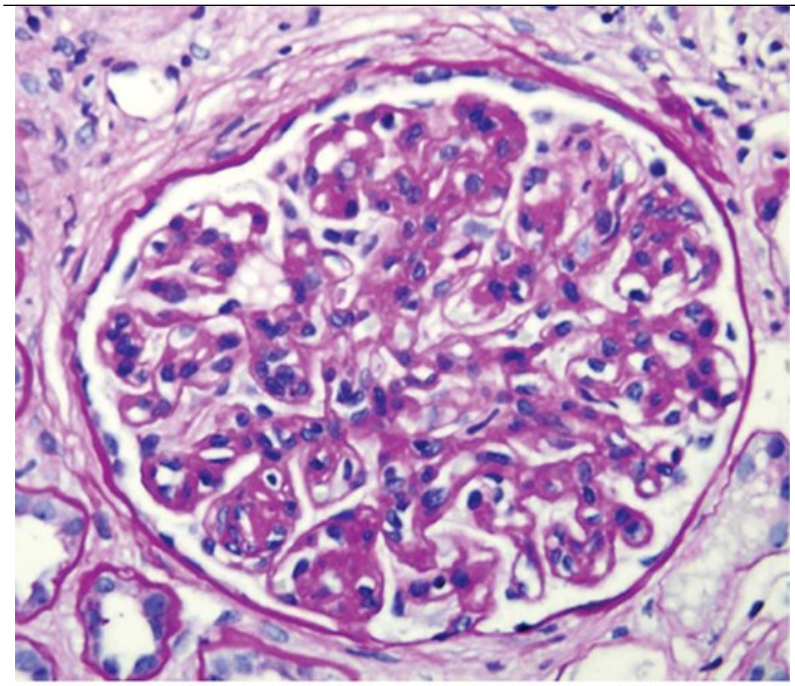
Immune complex MPGN in patients with hepatitis C is caused by mixed-essential cryoglobulinemia, which develops in some but not all patients with chronic hepatitis C infection. A cryoglobulin occurs when antibodies within the serum crosslink and precipitate into a gel of protein, particularly at temperatures colder than core body temperature (cryo = cold). A cryoglobulin can precipitate from the serum into various tissues (possible the skin, heart, kidneys, lungs, joints, GI track or brain), where the antibody precipitate can be large enough to impede capillary blood flow, and the crosslinked antibodies can also signal an inflammatory response.

Clinical Presentation

Immune-complex MPGN due to hepatitis C cryoglobulinemia is a nephritic or an overlap nephritic-nephrotic syndrome. A classic presentation is a patient who presents in the winter, when colder hands and feet will favor cryoglobulin formation, with a severe rash in the legs and hands, arthralgias of the hands, and nephritic syndrome with an active urine sediment on microscopy, hypertension, kidney failure, edema, and proteinuria that can be nephrotic-range. Kidney biopsy will show mesangial and variable endocapillary cell proliferation with circumferential extension of the mesangium into the subendothelial space of the capillary wall (mesangial interposition or mesangialization), resulting in thickening of the peripheral capillary wall. On silver stain, there is a “double contour” in the capillary walls (tram tracking), corresponding to reduplicated subendothelial lamina densa (**Fig. e66-11**).

FIGURE e66-11

Membranoproliferative glomerulonephritis. Light microscopy (PAS stain) showing thick capillary walls with GBM remodeling and replication, as well as mesangial hypercellularity and increased mesangial matrix. (Reproduced, with permission, from Reisner H. Pathology: A Modern Case Study. 2nd ed. New York: McGraw Hill; 2020. https://accessmedicine.mhmedical.com/ Accessed September 12, 2022.)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Immune complex MPGN due to monoclonal gammopathies is one of the monoclonal gammopathies of renal significance.[1] Much less common than hepatitis C–mediated MPGN, in these patients a monoclonal antibody is being produced by an overt or subclinical B-cell neoplastic disorder. The monoclonal antibody is occasionally a cryoglobulin, different than the "mixed essential" cryoglobulin described above, in which the antibody binds to itself at temperatures lower than 37°C to form a cryoglobulin. In other cases the monoclonal antibody is not a cryoglobulin, but when it binds to antigen, the result is an immune complex cascade that leads to MPGN. The clinical presentation of these monoclonal disorders is usually a nephrotic syndrome with mild hypertension and occasional but infrequent microscopic hematuria,[69] but nephritic features can be present, depending on the degree of inflammatory response elicited by the particular monoclonal antibody.

Treatment

All MPGN patients can be treated with maximally tolerated conservative therapy. Immune complex MPGN due to hepatitis C cryoglobulinemia should be treated, as expected, by eradicating the virus. Until 5 to 10 years ago, this was accomplished by a year of treatment with interferon/ribavirin, with only modest viral remission and significant side effects. The development of direct anti-viral therapy over the last 10 years has made viral remission highly successful, and with few side effects. If hepatitis C cryoglobulinemia is causing an RPGN, then urgent treatment is required, and in addition to viral eradication, immunosuppression with corticosteroids and either rituximab or cyclophosphamide is used to arrest production of the causal antibodies.[70] Immunosuppression will make hepatitis C titres flare, and so immunosuppression must be coupled with anti-viral therapy. For immune complex MPGN due to monoclonal disorders, treatment is directed at the B-cell or plasma cell clone that is creating the antibody, and therapy is often a collaboration with colleagues from hematology-oncology.[71] Treatment of the C3 glomerulopathies with regimens including rituximab, mycophenolate mofetil and corticosteroids has been described, as has the use of terminal complement blockade with eculizumab. These treatments are generally informed by expert opinion, largely based on case series.[72]

Hereditary Glomerulonephritis (Alport's Syndrome)

Alport's is not an inflammatory glomerular disease, but it presents with nephritic syndrome, and understanding the pathophysiology of Alport's syndrome will help clinicians appreciate the most severe form of inflammatory glomerulonephritis due to anti-GBM antibodies as discussed below. Alport's syndrome is rare and affects about 1 out of every 50,000 newborns. Mutations arise or are inherited in the genes that encode for the alpha-3, alpha-4, or alpha-5 subunits of type IV collagen. Mutations in any of three separate genes that encode these three subunits can cause Alport's syndrome. In ~ 80% of patients, the mutation is within the alpha-5 subunit on the X chromosome, leading to severe disease in males. In 10% to 15% of

patients, the inheritance is autosomal, due to mutations in the alpha 3 or alpha 4 subunits, which are encoded by separate genes arising from the same promoter on the long arm of chromosome 2. In less than 5% of patients, a causal mutation in these three genes was not identified.

The backbone of the glomerular basement membrane is formed from heterotrimers of these three proteins, so depending on the severity of the amino-acid change, the GBM will be weakened, prone to leaking albumin and blood across the GBM, and glomerulosclerosis will gradually ensue over a few decades. Microscopic hematuria begins during early childhood, followed by proteinuria and decreased kidney function as a teenager, and then ESKD between 20 and 40 years old. Less severe mutations can present as glomerulonephritis in later decades. Many patients with X-linked Alport's syndrome also have sensorineural deafness, because the alpha-5 subunit of type IV collagen is required for the basement membrane heterotrimers in the inner ear.

On kidney biopsy, light microscopy will reveal focal and segmental glomerulosclerosis, or global glomerulosclerosis, with "foam" cells (lipid laden macrophages and podocytes). Foam cells are not specific for Alport's and have been described in primary FSGS. Over time, kidney function is lost due to glomerulosclerosis, and sometimes this is mistaken as primary FSGS on biopsy. Immunofluorescence reveals absent GBM staining with an antibody to the alpha-5 subunit of type IV collagen. Mutations of alpha 3 and alpha 4 subunits also alter the filament structure enough to disrupt alpha-5 staining, so one antibody can "detect" mutations in any of the three subunits. On electron microscopy, the glomerular basement membranes will be thin in early disease (GBM thickness increases with age and can vary depending on how the GBM is sliced, perpendicular or angled, so pathologists make this measurement carefully). Over time the GBM becomes excessively thick, with splitting and fraying that is sometimes described as a basket-weave appearance.

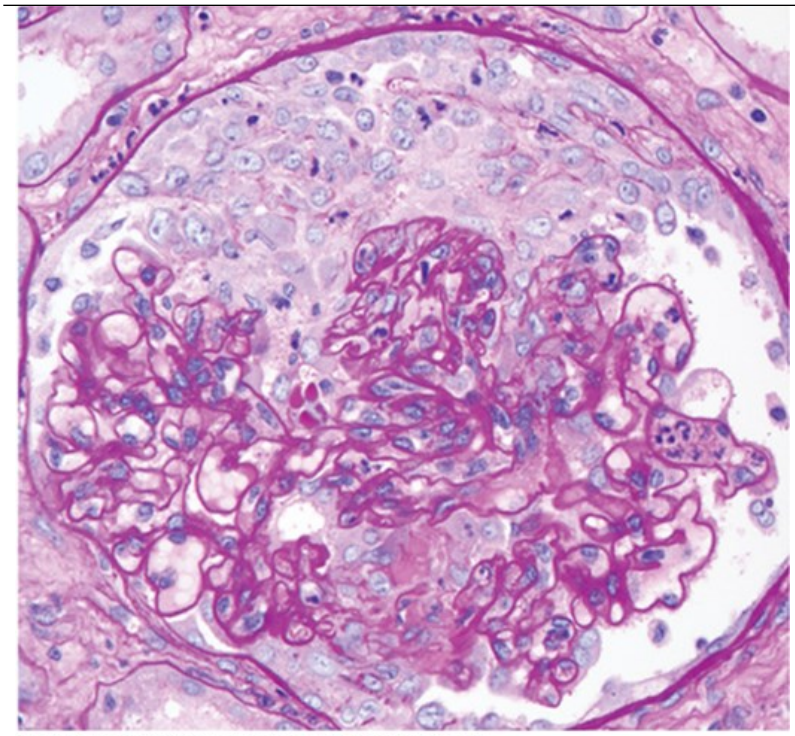
There is no specific treatment. Conservative measures for glomerular disease may help slow the rate at which Alport's reaches ESKD. Transplantation is the best treatment. There are reports of anti-GBM nephritis after transplantation, but this is quite rare and was largely confined to patients with a large deletion of the alpha 5 subunit who made no protein, such that their transplanted kidney contained a new protein that was "not self."

Rapidly Progressive Glomerulonephritis (RPGN)

Before describing the last few specific diagnoses of glomerular disease, which are lupus nephritis, ANCA-associated vasculitis, and anti-GBM nephritis, we should introduce the term RPGN, for rapidly progressive glomerulonephritis. RPGN is a subset of nephritic syndrome in which patients are losing at least 50% of kidney function in less than 6 weeks (and usually faster). On kidney biopsy, all patients with RPGN have glomerular crescents, which are necessary to make the diagnosis of RPGN. Crescentic GN and RPGN are interchangeable terms for the same patient: the former term describes the kidney biopsy, and the latter describes the nephritic syndrome with rapid loss of kidney function. **Figure e66-12** illustrates a typical glomerular crescent, which is initially made of parietal glomerular epithelial cells (podocytes are the visceral epithelial cells and are not part of these crescents; parietal epithelial cells are normally located on the other side of Bowman's space and have different biological properties than podocytes). As time progresses, inflammation from RPGN recruits macrophages and then fibroblasts into a cellular crescent. As fibroblasts secrete extracellular matrix it transitions into a fibro-cellular crescent, and eventually an entirely sclerotic glomerulus. Cellular crescents should respond to aggressive immunosuppression and enable salvage of that glomerulus. During the transition to fibrocellular crescents, salvaging a glomerulus with immunosuppression becomes increasingly difficult with aggressive chemotherapy, and once the crescent is sufficiently fibrous, the glomerulus and thus the entire nephron will be lost.

FIGURE e66-12

Crescentic glomerulonephritis with a large cellular crescent composed predominantly of proliferating epithelial cells (PAS stain). (Reproduced, with permission, from Reisner H. Pathology: A Modern Case Study. 2nd ed. New York: McGraw Hill; 2020. https://accessmedicine.mhmedical.com/ Accessed September 12, 2022.)



The cause of RPGN/crescentic GN is classified according to the staining of the glomerulus by immunofluorescence. First, if the glomerular capillary loops have a *granular antibody staining pattern* on immunofluorescence, then the cause of RPGN is an immune complex disorder, most often lupus nephritis. At lesser frequencies, one of the previously described immune complex glomerular diseases can cause RPGN, including hepatitis C cryoglobulinemia, monoclonal gammopathies causing MPGN, infectious glomerulonephritis, or IgA nephropathy. Second, if the glomerular capillary loops have *negative staining* with all common antibodies on immunofluorescence, then the cause of RPGN is a "pauci-immune" disorder, almost always due to ANCA-associated vasculitis. Lastly, if the glomerular capillary loops have a *linear staining pattern* on immunofluorescence, usually with IgG and only one of the light chains, then the cause of RPGN is anti-GBM glomerulonephritis, also called Goodpasture's disease.

Two more concepts related to the causes of RPGN should be discussed; namely, the range of severity of kidney disease, and the range of organs that are affected. First, anti-GBM nephritis almost always presents as an RPGN, but the other causes of RPGN listed above with granular or pauci-immune staining can also cause a milder glomerulonephritis that does not change serum creatinine by 50% in less than six weeks. There is a spectrum of disease. Second, all forms of RPGN listed above can affect just the kidney, in which case we use the term "renal vasculitis," or can affect the kidney as well as other organs, such as the lungs, heart, brain or nervous system, in which case we use the term "systemic vasculitis." Pulmonary-renal syndrome is an example of systemic vasculitis. In patients with systemic vasculitis, even if the symptoms in the kidney are less severe than the symptoms in another organ (such as alveolar hemorrhage from pulmonary vasculitis), kidney biopsy is more sensitive, and therefore has a higher yield for making the diagnosis.

Lupus Nephritis

The most common cause of RPGN with granular immune deposits is systemic lupus erythematosus (SLE), a multisystem, autoimmune disease with antibodies directed against a wide variety of cellular constituents. SLE can affect the kidney in many other ways or can affect other organs and never affect the kidney. SLE is a syndrome of autoimmunity, not a single disease that follows the same molecular mechanism in every patient. The immune system in patients with SLE can attack one or more of the following organ systems: skin, joints, serous membranes, heart, peripheral nervous system, central nervous system, white blood cells, red blood cells, platelets, skin, and kidneys. When discussing lupus nephritis, we are referring to primary SLE, not lupus secondary to drugs such as hydralazine and procainamide, which almost never causes kidney disease.

SLE is diagnosed more often in women than men (roughly 6:1 ratio), and in the United States, SLE is most often diagnosed in young Black women, but

the significance of this is uncertain because, as some experts have noted, SLE is quite rare in sub-Saharan Africa. Experts speculate that a complex predisposition involving both environment and genetics underlies SLE, but a clear molecular mechanism remains elusive. A person whose first degree relatives have SLE is 10 to 20 times more likely to develop SLE, but this is far less than Mendelian frequency. More than 100 susceptibility genes have been identified, many of which involve the HLA-locus. Changes in B-cell function, T-cell function and the cytokine milieu are all implicated in the pathogenesis of SLE.[73,74]

Depending on definitions, kidney involvement is found among less than 50% of patients with SLE, but when it arises it is one of the most serious complications. The diagnosis of lupus nephritis relies on a combination of clinical features, laboratory results from blood and urine, and histopathologic appearance on kidney biopsy. Lupus can affect the entire body in many different patterns, and it can also affect the kidney in many different patterns of disease. The easiest way to understand the breadth possible symptoms and treatments of lupus nephritis is to start with the World Health Organization classification, which is based on kidney biopsy (see **Table e66-1**). Each of the WHO classes of lupus nephritis on kidney biopsy has a typical clinical presentation, and the WHO class on kidney biopsy is instrumental in directing therapy.[75]

Patients with sub-nephrotic proteinuria and either WHO class 1 or 2 on biopsy are treated with conservative therapy. Patients with WHO class III and class IV on biopsy are considered to have "proliferative lupus nephritis," and are treated aggressively. Proliferative lupus typically presents with microscopic hematuria with an active urine sediment under microscopy (dysmorphic red cells +/− red cell casts), sub-nephrotic proteinuria, and rising serum creatinine (the full nephritic syndrome), combined with a variable number of extra-renal manifestations of lupus, such as arthralgias, serositis, anemia, or a sun-sensitive rash. Anti-nuclear antibody titre is almost universally elevated, which is a sensitive but not specific test (so a negative test argues against disease, but a positive test is not enough to confirm the diagnosis). Serologies with high specificity for proliferative nephritis include antibodies to **d**ouble **s**tranded DNA (anti-**d**s DNA) or to the Smith antigen (anti-Sm). Serum levels of complement (C3, C4, or total complement CH50) are often low, because immune complex deposition is activating and consuming complement components. We do not consider class III and class IV mechanistically different, just part of a spectrum of proliferative lupus nephritis. Class III disease is defined as less than 50% of glomeruli affected and can present as RPGN but often has a milder nephritic syndrome, with mild-moderate extra-renal symptoms. Class IV disease, with greater than 50% of glomeruli affected, is the severe end of the spectrum; patients more often meet criteria for RPGN, and sometimes have pulmonary-renal syndrome. The division between class III and class IV based on +/− 50% glomerular involvement is arbitrary, especially given the small sample size of a kidney biopsy. In fact, while class III is "milder," the long-term kidney-survival and patient survival data are similar or even a bit worse for class III disease, which may be the result of less aggressive treatment. In keeping with the notion that class III and IV diseases are not pathophysiologically different, the KDIGO recommendations for treatment of both classes of disease are very similar, with maximal conservative therapy, plus hydroxychloroquine, plus aggressive immunosuppression with corticosteroids and either intravenous cyclophosphamide or oral mycophenolate.

Remission in class III, IV, or V disease is based on stabilization or improvement in kidney function over 6 to 12 months and improvement in proteinuria to less than 0.5 g/day.[15] Some experts also desire absent microscopic hematuria for remission, but this is not part of the current definition. During the use of aggressive immunosuppression, similar to the use of terms in oncology, there is an "induction phase" with a goal of achieving remission, followed by a transition to "maintenance phase" immunosuppression for another 18 to 36 months when patients take either mycophenolate or azathioprine. With aggressive immunosuppression, the survival of patients with classes III and IV disease has improved during the last two to three decades to approximately 80% at 10 years. The major cause of death in people treated with immunosuppression is infection including sepsis. This illustrates the balance of risk and benefit. Immunosuppression prolongs life and prolongs kidney function but is also predisposes to life-threatening infections. Careful monitoring is required.

Recurrence of lupus nephritis is unfortunately common and can be surprising. A patient who initially presented with class III lupus can recur with class III but could also recur with class IV + V combined disease for which aggressive immunosuppression is needed, or with class II disease for which repeat immunosuppression would not be indicated. For this reason, patients with lupus nephritis undergo multiple kidney biopsies throughout the course of their disease.

ANCA-Associated Vasculitis

RPGN with pauci-immune staining on immunofluorescence is caused by ANCA-associated vasculitis. Similar to proliferative lupus nephritis, ANCA-associated vasculitis can also cause a milder nephritic syndrome that does not meet criteria for RPGN. Using the 2012 Chapel Hill Consensus on how to classify ANCA-disease, we sub-classify patients as having either granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), or eosinophilic granulomatosis with polyangiitis (EGPA). GPA was formerly called Wegner's granulomatosis, and EGPA was formerly called Churgh-Strauss, but these

eponyms have fallen out of favor. ANCA-associated vasculitis is in fact, associated with autoantibodies, so the absence of antibody staining on biopsies may seem peculiar, and this simple observation is part of a complex pathophysiology of disease.[76] Anti-neutrophil cytoplasmic antibodies (ANCA) are found in 90% of patients with pauci-immune vasculitis, usually in association with high titres of autoantibodies to myeloperoxidase (anti-MPO) or proteinase 3 (anti-PR3). Serum complement levels are normal which, like the absence of staining on immunofluorescence, is peculiar among antibody-mediated diseases. Similar to the range of organ involvement in SLE, ANCA-associated vasculitis can be a renal-limited vasculitis that affects only the kidney, or can be a systemic vasculitis that affects the kidney as well as other organs of the body such as a pulmonary-renal syndrome.

With all of these complexities in mind, the 2012 Chapel Hill consensus proposed three clinical syndromes, each of which is most-often associated with a particular pattern of ANCA, a particular auto-antibody on ELISA, and a particular predisposition to involvement of organs in addition to the kidney (see **Table e66-4**).[15,77]

TABLE e66-4

Sub-Classification of ANCA-Associated Vasculitis

Disease	Pattern of ANCA	ELISA Auto-antibodies	Most Frequent Extra-Renal Organ Involvement	Less Frequent Extra-Renal Organ Involvement
GPA	C-ANCA on IF	Anti-PR3	90% also have respiratory involvement that ranges from sinusitis to pharyngitis to walking pneumonia to life-threatening alveolar hemorrhage. Because the presentation is smoldering, patients are often diagnosed with sinusitis or pneumonia for weeks to months before all the facts are put together. Most patients are more aware of their upper respiratory symptoms than they are of the more serious kidney symptoms until lab testing is performed.	Each of the following organ systems is affected in 40%-60% of patients: - skin (rash, often ears or nose, can erode the nasal bridge) - musculoskeletal (weakness, myalgias) - neurologic (mononeuritis multiplex, meaning a single peripheral nerve is affected, such as gaze deviation with CN VI, or foot drop with peroneal nerve) - gastrointestinal (ranging from decreased appetite and nausea to mesenteric vasculitis causing ischemia, with abdominal pain and bloody stools)
MPA	P-ANCA on IF	Anti-MPO	May be renal-limited disease. Each of the following organ systems is affected in 30%-60% of patients: - musculoskeletal (weakness, myalgias) - neurologic (mononeuritis multiplex like GPA) - gastrointestinal (like GPA)	- Upper respiratory / sinus involvement is quite rare. - Lower respiratory tract involvement with the appearance of pneumonia due to interstitial fibrosis or usual interstitial pneumonia is seen in roughly 30% of patients
EGPA	P-ANCA (but up to 50% are ANCA negative)	Anti-MPO	Invariably presents as asthma, and then astute health providers note asymptomatic nephritic syndrome. - neurologic (mononeuritis multiplex, see GPA).	Each of the following organ systems is affected in 50%-70% of patients: - skin (like GPA) - -upper respiratory (like GPA) - lower respiratory (like MPA) - musculoskeletal (like GPA) - gastrointestinal (like GPA)

WHO, Word Health Organization; ANCA, antineutrophil cytoplasmic autoantibody; GBM, glomerular basement membrane; GPA, granulomatosis with polyangiitis; EM, electron microscopy; CKD, chronic kidney disease; IF, immunofluorescence; LM, light microscopy; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PAS, periodic acid–Schiff stain; PR3, serine protease-3; SLE, systemic lupus erythematosus; TMA, thrombotic microangiopathy; EGPA, eosinophilic granulomatosis with polyangiitis.

ANCA-associated vasculitis can also be a secondary disease due to various drugs such as etanercept, hydralazine, propylthiouracil, minocycline, or

cocaine. Drug-induced ANCA-associated vasculitis most often causes high titre of anti-MPO, but can also cause simultaneous anti MPO with anti-PR-3, which does not occur with primary ANCA-associated vasculitis. Cocaine associated vasculitis is thought to arise from "cutting" the cocaine with levamisole, an anti-helminth drug in powder form that has affinity for many ion-channels and receptors at the molecular level, and complex effects on the immune system overall. Instead of aggressive immunosuppression, the best treatment is simple: cessation of the medication that is causing ANCA vasculitis.[77]

Treatment of Primary ANCA-associated vasculitis often relies on combined use of high-dose corticosteroids and cyclophosphamide, similar to inflammatory lupus nephritis. Unlike lupus nephritis, the alternative to cyclophosphamide is rituximab, not mycophenolate. In the 2020 KDIGO draft for glomerular disease, cyclophosphamide and rituximab carry equal weight for all sub-classifications of ANCA-associated vasculitis, and the final choice of treatment depends on weighing the side effects and individual patient characteristics. Reasons to opt for rituximab include a desire for future fertility (especially in children and young adults), frail elderly patients, and possibly PR-3 disease. Reasons to opt for cyclophosphamide including a difficulty accessing rituximab, which must be administered at licensed infusion centers, and possibly severe RPGN with pulmonary-renal syndrome.[15]

Remission is clinically assessed by the absence of microscopic hematuria, which is different than lupus nephritis, in which remission is defined by resolution of proteinuria. With ANCA vasculitis, the optimal result is resolution of all features of the nephritic syndrome, but it is recognized that proteinuria may persist after active disease has resolved due to residual damage that has caused secondary glomerulosclerosis. Once remission is achieved as assessed by resolution of hematuria, patients are transitioned to maintenance therapy using azathioprine or rituximab. This is another difference with lupus nephritis, where maintenance therapy is usually mycophenolate. The optimum length of maintenance therapy is not known but is typically 2 to 3 years. Patients who had upper respiratory disease often received trimethoprim-sulfamethoxazole during this time, based on modest clinical trial data that this may reduce the frequency of future relapse.

Anti-Glomerular Basement Membrane Glomerulonephritis

RPGN with linear staining of antibodies on immunofluorescence is caused by anti-glomerular basement membrane (anti-GBM) nephritis. The disease occurs most often in young adult males, but anti-GBM nephritis can occur in both sexes at all age ranges. Anti-GBM nephritis arises when an autoantibody is directed against the alpha-3 subunit of type 4 collagen.[78] It is not certain what triggers the formation of these autoantibodies. In some cases, it is believed that another process damages the GBM, changing the way that type 4 collagen protein within heterotrimers has folded, uncovering an epitope on the alpha-3 subunit that is ordinarily buried. When this epitope, the NC1 domain of the alpha-3 subunit, is recognized as "not self," antibodies form to directly attack this epitope, which damages the glomerular basement membrane. In animal models, progression from disease onset to ESKD can occur in less than two weeks, and while human disease may be a bit slower, it is nonetheless a fulminant process. There are no tests to predict who will develop disease, and so patients usually present only once the nephritic syndrome causes symptoms. A typical scenario might be an otherwise healthy young man, who feels horrid, seeks care in an emergency room, and learns he has kidney failure and might need dialysis immediately. Around half of patients (25%-60% in studies) will also have shortness of breath with a bloody cough due to lung involvement. Of the 3 staining patterns on IF, the linear pattern of anti-GBM nephritis is the least common cause of RPGN, but it is the most common among patients with pulmonary-renal syndrome. This is because the heterotrimers of collagen type 4 that make basement membrane in alveoli do not use the same 3 subunits as the kidney, but they do have one subunit in common, and that is alpha-3. Just as the auto-antibody attacks the alpha 3 subunit in the GBM, making holes that allow blood and protein to leak into the urine, the auto-antibody attacks the alveolar basement membrane, making holes that allow blood and protein to leak into the alveolar airspace. Clinically this is called "diffuse alveolar hemorrhage" and can suffocate gas exchange within the lungs.

The diagnosis of anti-GBM nephritis is made with a kidney biopsy showing necrotizing and crescentic glomerulonephritis on light microscopy, with linear staining for IgG along the glomerular basement membrane on immunofluorescence. Anti-GBM antibodies are detectable in the serum of the vast majority of patients.[79] Patients are treated with aggressive immunosuppression to stop new antibody formation. Steroids, cyclophosphamide, and plasmapheresis are recommended in all patients with a few exceptions. If patients have symptomatic disease only in the kidney, are already on dialysis, and had crescents in 100% of glomeruli on an adequate kidney biopsy, then treatment can be withheld. Plasmapheresis is continued for two weeks, or until the serum anti-GBM antibodies become negative.[14,79] Clinical recurrence of anti-GBM nephritis after kidney transplant has been reported and for this reason, transplantation should be delayed until the anti-GBM antibody is undetectable for at least 6 to 12 months.

CLINICAL BOTTOM LINE

A better understanding of the pathogenetic mechanisms leading to glomerular injury has led to marked improvements in the treatment of glomerular diseases. However, the glomerulopathies are a heterogeneous group of immune disorders with different clinical courses, prognoses, and responses to current immunologic and nonimmunologic therapies. The optimal treatment strategy for patients should be personalized based on the natural history and prognosis of their glomerular disease, and the risks and benefits of aggressive immunosuppression for that particular patient. Clinicians who wish additional involvement in the clinical care of patients with glomerular disease should consult the KDIGO guidelines.[14,15]

ABBREVIATIONS

ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ANCA	antineutrophil cytoplasmic autoantibody
ARB	angiotensin II receptor blocker
EGPA	eosinophilic granulomatosis with polyangiitis
ESKD	end-stage kidney disease
GBM	glomerular basement membrane
GFR	glomerular filtration rate
GPA	granulomatosis with polyangiitis
FSGS	focal segmental glomerulosclerosis
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HMG-CoA	β-hydroxy-β-methylglutaryl-coenzyme A
LDL	low-density lipoprotein (cholesterol)
MPA	microscopic polyangiitis
MPGN	membranoproliferative glomerulonephritis
MPO	myeloperoxidase
NEP	neutral endopeptidase
NSAIDs	nonsteroidal anti-inflammatory drugs
PAS	periodic acid–Schiff stain
PR3	serine protease-3

PIGN	post-infectious glomerulonephritis
PSGN	post-streptococcal glomerulonephritis
RAAS	renin-angiotensin-aldosterone system
RPGN	rapidly progressive glomerulonephritis
SLE	systemic lupus erythematosus

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SELF-ASSESSMENT QUESTIONS

1. Which of the following is more common in patients with nephritic syndrome compared to those with nephrotic syndrome?

   A. red blood cell casts

   B. edema

   C. hyperlipidemia

   D. hypercoagulable state

   E. proteinuria

2. Albuminuria above the normal threshold of ~ 30 mg/day (or 30 mcg/mg urine creatinine [3.4 mg/mmol creatinine]) is associated with

   A. increased all-cause mortality.

   B. increased risk of progression to ESRD.

   C. increased risk of fatal cardiovascular events.

   D. increased risk of nonfatal cardiovascular events.

E. all of the above.

3. Patients with nephrotic syndrome are commonly advised to

   A. restrict sodium intake.

   B. restrict potassium intake.

   C. initiate RAAS blockade at the maximum tolerated dosed.

   D. target blood pressure of less than 140/80.

   E. Options A and C only.

4. Which of the following may be used to reduce proteinuria for patients with glomerulonephritis?

   A. angiotensin-converting enzyme (ACE) inhibitor

   B. combined use of angiotensin-converting enzyme (ACE) inhibitor and angiotensin II receptor blocker (ARB)

   C. verapamil

   D. spironolactone

   E. A, C, and D

5. Use of statins in patients with glomerulonephritis has been proven to

   A. reduce LDL cholesterol and total cholesterol levels.

   B. reduce risk for cardiovascular disease.

   C. reduce renal function decline.

   D. reduce the proteinuria progression.

   E. all of the above.

6. Pediatric patients with minimal-change nephropathy often respond well to steroid therapy. Which of the following lesions is often found on kidney biopsy in patients who are resistant to steroid therapy?

   A. lupus nephritis

   B. focal segmental glomerulonephritis

   C. immunoglobulin A nephropathy

   D. membranous nephropathy

   E. membranoproliferative glomerulonephritis

7. Which of the following agents is/are often used as first-line therapy for inducing remission in patients with recently diagnosed minimal-change nephropathy?

   A. steroids

   B. steroids and cyclosporine

C. steroids and azathioprine

D. steroids and cyclophosphamide

E. steroids and mycophenolate mofetil

8. Which of the following is correct regarding the use of cyclosporine for the treatment of minimal-change nephropathy?

A. Cyclosporine is often effective in inducing remission during relapse.

B. Cyclosporine is useful for patients who are steroid dependent.

C. The disease-free period is not often sustained after therapy discontinuation of cyclosporine.

D. Nephrotoxicity is a concern after long-term use.

E. All of the above are correct.

9. Which of the following are risk factors associated with rapid kidney function decline in patients with focal segmental glomerulonephritis?

A. severe proteinuria

B. high serum creatinine concentration at initial diagnosis

C. initial steroid resistance

D. interstitial fibrosis on kidney biopsy

E. all of the above

10. A patient with IgA nephropathy who has proteinuria of 0.5 to 1 g/day should be treated with

A. ACE-i or ARB to control blood pressure and reduce urinary protein excretion

B. fish oil

C. steroid treatment

D. cytotoxic agents

E. mycophenolate mofetil

11. Which of the following is/are commonly considered when selecting the optimal treatment for patients with lupus nephritis?

A. disease activity according to pathologic findings

B. duration of symptoms

C. extent of proteinuria

D. history of medication non-compliance

E. all of the above

12. Which of the following is frequently used for chronic maintenance treatment of lupus nephritis?

A. systemic steroids

B. cyclophosphamide

C. cyclosporine or tacrolimus

D. mycophenolate mofetil

E. fish oil

13. Annual eye examination for possible retinal toxicity should be conducted for patients receiving long-term use of which medication?

A. fish oil

B. cytotoxic agent

C. cyclosporine

D. mycophenolate mofetil

E. hydroxychloroquine

14. Which of the following therapies is recommended for maintenance therapy of severe ANCA-associated vasculitis with kidney involvement?

A. methotrexate

B. azathioprine

C. mycophenolate mofetil

D. rituximab

E. either B or D

15. In patients with nephritic syndrome 2 to 3 weeks after streptococcal pharyngitis the best treatment is

A. rapid administration of intravenous antibiotics.

B. tonsillectomy after pre-operative clearance is obtained.

C. intravenous steroid therapy to reduce inflammation.

D. symptomatic treatment only.

E. both A and C.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** The reliable identification of red cell casts on urine microscopy indicates a nephritic syndrome. All other options (edema, hyperlipidemia, hypercoagulable state, and proteinuria) are more characteristic findings in patients with the nephrotic syndrome.

2. **E.** While albuminuria can be a transient finding in patients with tubular injury, patients with persistent albuminuria (either >30 mg/day, or greater than 300 mcg/mg urine creatinine [34 mg/mmol creatinine]) have increased risks for multiple adverse outcomes, including all-cause mortality, fatal cardiovascular events, major nonfatal cardiovascular events, and progression to ESRD.

3. **E.** Conservative therapy of both nephritic and nephrotic syndrome includes restricting sodium intake (which helps reduce blood pressure and edema) and therapy with an ACEI or ARB at the maximally tolerated dose. Potassium is NOT restricted, because in general potassium is handled in the inverse manner as sodium, such that a high potassium diet tends to reduce blood pressure and edema. If concerning hyperkalemia develops that cannot be easily controlled by diuretics, only then is dietary potassium restricted. The target blood pressure is at least less than 130/80, and probably lower than 125/75 for patients with nephritic and nephrotic syndrome, so the target of 140/80 is incorrect.

4. **F.** Maximally tolerated ACEI or ARB therapy should be used, but dual blockade is no longer recommended due to the increased risk of adverse outcomes including AKI and significant hyperkalemia. Patients who cannot tolerate an ACEI or ARB due to allergies, or who need additional blood pressure control, can use a non-dihydropyridine calcium channel blocker (verapamil or diltiazem) which lowers blood pressure and has a modest anti-proteinuric effect. Dihydropyridine calcium channel blockers, while excellent at reducing blood pressure, tend to raise intra-glomerular pressure and do not have a beneficial anti-proteinuric effect. Spironolactone has a significant anti-proteinuric effect in diabetic glomerular disease and in patients with proteinuria of diverse causes.

5. **A.** Statin therapy reduces total cholesterol and LDL in patients with hyperlipidemia due to the nephrotic syndrome. Unlike conventional heart disease, however, we do not have clinical proof that these reductions in lipid levels lead to reduced major adverse cardiac events, so answer B is incorrect. Some studies have shown reduced proteinuria and reduced rates of CKD progression with statin therapy as described in answers C and D, but these benefits have not been consistent across studies and are not regarded as proven yet.

6. **B.** Because minimal change disease is a “pure” nephrotic syndrome, this question is asking, in children who fail steroid therapy, what is the most common cause of nephrotic syndrome. The overwhelming number of these children have focal and segmental glomerulosclerosis. If the same question were asked of adults who fail empiric steroid therapy, the biopsy findings would be a fairly close split of FSGS and membranous nephropathy; and overall, FSGS is slightly more common among adults.

7. **A.** Empiric therapy with steroids alone for 3 to 6 months. About 95% of children with nephrotic syndrome will respond to empiric steroids (without biopsy) with a complete remission. While the response rate is a bit lower in adults with biopsy-proven minimal change disease, the efficacy of steroids is still very high, and alternative therapies are considered only if the adult has relative or absolute contraindications to systemic steroid therapy.

8. **E.** Alternatives to steroid therapy include the calcineurin inhibitors tacrolimus and cyclosporine. Both calcineurin inhibitors are effective at inducing a remission of proteinuria, are good choices for patients who are steroid dependent or have contraindications to steroid therapy, but there are two caveats. If the calcineurin inhibitor is discontinued, nephrotic syndrome often returns fairly rapidly, but if the calcineurin inhibitor is continued for many years, nephrotoxicity becomes a long-term complication.

9. **E.** The absolute level of proteinuria has an adverse long-term prognosis for most glomerular diseases, which is why decreasing proteinuria is an acceptable therapeutic target. For most causes of kidney disease, it is also not surprising that the higher the creatinine at initial diagnosis, the worse the long-term outcome. Steroid responsiveness is much less common in FSGS than minimal change disease, and is associated with a better long-term prognosis, because steroid responsiveness means less proteinuria and often a slight improvement in serum creatinine; conversely, steroid resistance is an adverse prognostic sign. And the extent of tubule-interstitial fibrosis on kidney biopsy is for kidney diseases that range from diabetes to the most rare glomerular disease, one of the most reliable histopathologic findings of long-term prognosis. There are exceptions, due to sampling error, but in general, if the biopsy shows extensive fibrosis, a patient will not respond well to therapy.

10. **A.** The optimal treatment for IgA nephropathy may change in the next 2 to 10 years due to multiple ongoing clinical trials, but at present, patients with 1 g/day or less of proteinuria are treated with maximal ACEI or ARB and sodium restriction only. No immunosuppression is recommended. The benefit of fish oil has not been consistently demonstrated.

11. **E.** Systemic lupus is one of the most complex kidney diseases (and one of the most complex syndromes in medicine). The optimal choice of immunosuppressant depends on the pathology description on kidney biopsy, extra-renal symptoms, the extent of proteinuria, and whether the patient is likely to take daily oral therapy versus receipt of intermittent intravenous therapy.

12. **D.** Induction therapy for lupus nephritis depends on the findings on biopsy, and the goal is to achieve clinical remission within 3 to 6 months. After this, a patient is switched to maintenance therapy, usually with mycophenolate, or sometimes rituximab. Steroids are used sparingly if at all during the maintenance phase.

13. **E.** Hydroxychloroquine has a 1% to 10% chance of retinal toxicity, which is reversible if detected early, leading to medication discontinuation. Yearly ophthalmologic dilated exams are recommended for all patients who are prescribed hydroxychloroquine.

14. **E.** ANCA-associated renal vasculitis is treated slightly differently than lupus nephritis, in that the most common medication of the maintenance phase is azathioprine instead of mycophenolate. If azathioprine is not used, the second choice is rituximab.

15. **D.** In patients with nephritic syndrome 2 to 3 weeks after streptococcal pharyngitis, the most likely cause is post-infectious glomerulonephritis. This is sometimes clinically assumed in children, but in adults nearly all patients would undergo kidney biopsy to prove by histopathology. The optimal treatment for post-infectious GN is supportive. Antibiotics are not needed, because the infection is over. Steroids have not been shown to provide benefit in clinical studies, and are used only in selected patients based on expert assessment of an individual's risks versus benefits.