Glomerular and Tubulointerstitial Diseases
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Glomerular disease is a common condition with the potential to cause considerable morbidity; United States Renal Data System (USRDS) data reveal that glomerulonephritis (GN) accounts for roughly 10% of incident end-stage renal disease (ESRD). Some glomerular disorders, such as those that cause the nephrotic syndrome, may be readily diagnosed because of their acute and obvious symptoms, whereas others may be discovered only in the setting of an abnormal urinalysis or serum creatinine value. Tubulointerstitial disease can be even more subtle, presenting only with an elevated creatinine value and often diagnosed merely as “chronic renal insufficiency.” It is critical to identify renal disease and to ascertain its root cause so as to treat acute symptoms and to manage the underlying condition definitively. Because many of these diseases are progressive and lead to irreversible sclerotic and atrophic changes in the kidney, prompt recognition and management of glomerular and tubulointerstitial diseases can forestall the deterioration of renal function and the necessity of renal transplantation or dialysis. The primary goal of this article is to serve as a concise review of the more common glomerular and tubulointerstitial diseases seen in the adult and adolescent population, highlighting factors and clues that can aid in recognition and diagnostic workup. Information about current treatment is also included so that the practitioner can anticipate and understand recommendations from the nephrologist, and thus help to guide discussions with the patient. The first two sections of this article deal with...
diagnosis and management of glomerular diseases, whereas the final section addresses tubulointerstitial processes.

The ability to categorize a patient's urinary abnormalities and other signs and symptoms into one (or more) of the following syndromes allows the practitioner to narrow the differential diagnosis to a particular subset of disease entities. It cannot be overemphasized that there is considerable overlap and that a single disorder may present variably as one or another syndrome depending on the severity or tempo of the glomerular disease process. The evaluation of asymptomatic proteinuria or hematuria has already been discussed in the article by Lerma elsewhere in this issue. It is not discussed further other than to say that these urinary abnormalities may represent early stages of glomerular disease that may later become more symptomatic.

The **nephrotic syndrome** is defined by the relatively acute onset of edema, nephrotic range proteinuria (defined as greater than 3.5 g/d per 1.73 m² of body surface area), hypoalbuminemia, hyperlipidemia, and lipiduria, all of which occur with minimal impairment of the glomerular filtration rate (GFR). The **acute nephritic syndrome** in its full-blown form is characterized by edema; hypertension; azotemia with the variable presence of oliguria; and a "nephritic" urinary sediment marked by the presence of erythrocytes (red blood cells [RBCs]), leukocytes (white blood cells [WBCs]), cellular casts (especially RBC casts), and mild to moderate proteinuria. GN may commonly occur in a less fulminant fashion, characterized merely by nephritic sediment with only mild or no decrease in renal function. **Rapidly progressive glomerulonephritis** (RPGN), which may be caused by the same disease processes that lead to the nephritic syndrome, is loosely defined by rapid deterioration of renal function associated with evidence of GN on urinary sediment. It is often a true renal emergency that requires immediate attention and treatment. In contrast to the glomerular syndromes, chronic tubulointerstitial diseases typically present with slowly progressive renal dysfunction, mild proteinuria, and the variable presence of RBCs and WBCs in the urine.

A brief review of the structure and function of the glomerulus is helpful to understand the clinical manifestations of glomerular diseases and the aforementioned syndromes better. Glomerular capillaries are efficient filters that retain most plasma proteins and cellular elements, although allowing the free filtration of water, electrolytes, and other small solutes. The glomerular filtration barrier is composed of three primary elements: a fenestrated capillary endothelium, the glomerular basement membrane (GBM), and visceral glomerular epithelial cells (podocytes). Specialized structures known as slit diaphragms bridge the filtration slits between adjacent podocyte foot processes and form the final barrier to prevent plasma proteins leaking into the urinary space [1]. Proteinuria in many nephrotic diseases is the end result of damage or hereditary defects of the podocyte and disruption of the highly structured slit diaphragm. GN, often instigated by the deposition of immune complexes within the glomerulus, involves leukocyte infiltration,
inflammatory disruption of the filtration barrier, and consequent leakage of protein, RBCs, and WBCs into the urinary space. Structural defects in the GBM, as in hereditary nephritis, can also lead to derangements in glomerular function.

Glomerular diseases have traditionally been named according to their appearance on light microscopy of the renal biopsy rather than according to the underlying cause per se. A brief glossary of some of the common terms may help to decipher the otherwise confusing and esoteric names. The term membranous (as in membranous nephropathy [MN] or membranoproliferative glomerulonephritis [MPGN]) refers to an abnormal thickening of the GBM. The term diffuse implies that most glomeruli are affected more or less uniformly, whereas the terms focal and segmental mean that only some glomeruli are partially affected by the disease process. A proliferative lesion is the term used to refer to a hypercellular inflammatory process that involves infiltrating leukocytes and proliferation of intrinsic glomerular cells. The term sclerosis describes a degenerative process by which normal structures are replaced by the accumulation of fibrous scar tissue. The utility of assigning glomerular diseases to such histopathologic groups is that such entities tend to have a similar clinical course. For example, a diffuse proliferative process, such as poststreptococcal glomerulonephritis (PSGN), tends to cause acute symptoms, diminished GFR, and often gross hematuria because of active inflammation occurring in most or all glomeruli. Conversely, a less-intense focal proliferative lesion, such as IgA nephropathy (IgAN), may present with relatively asymptomatic urinary findings and normal renal function.

The nephrotic syndrome

The nephrotic syndrome frequently comes to clinical attention because of edema or anasarca of recent onset. Urinalysis and protein quantification, which should always be performed in the absence of another clear explanation for lower extremity edema, should reveal heavy proteinuria. Findings on microscopic examination of the urine typically include oval fat bodies and fatty casts, which have a characteristic “Maltese cross” appearance of the fat droplets when observed under polarized light. Further laboratory testing shows hyperlipidemia and low levels of serum albumin, usually in the setting of normal renal function. The differential diagnosis of nephrotic syndrome includes focal and segmental glomerulosclerosis (FSGS), collapsing GN, minimal change disease (MCD), MN, diabetic nephropathy (DN), and disorders associated with plasma cell dyscrasias like amyloidosis (Table 1). MPGN can also cause the nephrotic syndrome but is typically associated with significant hematuria and is classified as a mixed nephrotic-nephritic condition. Some of the secondary causes, especially secondary FSGS, may not present with the nephrotic syndrome per se, although heavy proteinuria is a consistent feature.
Before a discussion of the specific causes of the nephrotic syndrome, general treatment issues for the nephrotic state are reviewed. The length of time that a patient remains nephrotic before he or she achieves disease remission is extremely variable and usually not predictable; thus, these general measures should be initiated early in the course of disease. Aggressive attempts should be made to reduce proteinuria through the use of an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB), which acts to decrease intraglomerular pressure. The dose should be increased until there is no further reduction in proteinuria or the patient develops symptomatic hypotension, hyperkalemia, or more than a small increase in serum creatinine (0.3-0.5 mg/dL). In the absence of side effects from an ACEI, further reductions in proteinuria may occur with the addition of an ARB. Edema is managed with dietary salt restriction and loop diuretics, which also help to limit the hyperkalemia induced by an ACEI or ARB. Occasionally, oral diuretics are not initially effective because of edema of the intestinal wall; in that case, intravenous diuretics may be
necessary until oral agents can be better absorbed. Goal blood pressure should be 125/75 or lower, and if it is not controlled with an ACEI, an ARB, and diuretics, additional agents should be used. The hyperlipidemia associated with the nephrotic syndrome can be effectively managed with statins. The nephrotic syndrome is a prothrombotic state attributable to urinary loss of coagulation inhibitors, and renal vein and deep vein thromboses and pulmonary embolism are not infrequent complications [2]. A previous history of thrombosis and severe hypoalbuminemia (<2.0 g/dL) are risk factors for pulmonary embolism, and such patients should undergo anticoagulation. It should be mentioned that nephrotic patients who have anasarca are at increased risk for infections, such as pneumococcal peritonitis, especially in the pediatric setting [3].

**Minimal change disease**

As the name implies, MCD is characterized by normal renal biopsy findings by light and immunofluorescence microscopy; the only change seen by electron microscopy is diffuse effacement of the podocyte foot processes. The causative agent is not fully understood but likely involves a circulating factor that is somehow injurious to the podocyte and may be linked to T-cell–mediated immunity. Idiopathic MCD is the primary cause of nephrotic syndrome in children, accounting for 90% of cases in children younger than 10 years of age and 50% of cases in older children. It presents with the rapid onset of anasarca accompanied by severe hypoalbuminemia, hyperlipidemia, and proteinuria. MCD is responsible for 15% to 20% of cases of idiopathic adult nephrotic syndrome and may be seen even in the geriatric population. In this classic idiopathic form, MCD is not associated with hypertension or severely diminished renal function. Drug allergy, especially to nonsteroidal anti-inflammatory drugs (NSAIDs), is an important secondary cause of MCD in adults and is often accompanied by interstitial nephritis and acute renal failure [4,5]. MCD may also occur in conjunction with Hodgkin's lymphoma [6].

There are no diagnostic tests for MCD other than renal biopsy. Because most childhood cases of nephrotic syndrome are attributable to MCD, biopsy in children is reserved for atypical cases or those that fail to respond to therapy. In contrast, because only 15% to 20% of cases of adult nephrotic syndrome are attributable to MCD, individuals older than the age of 16 years usually undergo a renal biopsy to make a definitive diagnosis, and thus guide therapy. Analysis of the urine reveals nephrotic amounts of protein and lipiduria in the form of oval fat bodies and fatty casts. Microscopic hematuria may be seen, but RBC casts are absent. A history of NSAID use should be sought in any adult presenting with sudden onset of the nephrotic syndrome, especially if associated with acute renal failure, and even in the absence of the fever and eosinophilia typically seen in classic cases of allergic acute interstitial nephritis.
Steroids are the mainstay of therapy in children and adults, although the time required to achieve complete remission is different. Half of children attain remission within 2 weeks, with nearly all the rest attaining remission within 8 weeks. Remission is characterized as an abrupt decrease in proteinuria to near-normal levels, whereas partial remission is uncommon. More than 90% of adults also achieve complete remission, although it may take several months. More than half of adults and children have one or more relapses. Those that become steroid dependent or relapse frequently are generally treated with an immunosuppressive agent. Cyclophosphamide has traditionally been used in such cases, but cyclosporine and mycophenolate mofetil are gaining favor for maintenance of remission [7]. Potential offending medications should clearly be discontinued.

Focal and segmental glomerulosclerosis

Although MN was once taught to be the most common cause of the nephrotic syndrome in whites and FSGS the leading cause in blacks, recent epidemiologic studies have shown that FSGS is surpassing MN as the most common etiology, even in whites [8]. It is important to note that FSGS, like many of the other glomerular disorders, is not a disease unto itself but rather a pattern of glomerular injury and a final common pathway by which normal glomerular structures are replaced by the accumulation of fibrous scar tissue. Multiple processes, acquired and, as more recently recognized, inherited, lead to podocyte injury, dysfunction, or loss [9], which seem to be the common etiologic factors in all forms of FSGS.

Primary (or idiopathic) focal and segmental glomerulosclerosis

Primary FSGS is typified by rapid onset of anasarca, nephrotic range proteinuria, hypoalbuminemia, and hyperlipidemia. Hypertension is present in 50% to 60% of cases, and more than 25% have some degree of renal insufficiency. The clinical picture in young children is often similar to that of MCD. What distinguishes the two is that 90% of patients who have MCD respond to steroids, whereas primary FSGS is less commonly steroid responsive. There are no serologic markers for FSGS, and diagnosis relies on renal biopsy, although even this is not always definitive. Electron microscopy of the biopsy reveals diffuse effacement or “simplification” of podocyte foot processes; however, in contrast to MCD, there are also areas of sclerosis in the glomerulus. Because of sampling error during the biopsy process, however, these sclerotic glomeruli can be missed in early disease, giving a histologic picture identical to MCD. Indeed, some think that MCD and primary FSGS lie within the same spectrum of disease. Although much work has been done in both diseases to identify a causative circulating factor, primary FSGS and MCD remain unexplained at a pathophysiologic level. Untreated primary FSGS frequently progresses to ESRD.
It is critical to understand that therapies for primary and secondary FSGS are quite different, because immunosuppressive therapy is indicated for the former but not for the latter. For primary disease, initial treatment is typically oral prednisone administered at a daily dosage of 1 mg/kg for 12 to 16 weeks, with serial evaluation of proteinuria and other clinical parameters. If there is no significant decline in proteinuria, cyclosporine is usually added to the regimen [7]. An ongoing National Institutes of Health (NIH)-sponsored trial is comparing the newer agent mycophenolate combined with pulse steroids with cyclosporine for treatment of primary FSGS. Approximately 70% of patients achieve complete or partial remission with these immunosuppressive drugs, although relapse is common, even as the medications are being tapered. The most important prognostic factor in primary FSGS is response to treatment, because continued heavy proteinuria leads to progressive loss of renal function.

Secondary focal and segmental glomerulosclerosis

Secondary FSGS is an entirely separate entity best thought of as damage or loss of functioning glomeruli. A variety of conditions, such as renal agenesis, surgical removal of a kidney, vesicoureteral reflux (VUR), obesity, sickle cell disease, or prior GN, can all lead to secondary FSGS. As a result of the nephron loss seen in these conditions, there is a compensatory response in the remaining glomeruli with hypertrophy and hyperfiltration, which eventually proves to be maladaptive and leads to further nephron loss and sclerosis. Whereas primary FSGS generally presents with florid nephrotic syndrome, secondary FSGS lacks many of these features and typically has a more gradual onset. Although proteinuria can be in the nephrotic range, there is minimal edema and hypoalbuminemia [10].

There are no telling serologic clues, although sickle cell disease could be investigated through the use of hemoglobin electrophoresis in at-risk patients. Identification of associated disorders is aided by history or radiologic imaging. Ultrasound or CT can reveal if a kidney is absent or malformed. A lobulated scarred kidney unilaterally or bilaterally is typical of advanced VUR or other urinary tract malformations.

Because there is no active immunologic insult in secondary FSGS, immunosuppressive therapy is not indicated; instead, treatment is long-term conservative therapy with an ACEI or ARB, blood pressure control, diuretics, and statins, as noted previously in the discussion of general treatment strategy for the nephrotic syndrome. Attempts should be made to correct underlying conditions, such as obesity, and to treat aggravating factors, such as urinary infections and sickle cell crises.

Inherited focal and segmental glomerulosclerosis

Analysis of familial forms of nephrotic syndrome and FSGS has led to the discovery of mutations of specific podocyte proteins, including nephrin
scopic is seen in up to 50% cases, RBC casts are rare. The remainder is identified as a result of subnephrotic levels of proteinuria. Microscopic hematuria is seen in up to 50% of cases, although RBC casts are rare.

Collapsing glomerulopathy

Collapsing glomerulopathy is recognized as a variant of FSGS [15], although some authorities consider it to be a separate disease because of its particularly aggressive features [16]. It presents with massive amounts of proteinuria, usually greater than 10 g/d, and is often characterized by elevated creatinine at diagnosis with rapid progression to ESRD. HIV-associated nephropathy (HIVAN) is the most frequent cause of collapsing glomerulopathy. Many other cases are idiopathic, but collapsing glomerulopathy has also been associated with the use of pamidronate in patients who have myeloma or breast cancer [17], and possibly with other viruses, such as parvovirus B19. HIVAN is dominated by this collapsing picture and also involves microcystic change in the tubules that gives a large echogenic appearance to the kidney on ultrasound and is responsible for the enormous waxy casts seen on urinary sediment (see the article by Rajashekar and colleagues elsewhere in this issue). Edema is often absent or quite mild despite the severe proteinuria, and hypertension is infrequent. Treatment of idiopathic collapsing glomerulopathy has been disappointing, although some recommend a 6-month trial of oral steroids in addition to adjunctive therapy with an ACEI or ARB [18]. Improvement in HIVAN has been reported in patients treated with highly active retroviral therapy (HAART), and the widespread use of HAART was accompanied by a marked decline in the incidence of HIVAN.

Membranous nephropathy

MN is a frequent cause of idiopathic nephrotic syndrome in adults. It is so named because the immune deposits that form beneath the foot processes, likely caused by autoantibodies against a podocyte protein, cause a thickening of the GBM. Most cases of idiopathic MN occur in patients between the ages of 30 and 60 years, with men twice as likely to be affected as women. Eighty percent present with the nephrotic syndrome, with the remainder identified as a result of subnephrotic levels of proteinuria. Microscopic hematuria is seen in up to 50% of cases, although RBC casts are rare.
Hypertension and impaired renal function are uncommon at the onset of disease and are more likely to occur with disease progression. MN is most often idiopathic, but secondary forms can be associated with systemic lupus erythematosus, hepatitis B antigenemia, chronic infections (eg, secondary syphilis, schistosomiasis), or antirheumatic treatments. In idiopathic cases, approximately 33% resolve spontaneously without treatment, whereas up to 30% inexorably progress to ESRD. The remaining patients continue to have proteinuria but with normal or only mildly decreased renal function.

Diagnosis can only be made by renal biopsy, and the results of serologic studies, including complement levels, are all normal in idiopathic MN. Secondary causes of MN may be detected by antinuclear antibodies (ANAs), hepatitis B antigenemia, or the presence of concurrent infection with schistosomiasis or secondary syphilis. There have been associations of MN with malignancy in older individuals, which seems to occur more frequently than chance alone would predict [19,20]. Therefore, patients older than the age of 60 years with a new diagnosis of MN should be screened for cancer of the gastrointestinal tract, prostate, and breast and for lung cancer in smokers.

In view of the relatively high spontaneous remission rate in MN, newly diagnosed patients who have nephrotic syndrome and normal renal function can be managed initially with an ACEI or ARB, diuretics, salt restriction, and statins [21]. If proteinuria is asymptomatic and renal function remains normal, such conservative treatment can be continued. Patients who remain nephrotic after 6 months, or who initially present with (or develop) an elevated serum creatinine level, should be with treated with an immunosuppressive agent. There are several clinically validated protocols, although various combinations of prednisone and cyclophosphamide for 6 to 12 months are typical. Cyclosporine is an alternative agent; however, remission is generally only partial, and relapse is common soon after treatment is terminated [7]. Recent reports of small trials indicate that rituximab, tacrolimus, corticotropin, and mycophenolate might also be effective alternatives, although the data are limited at this time.

**Diabetic nephropathy**

DN, the most common cause of nephrotic syndrome in adults, is fully discussed in the article by Rajasekar and colleagues elsewhere in this issue. It generally follows a predictable course that begins with glomerular hyperfiltration, which then leads to microalbuminuria, and in the absence of therapeutic interventions, such as blood pressure and glycemic control, is followed by frank nephrotic range proteinuria and rapid progression to ESRD [22,23]. It should always be considered in the differential diagnosis of the nephrotic syndrome. Proteinuria may be asymptomatic but is usually accompanied by other features of the nephrotic syndrome. Microscopic hematuria is present in approximately 15% of patients. In the appropriate clinical context (ie, long history of poorly controlled diabetes, with
associated neuropathy and retinopathy) and with the absence of atypical features, a renal biopsy is usually not indicated. Unfortunately, when a diabetic patient presents with nephrotic range proteinuria, the progression to ESRD is usually rapid and inevitable. Conversely, timely intervention with ACEI or ARB therapy has been shown to slow the loss of renal function in type 1 and type 2 diabetes substantially. Optimal control of blood pressure and hyperglycemia is required, as is early referral to a nephrologist.

Monoelonal immunoglobulin deposition diseases

Monoclonal immunoglobulin deposition diseases (MIDDs) that affect the kidneys include multiple myeloma, primary (AL) amyloidosis, and monoclonal gammopathy of unknown significance (MGUS). They are relatively common in the elderly population and may have glomerular involvement leading to the nephrotic syndrome.

AL amyloidosis, the most common form of systemic amyloidosis, results from deposition of monoclonal light chains as insoluble amyloid fibrils in the glomerulus [24]. The bone marrow burden of dysplastic plasma cells is typically low, on the order of 5% to 10%. Approximately 10% to 15% of AL amyloidosis is associated with multiple myeloma, however. The kidney is the organ most commonly involved, but amyloid deposits occur throughout the body, particularly in the heart, causing a restrictive cardiomyopathy; in the liver, leading to hepatomegaly and obstructive cholestasis; and in the peripheral nerves, causing autonomic dysfunction and peripheral neuropathy. The incidence of AL amyloidosis is in the range of 10 cases per million per year, with a median age of diagnosis older than 60 years. It is rare in individuals younger than the age of 40 years. Median survival without treatment is approximately 3 years. Poor prognostic indicators include the number of organs involved at diagnosis, and especially the extent of cardiac involvement. The most common presenting symptoms are fatigue and weight loss. Renal disease is manifested by severe proteinuria (much more so in λ light chain–associated AL amyloidosis), anasarca, and progressive deterioration of renal function. Hypertension is characteristically not seen in this disorder, largely because of associated cardiomyopathy and autonomic dysfunction.

Amyloidosis should be suspected in older nondiabetic individuals who present with severe albuminuria, especially in the presence of other features, such as congestive heart failure, hepatomegaly, or peripheral neuropathy. Macroglossia is another telling clue. Definitive diagnosis relies on the detection of amyloid fibrils by Congo red staining; this can occur on a renal biopsy but may be less invasively performed by aspiration of abdominal fat or a rectal biopsy. Most cases of AL amyloidosis have circulating and urinary free light chains, typically of the λ variety; thus, immunofixation analysis of the serum and urine should be performed. Protein electrophoresis may not be sensitive enough to detect the monoclonal light chain,
because the monoclonal peaks are generally small. Analysis of free light chains is another promising method that is now clinically available. Detection of abnormal amounts or ratios of free light chains in the urine in the presence of renal dysfunction signifies amyloidosis, light chain deposition disease (LCDD), myeloma cast nephropathy, or cryoglobulinemia.

Patients should be referred to a center that specializes in the treatment of amyloidosis. The most effective treatment is myeloablative with melphalan, followed by autologous stem cell replacement to reconstitute the bone marrow [25,26]. Remission occurs in approximately 50% of patients, providing extended survival for patients who have an otherwise rapidly fatal disease. The treatment itself has substantial morbidity and mortality rates, however, and not all patients are candidates because of underlying organ dysfunction, particularly cardiac. As with other proteinuric conditions, edema and proteinuria should be treated with diuretics and an ACEI or ARB; however, hypotension is often an issue in amyloidosis as mentioned previously.

LCDD is another related cause of the nephrotic syndrome that can be associated with MGUS or frank myeloma [27]. Light chains accumulate in the glomerulus as in AL amyloidosis; however, because of the variable properties of the individual monoclonal light chain species, they form Congo red-negative amorphous deposits rather than amyloid fibrils. The deposition and resultant accumulation of extracellular matrix causes nodular glomerulosclerosis similar to that seen in DN. Clinically, patients may present with the nephrotic syndrome or nephrotic range proteinuria. Microscopic hematuria is common, and blood pressure and serum creatinine are usually elevated at presentation. Other organs are often affected, as in amyloidosis. Like amyloidosis, LCDD causes progressive renal failure and has been effectively treated with myeloablative therapy and autologous stem cell replacement. The importance of considering LCDD in a patient who has known or newly diagnosed MGUS is that treatment of the plasma cell dyscrasia is warranted without waiting for frank myeloma to develop [28].

The nephritic syndrome

The features of GN and the acute nephritic syndrome, in contrast to those of the nephrotic syndrome, are consequences of inflammation within the glomerulus. The intensity and tempo of the inflammatory response define the clinical course of the disease. Mild inflammation may yield only subclinical hematuria, as may occur in IgAN, whereas a fulminant small-vessel vasculitis, such as Wegener’s granulomatosis (WG), can cause foci of intense glomerular inflammation and necrosis that are often associated with RPGN (Table 2). Such a spectrum of disease presentation requires the primary care physician to assess the urgency of referral, treatment, or even hospitalization. Details like a decline in urine output, smoky urine, or frank hematuria; the presence or absence of systemic features, such as dyspnea or hemoptysis, arthralgia, or purpura; and the serum creatinine level at presentation and
over the next days to weeks aid in this determination. Early consultation with a nephrologist is recommended if there is any degree of uncertainty, because the management of GN can be a matter of urgency.

When assessing potential causes of the acute nephritic syndrome or GN defined by urinary sediment, a small number of laboratory tests are useful to narrow down the differential diagnosis quickly. Because lupus nephritis is prevalent and has variable presentations, ANA and anti-double-stranded DNA titers should be obtained. Local and systemic immune complex deposition, as occurs in lupus nephritis and many of the other commonly encountered causes of the nephritic syndrome, results in complement activation and consumption of complement factors. Whereas complement levels are normal in nephrotic disorders, complement factors C3 and C4 are variably altered in cases of GN, and the pattern can suggest or rule out the presence of specific disorders. C3 is common to the classic and alternate pathways of complement activation, whereas C4 is limited to the classic (antibody-mediated) pathway. A low C3 value in the presence of a normal C4 value suggests PSGN or the rare dense deposit disease (DDD; MPGN type 2). C3 and C4 values can both be depressed in lupus nephritis (classes III and IV) or GN associated with a chronic infection, such as endocarditis,

Table 2

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<tr>
<th>Clinical syndrome and differential diagnosis</th>
<th>Secondary associations</th>
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<td>Asymptomatic hematuria</td>
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<td>Thin basement membrane disease</td>
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<td>IgA nephropathy</td>
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<td>Postinfectious GN</td>
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<td>SLE nephritis (ISN RPS classes II, III, and IV)</td>
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<td>Mixed nephritic-nephrotic syndrome</td>
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<td>MPGN, type I</td>
<td>Chronic infection, especially HCV; cryoglobulinemia; SLE: non-Hodgkin's lymphoma</td>
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<td>MPGN, type II (dense deposit disease)</td>
<td>C3Nef-associated partial lipodystrophy, factor H deficiency</td>
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<td>Hereditary nephritis (Alport's syndrome)</td>
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<td>Rapidly progressive GN</td>
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<td>Immune complex mediated GN</td>
<td>SLE, IgAN, acute bacterial endocarditis</td>
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<td>Pauci-immune (usually ANCA-positive) GN</td>
<td>Renal limited pauci-immune GN</td>
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<td>Anti-GBM disease</td>
<td>Goodpasture's syndrome</td>
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Abbreviations: C3Nef, C3 nephritic factor; PTU, propylthiouracil; SLE, systemic lupus erythematosus.
hepatitis C-associated MPGN type I, or mixed cryoglobulinemia. Small vessel vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) and anti-GBM disease are characterized by normal levels of complement. The serologic diagnosis of these entities is discussed further in the section on rapidly progressive GN: ANCA and anti-GBM serologies should not be routinely sent in all cases of GN.

_IgA nephropathy_

IgAN is the most common cause of GN worldwide. All age groups may be affected, although it is more common in children and young adults and occurs more often in boys and men. There are also ethnic differences, with blacks uncommonly affected in comparison to Asians and whites. Pathophysiologically, there is deposition of IgA polymers in the mesangium of the kidney, which is thought to be attributable to aberrant O-glycosylation of the IgA1 molecule [29]. IgAN commonly presents with asymptomatic microscopic hematuria and mild (less than 1 g/d) proteinuria, which is often found on routine urinalysis. Another characteristic presentation for IgAN is recurrent episodes of macroscopic hematuria (usually brown in color without blood clots) that may be associated with flank pain and typically coincide with or closely follow an upper respiratory tract infection (URI) [30]. Microscopic hematuria is present between episodes of gross hematuria. Less commonly, IgAN may present with nephrotic range proteinuria or RPGN. It may be associated with rheumatic conditions, such as rheumatoid arthritis or the spondyloarthopathies, or with gastrointestinal disorders, such as celiac disease or chronic liver disease. IgAN is one of the more common renal disorders seen with HIV infection. Henoch-Schönlein purpura (HSP) is a systemic small vessel vasculitis more common in children than in adults that features IgAN, purpuric lesions on the legs and forearms but sparing the trunk, and arthralgia and abdominal pain from intestinal vasculitis.

Children and young adults that present with gross hematuria coincident with an URI are likely to have IgAN. IgAN usually requires a renal biopsy for definitive diagnosis, however. Despite the proposed central pathologic finding of abnormal IgA1 molecules in this disease, there are currently no serologic assays to identify the disease. Total IgA levels may be mildly increased in up to 50% of patients, and complement levels are normal. Finding IgA in a biopsy of a purpuric skin lesion in a patient who has GN is strongly suggestive of HSP.

The range of possible presenting features and variable course of the disease make management of IgAN less than straightforward [31]. Treatment decisions should be based on the presence or absence of poor prognostic indicators, which include hypertension, more than 1 g/d of protein excretion, and impaired renal function at diagnosis, in addition to evidence of advanced tubulointerstitial scarring, glomerulosclerosis, or crescents on renal biopsy. Patients who have asymptomatic hematuria, normal renal function,
and no proteinuria require follow-up but no treatment. Those with low-grade (less than 1 g/d) proteinuria and mild histologic changes should be treated with an ACEI or ARB to maintain blood pressure at or less than 125/75. Addition of high-dose ω-3 fatty acid (fish oil) supplements may be beneficial for those patients who have nephrotic range proteinuria and mildly impaired renal function. In patients who have severe hypertension, nephrotic range proteinuria, rapidly deteriorating renal function, or proliferative and crescentic lesions on biopsy, therapy with immunosuppressive agents (steroids or cytotoxic agents) is indicated. HSP is treated similar to IgAN, except that high-dose steroids are absolutely indicated for those patients who have abdominal crises.

**Glomerulonephritis in systemic lupus erythematosus**

GN attributable to systemic lupus erythematosus (lupus nephritis) is a relatively common cause of renal disease and is extensively discussed in the article by Rajashekar and colleagues elsewhere in this issue. As a common cause of immune complex-mediated GN, it should be strongly considered as a potential cause of urinary abnormalities in a patient of the appropriate demographic group (especially young women of black and Hispanic ethnicity), and it is essential to check for ANAs and anti-double-stranded DNA antibodies. The absence of a positive high-titer ANA value generally excludes glomerular disease attributable to lupus, with the exception of membranous (International Society of Nephrology/Renal Pathology Society [ISN/RPS] class V) lupus nephritis. In this situation, heavy proteinuria may be clinically evident before the detection of ANAs, although these antibodies usually appear later in the course of the disease.

**Poststreptococcal glomerulonephritis**

PSGN is the prototypic example of the acute nephritic syndrome. It typically occurs 2 to 3 weeks after an episode of pharyngitis or skin infection caused by a nephritogenic strain of group A β-hemolytic *Streptococcus*. PSGN usually occurs in children but is also seen in adults and is clinically manifested by gross hematuria, nephrotic or subnephrotic proteinuria, edema, and severe hypertension. Azotemia is common, with oliguria occurring less frequently.

The diagnosis of PSGN is often suggested by the characteristic history. The latent period between the initial streptococcal pharyngitis and hematuria is, on average, 10 days and may be up to 3 weeks after an episode of impetigo or erysipelas. This is in contrast to IgAN, which occurs coincident with or shortly after a viral URI. Hypocomplementemia is almost universally present in PSGN with a low C3 value but normal C4 value (reflecting activation of the alternate pathway), and anti-streptolysin O (ASO) titers are often elevated when the preceding illness is a streptococcal pharyngitis.
When PSGN occurs after a streptococcal skin infection, ASO titers may not increase but antibodies against DNase B or hyaluronidase may be positive. Because the GN is typically self-limited, management is focused on addressing symptomatic issues, such as edema and hypertension. The renal prognosis is favorable in children, although it may take months for complete resolution of the urinary changes. In adults, PSGN can result in persistent azotemia; in such cases, treatment with an ACEI or ARB is indicated for long-term renoprotection.

**Endocarditis-associated glomerulonephritis**

Acute bacterial endocarditis and subacute bacterial endocarditis are other potential etiologies of infection-related immune complex-mediated GN; in the United States, they tend to occur in intravenous drug abusers or in patients who have prosthetic heart valves. With subacute involvement of the right side of the heart, extrarenal symptoms, such as myalgias, arthralgias, and purpura, are less common than with left-sided endocarditis, although renal involvement is more common. Urinary findings include hematuria and subnephrotic proteinuria, and low serum C3 and C4 values (reflecting activation of the classic complement pathway in this case) can be noted along with leukocytosis and an elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Acute endocarditis with *Staphylococcus aureus* can be associated with acute renal failure from diffuse proliferative GN. Treatment is targeted to the underlying infection, with prognosis determined by response to antibiotic (or surgical) therapy. Most renal disease resolves within weeks.

**Membranoproliferative glomerulonephritis**

*Type 1 membranoproliferative glomerulonephritis*

Idiopathic type 1 MPGN is most often seen in adolescents and young adults as a renal-limited disorder presenting with severe proteinuria or nephrotic syndrome and accompanying nephritic features, particularly hematuria and RBC casts. Azotemia and hypertension may be present. The clinical presentation is similar in adults; however, the disease is usually secondary to a chronic or subacute infectious process, systemic autoimmune disorder, or lymphoma. Hepatitis C virus (HCV) is the most common underlying cause of type 1 MPGN in adults [32], and a careful history generally reveals past exposure. There is frequently no overt clinical evidence of liver disease, and the results of liver function studies may be completely normal. Some patients who have HCV-associated MPGN have a systemic autoimmune disease called mixed cryoglobulinemia. This manifests with cutaneous vasculitis, causing purpura and painful skin ulcers, arthralgia, abdominal pain, and systemic symptoms of malaise and fever in addition to the renal manifestations noted previously.
Type I MPGN is also seen in infective endocarditis and other subacute or chronic infections, and it occasionally accompanies non-Hodgkin’s lymphoma. Class IV lupus nephritis may also manifest with type I MPGN-like pathologic features. Similar clinical and pathologic features may occur in patients who have thrombotic microangiopathy, particularly when associated with antiphospholipid antibody (APA) syndrome. Clues to the diagnosis of APA are a history of recurrent venous or arterial thromboses or recurrent spontaneous abortions.

Low levels of complement C3 and C4, consistent with immune complex-induced activation of the classic pathway, are an excellent clue to the presence of type I MPGN in a patient with a mixed nephritic-nephrotic presentation. A renal biopsy should document the histologic features of type I MPGN, such as duplication of the GBM (“tram-tracks”); however, the etiology is established by a combination of clinical and serologic features. Idiopathic type I MPGN is a diagnosis of exclusion. Negative findings for ANAs and anti–double-stranded DNA antibodies exclude lupus nephritis. Positive HCV serology and viral RNA levels establish the diagnosis of HCV-associated MPGN; in patients with systemic symptoms suggestive of cryoglobulinemia, blood should be drawn and transported to the laboratory at 37°C to measure the cryocrit. In the absence of HCV and lupus serology, adults with type I MPGN should be investigated further for evidence of an occult infectious process or non-Hodgkin’s lymphoma.

Idiopathic type I MPGN is frequently refractory to treatment and follows a slowly progressive course to ESRD in 40% to 50% of cases followed for longer than 10 years. Lowering of blood pressure to less than 125/75 with a regimen containing an ACEI or ARB and control of hyperlipidemia are indicated as in other progressive kidney diseases for renal and cardiovascular protection, together with judicious use of loop diuretics for control of edema. Long-term treatment with high-dose alternate-day prednisone has been advocated and adopted by most pediatric nephrologists; however, the outcome is generally disappointing, with substantial side effects in terms of growth retardation, cataract formation, aggravation of hypertension, and glucose intolerance. HCV-associated MPGN generally follows an indolent course; when accompanied by cryoglobulinemia, it may manifest as acute exacerbations and partial remissions. Treatment of HCV with an extended course of pegylated interferon-α and ribavirin has been reported to induce a sustained virologic response in up to 80% of patients with a sensitive viral genotype and has been applied with good effect in some patients who have HCV-associated MPGN and cryoglobulinemia [33,34]. Unfortunately, the use of ribavirin is limited to patients with well-preserved renal function because of severe hemolytic anemia in patients who have renal failure. Such therapy is best administered by a hepatologist in consultation with a nephrologist familiar with this condition. Acute exacerbations are empirically treated with a combination of steroids and immunosuppressives. Plasma exchange is often used in such cases; however, its benefit is not firmly
established. A trial is presently being conducted at the NIH to test the efficacy of the anti-B-cell agent rituximab in patients who have HCV-associated cryoglobulinemia.

Dense deposit disease (type 2 membranoproliferative glomerulonephritis)

DDD is a rare disorder that usually presents with nephrotic syndrome in childhood and adolescence [35]. A low level of C3 (and normal C4 level) is characteristic in DDD and is the result of unregulated activation of the alternate complement pathway. Hypertension is often present, and microscopic hematuria is typical. The condition is usually limited to the kidneys, but it is sometimes accompanied by partial lipodystrophy. Most often, DDD is attributable to C3 nephritic factor, an autoantibody that stabilizes the convertase responsible for activating C3. In rare cases, hereditary deficiency of a complement regulatory protein, especially factor H, produces a similar effect. Most patients progress to ESRD over several years; however, some follow a rapidly progressive course. There is no effective treatment for DDD, and the disease recurs in approximately 50% of cases after renal transplantation.

Rapidly progressive glomerulonephritis

RP GN is a clinical syndrome that deserves special mention because it is a true medical emergency. Virtually all the nephritic glomerular disorders, when severe, can cause RPGN. Those associated with small-vessel vasculitis or autoantibodies against the GBM have a special predilection to cause RPGN. RPGN has traditionally been subdivided into immune complex-mediated, pauci-immune, and anti-GBM disorders based on immunofluorescence microscopy of the glomerulus. IgAN, lupus nephritis, and infection-related GN are examples of immune complex GN and are associated with granular mesangial or glomerular capillary immunoglobulin deposits. Anti-GBM disease (or Goodpasture’s syndrome, when associated with pulmonary hemorrhage) displays an even ribbon-like staining of IgG over the entire GBM. Immune deposits are absent or scant in the “pauci-immune” disorders, also known as ANCA-associated GN. These collective disorders, when associated with RPGN, are often typified on renal biopsy by crescentic lesions, an aggressive inflammatory focus in the glomerulus that often compromises glomerular filtration.

Antineutrophil cytoplasmic antibody-associated glomerulonephritis

ANCA-associated GN is the most common cause of RPGN. It may be limited to the kidneys or associated with systemic vasculitis. The renal presentations are identical. WG and microscopic polyangiitis (MPA) are the most commonly encountered ANCA-associated systemic vasculitides and often present with a clinical picture of RPGN. The Churg-Strauss syndrome
and certain therapeutic agents, such as propylthiouracil, allopurinol, and hydralazine, can also cause ANCA-associated GN. Despite the presence of circulating ANCs and their proposed pathogenetic role, there is no immune complex deposition in the glomeruli. WG and MPA are systemic small-vessel vasculitides that typically affect multiple organ systems and are associated with nonspecific features of inflammation, such as fever, malaise, myalgia, arthralgia, and weight loss, with a peak age of onset in the seventh and eighth decades [36]. WG is characterized by granulomatous inflammation involving upper respiratory tract structures and can be manifested by sinusitis, rhinitis, otitis, or even ocular inflammation. WG and MPA can cause diffuse alveolar hemorrhage with consequent cough, dyspnea, hemoptysis, microcytic anemia, and abnormalities on chest radiographs. Cutaneous vasculitis is evidenced by palpable purpuric lesions, often occurring in crops on the lower extremities. The renal features of ANCA-associated vasculitis are variable and include oliguria, hematuria, and proteinuria in addition to RBC casts. Serum creatinine may or may not be elevated on initial presentation but generally increases rapidly over days to weeks without treatment. The clinical manifestations of these small-vessel vasculitides vary widely according to the disease, sites involved, and activity (versus chronicity) of the disease process. There must be a high index of suspicion for these disorders because of the often nonspecific symptoms.

Approximately 80% of patients who have pauci-immune crescentic GN have a positive test result for ANCs on initial presentation with RPGN. Therefore, the presence of ANCs can obviate the need for a renal biopsy, at least for initial management. Any patient who presents with such findings, especially with evidence of alveolar hemorrhage, must have serum sent for ANCs and anti-GBM. Initially, the serum is screened by a microscopic immunofluorescence assay to look for staining of ethanol-fixed leukocytes in a perinuclear (p-ANCA) or cytoplasmic (c-ANCA) pattern. A positive ANCA screen necessitates determining the specificity of the antibodies, which is performed by ELISA. Antibodies directed against proteinase 3 are usually associated with c-ANCA and with WG, whereas antibodies against myeloperoxidase, generally seen in MPA and renal-limited disease, give a p-ANCA pattern. RBC casts are frequently seen in the urinary sediment in the setting of RPGN. Diffuse pulmonary infiltrates on chest radiographs and a microcytic anemia are suggestive of concurrent alveolar hemorrhage. The major pathologic lesion found on renal biopsy in ANCA-associated vasculitis is crescentic GN, with or without features of necrosis [37]. MPA, perhaps because of the decreased incidence of easily identified upper respiratory symptoms, often presents with more advanced renal lesions, such as interstitial fibrosis or glomerulosclerosis.

Untreated, most patients who have ANCA-associated GN rapidly develop ESRD, and those with systemic vasculitis have a high 1-year mortality rate. Treatment is divided into two stages: induction of remission and
maintenance therapy. Induction of remission typically involves aggressive therapy in an attempt to control ongoing inflammation and prevent further organ damage. Cyclophosphamide and pulsed intravenous methylprednisolone followed by daily oral steroids is standard therapy. Addition of plasma exchange may benefit those patients who are dialysis dependent on presentation [38]. Although evidence supporting the use of plasma exchange in the setting of diffuse alveolar hemorrhage is not as strong as it is in the case of Goodpasture’s syndrome, a small study has suggested that it may be beneficial [39]. Once remission has been induced with 3 to 6 months of cyclophosphamide, azathioprine has been effectively used for maintenance therapy [40]. If relapses occur, they are treated similar to the initial presentation. Several trials are investigating newer agents, such as rituximab or mycophenolate mofetil, for induction and maintenance therapy.

Anti-glomerular basement membrane disease

Anti-GBM GN is an uncommon cause of RPGN but requires prompt diagnosis and treatment because of its association with pulmonary hemorrhage (Goodpasture’s syndrome) and its propensity to cause irreversible renal failure if treatment is delayed. The disorder stems from the presence of autoantibodies that are directed against an antigen in the α3 chain of type IV collagen in glomerular and alveolar basement membranes [41]. Risk factors for pulmonary hemorrhage are cigarette smoking and long-term exposure to volatile hydrocarbons. The diagnosis is made on the basis of renal biopsy by finding the characteristic linear immunofluorescence staining pattern and by detecting circulating anti-GBM. Clues to the diagnosis include RPGN in association with cough, hemoptysis, dyspnea, rales, or pulmonary infiltrates and microcytic anemia from alveolar hemorrhage. Urinary findings on presentation include hematuria, RBC casts, and nonnephrotic proteinuria. Most patients have impaired renal function on presentation, and those who are oliguric and have serum creatinine values greater than 6 mg/dL almost never respond to treatment. Immediate treatment with pulse methylprednisolone, cyclophosphamide, and plasmapheresis often prevents and even reverses renal deterioration in those patients with less severely impaired renal function. Plasmapheresis and immunosuppression are mandatory life-saving measures for those with pulmonary hemorrhage.

Hereditary nephritis

Alport’s syndrome is the result of an inherited structural defect of the GBM caused by mutations in any of the three chains that make up the type IV collagen molecule in the GBM (α3, α4, and α5 encoded by COL4A3, COL4A4, and COL4A5, respectively) [41]. More than 80% of cases are X-linked and are attributable to mutations of COL4A5. Male patients are invariably affected with progressive kidney disease. Female
carriers of the X-linked mutation have microscopic hematuria and generally have normal renal function. Less commonly, Alport’s syndrome can also exhibit an autosomal recessive inheritance pattern in which both genders are equally affected because of homozygous or compound mutations in COL4A3 or COL4A4. Clinically, microscopic hematuria is present in affected male patients soon after birth, which progresses to severe proteinuria, hypertension, and ESRD in early adulthood. Sensorineural deafness is present in approximately 50% of cases, and some patients have ocular abnormalities.

The diagnosis of Alport’s syndrome can generally be made from a history of kidney disease, and possibly deafness in male family members, in a young male patient presenting with hematuria once imaging of the kidneys and bladder has ruled out other nonglomerular causes of hematuria. Renal biopsy is diagnostic and reveals characteristic fragmentation of the GBM on electron microscopy. Genetic testing can be performed in specialized laboratories when the diagnosis is in doubt.

Treatment is supportive, using an ACEI or ARB and aggressive control of blood pressure to slow renal deterioration. Renal transplantation is curative; however, a small proportion of patients who have Alport’s syndrome develop anti-GBM disease as a result of antibodies that form against the type IV collagen chains not previously seen by their immune system.

Thin basement membrane disease

Like female carriers of the X-linked mutation of COL4A5, heterozygous carriers of COL3A4 and COL4A4 mutations have persistent microscopic hematuria, generally with normal renal function and little or no proteinuria. On renal biopsy, such individuals are found to have unusually thin GBMs—hence, the name. This is a common condition that rivals IgAN in frequency as a cause of asymptomatic hematuria.

Tubulointerstitial disease

Tubulointerstitial disease represents a broad group of acute and chronic disorders that affect the tubular and interstitial components of the kidney. Renal tubules are important for reclamation of electrolytes, nutrients, and small proteins and for the maintenance of acid-base balance and control of total body sodium and water balance. Tubular dysfunction may be manifested by aminoaciduria or mild proteinuria (defects in resorption), increased urinary frequency and nocturia (concentration defect), or a renal tubular acidosis (RTA; defective urinary acidification). The renal interstitium, in addition to providing a structural matrix that supports the nephron, peritubular capillary network, and dendritic antigen-processing cells, contains cells that produce erythropoietin, and thus regulate erythrocyte mass in the body. Interstitial damage results in a relative deficiency of
erythropoietin, which is responsible for the anemia seen with chronic tubulo-interstitial renal disease.

Acute tubulo-interstitial disorders can be caused by toxic or ischemic tubular injury, as in acute tubular necrosis, or by inflammation, as in allergic interstitial nephritis or pyelonephritis. Only a subset of acute tubulo-interstitial disorders is discussed here, because other disorders are covered in the article by Khalil and colleagues elsewhere in this issue. Chronic tubulo-interstitial disease (or chronic interstitial nephritis [CIN]) is the end product of sustained renal disease from inherited, toxic, mechanical, obstructive, infectious, or other etiologies (Box 1) [42]. CIN can also result from a prolonged episode of acute interstitial nephritis that fails to resolve adequately or as a consequence of the heavy proteinuria and tubular damage that accompanies long-standing glomerular disease. In spite of these disparate etiologies, the clinical manifestations of CIN are similar. Because of damage to the tubular compartment and inability to concentrate the urine adequately, patients may note frequent urination and nocturia. Serum creatinine tends to be elevated, with a slow but appreciable rate of further decline in the absence of treatment. There is often mild proteinuria that is "nonselective" in nature and attributable to decreased tubular reabsorption of filtered proteins. Findings on renal ultrasonography may reveal changes of "medical renal disease," such as increased echogenicity of the renal parenchyma with loss of corticomedullary differentiation and prominence of the renal pyramids.

Drugs and toxins

The most frequent type of injury to the tubulo-interstitial component of the kidney involves ingested agents, which are usually therapeutic agents or environmental toxins. Interstitial nephritis is not an infrequent complication of the polypharmacy used in modern medicine, and an ever-growing list of medications can cause acute interstitial nephritis or CIN. Acute interstitial nephritis has been covered in the article by Khalil and colleagues elsewhere in this issue and is not covered further here. Suffice it to say that the inadvertent prolonged administration of an offending agent may eventually lead to chronic changes, such as tubular atrophy and interstitial fibrosis. The damage to the kidney need not always be acute, because there are several agents, such as chemotherapeutic and immunosuppressive agents, antiretrovirals, analgesics, and even proton pump inhibitors, that may cause insidious and progressive tubulo-interstitial damage with prolonged use [43-45]. The first and foremost treatment for these disorders, unless otherwise specifically mentioned here, is to identify and discontinue the offending agent whenever possible. In many cases, the tubulo-interstitial damage is largely irreversible, and treatment should be focused on blood pressure control, management of anemia with erythropoietin-stimulating agents if necessary, and consultation with a nephrologist.
Box 1. Causes of chronic interstitial nephritis

Drugs and toxins
- Analgesics
- Lithium
- Immunosuppressive and chemotherapeutic agents, antiretrovirals
- Heavy metals (eg, lead, cadmium)
- Chinese herbal therapies (eg, aristolochic acid)
- Phosphate-containing purgatives

Metabolic disturbances
- Hypercalcemia or nephrocalcinosis
- Hyperoxaluria
- Hyperuricemia
- Cystinosis
- Prolonged hypokalemia

Obstructive or mechanical
- Vesicoureteral reflux
- Bladder outlet obstruction
- Obstructive nephrolithiasis

Cystic disorders
- Nephronophthisis
- Adult medullary cystic disease
- Polycystic kidney disease

Immune mediated
- Systemic lupus erythematosus
- Sjögren's syndrome
- Tubulointerstitial nephritis with uveitis
- Sarcoidosis

Hematologic
- Multiple myeloma or light chain cast nephropathy
- Sickle cell disease
- Lymphoma (rare)

Prolonged injury
- Aging
- Hypertensive nephrosclerosis
- Chronic glomerular damage
- Ischemia

Lithium, the monovalent ion used in its most common application to treat manic-depressive illness, has several renal effects, the most pronounced of which is nephrogenic diabetes insipidus leading to polyuria. There is controversy regarding the association of lithium with CIN [46]. Biopsy findings in patients who had been treated with lithium for extended
periods showed tubular atrophy and dilatation, cyst formation, interstitial fibrosis, and glomerulosclerosis. When compared with patients who had other psychiatric disorders not treated with lithium, similar changes were seen on biopsy, however, calling into question whether this was a specific effect of the lithium therapy [47,48]. Whether or not lithium is the responsible agent in these cases, it is worthwhile asking a patient with evidence of CIN about a history of long-term lithium use; if the patient remains on lithium and has no other clear etiology for the renal disease, it may be beneficial to discontinue this medication if another effective alternative can be found.

Analgesic nephropathy is a form of chronic tubulointerstitial damage resulting from the long-term use of analgesics, commonly mixtures containing phenacetin, aspirin, and caffeine that were available as over-the-counter preparations in Europe and Australia [49]. In its classic form, analgesic nephropathy is characterized by renal insufficiency, papillary necrosis attributable to the presumed concentration of the drug to toxic levels in the inner medulla, and papillary calcifications on CT scan. Current analgesic preparations used in the United States in moderate chronic doses do not seem to cause this constellation of findings known as analgesic nephropathy [50]. This is not to say that analgesics, particularly nonselective NSAIDs and the related newer cyclooxygenase (COX)-2 selective inhibitors, cannot lead to renal dysfunction, and it is always worth inquiring about use of NSAIDs in a patient who has acute or chronic renal disease. In addition to the hemodynamic effects of this class of medications, they have a propensity to lead to acute interstitial nephritis or even MCD.

Acute phosphate nephropathy is another recently described iatrogenic form of tubulointerstitial disease about which the primary care physician should be aware [51,52]. It occurs after the administration of oral phosphate preparations given as bowel purgatives before colonoscopy and tends to cause renal failure in older women with low estimated glomerular filtration rate (eGFR) levels despite apparently normal or near-normal serum creatinine levels. Although most of the ingested phosphate is excreted in the stool, a significant amount is absorbed and excreted in the urine. In the setting of volume depletion, as can occur with catharsis and limited oral intake before the procedure, the filtered phosphate load can precipitate and cause tubular obstruction. Increased recognition of this disorder has led to improved product labeling warning against use of these products in individuals with impaired renal function; however, it is still being found as an insidious cause of renal dysfunction. The renal impairment is acute but may not be recognized until weeks or months later when that patient presents with uremic symptoms or has his or her renal function tested. The urinary sediment is usually bland, without proteinuria, and the creatinine may improve but usually does not return to baseline. Phosphate-containing cathartics should be avoided in all patients with even mildly reduced renal function (eGFR <60 mL/min), and in patients who have an unexplained increase
in creatinine, one should enquire about bowel preparations given for colonoscopy within the past several months.

Nontraditional (alternative or herbal) medications can also lead to tubulointerstitial disease, and it is critical to ask about these agents when conducting the medication history. In Chinese herbal nephropathy, which can be seen in women taking Chinese herbal preparations as part of a weight loss regimen, one of the offending agents has been identified as aristolochic acid. This chemical, after prolonged exposure, produces a hypocellular, fibrotic, interstitial lesion in the kidney and, importantly, has also been associated with bladder and ureteral cancer. Urine sediment is bland, with rare leukocytes and only mild proteinuria. Of note, there is recent evidence that Balkan nephropathy, an endemic CIN found primarily in towns along the tributaries of the Danube River, may also be linked to aristolochic acid as a result of contamination of local grain preparations [53,54].

Heavy metals, such as lead or cadmium, can lead to a CIN with prolonged exposure, although such exposures are no longer frequent because of the known health risks for lead and consequent removal of lead from most commercial products and fuels. Nonetheless, occupational exposure is possible in workers involved in the manufacture or destruction of batteries, removal of lead paint, or manufacture of alloys and electrical equipment (cadmium). In addition, ingestion of moonshine whiskey distilled in lead-tainted containers has been one of the more frequent exposures to lead. Early signs of chronic lead intoxication are attributable to proximal tubule dysfunction, particularly hyperuricemia as a result of diminished urate secretion. The triad of “saturnine gout,” hypertension, and renal insufficiency should prompt a practitioner to ask specifically about lead exposure. Unfortunately, evaluating lead burden is not as straightforward as ordering a blood test; the preferred methods involve measuring urinary lead after infusion of a chelating agent or by radiographic fluoroscopy of bone. Several recent studies have shown an association between chronic low-level lead exposure and decreased renal function [55], although either of these two factors may have been the primary event. In those patients who have CIN of unclear origin and an elevated total body lead burden, repeated treatments of lead chelation therapy have been shown to slow the decline in GFR [56].

Reflux nephropathy

Reflux nephropathy (formerly called chronic pyelonephritis) is the consequence of VUR or other urologic anomalies in early childhood. Affected adults are frequently asymptomatic, and the condition may be detected for the first time during pregnancy or during routine examination. It is characterized clinically by variable renal insufficiency, hypertension, mild to moderate proteinuria, and unremarkable urine sediment. VUR stems from abnormal retrograde urine flow from the bladder into the ureters and kidney because of an incompetent ureterovesical valve (primary reflux) or from any
condition that leads to an abnormally high pressure in the bladder (secondary reflux) [57]. High-pressure reflux, coupled with recurrent urinary infections in early childhood, leads to patchy interstitial scarring, tubular atrophy, and secondary FSGS, partially attributable to nephron dropout. When both kidneys are affected, the disease often progresses inexorably over several years to ESRD, despite the absence of ongoing urinary infections or reflux. A single affected kidney may go undetected, except for the presence of hypertension.

Clues to the diagnosis include a history of recurrent urinary infections, enuresis, and hypertension in childhood [58]. Renal ultrasound in adults characteristically shows asymmetric small kidneys with irregular outlines, thinned cortices, and regions of compensatory hypertrophy. Surgical intervention is not indicated in adolescents or adults; however, aggressive control of blood pressure with an ACEI or ARB and other agents is effective in reducing proteinuria and may significantly forestall further deterioration of renal function.

**Sickle cell nephropathy**

Advanced renal disease or ESRD may develop in as many as 20% of patients who have sickle cell disease. Much of the disease process is attributable to the chronic sickling that occurs in the inner medulla, a site suited to such a phenomenon because of its relative hypoxia and high osmolality. Microvascular occlusion leads not only to nephron loss and secondary FSGS but to chronic damage to the medullary circulation, resulting in severe changes in the tubulointerstitial compartment. The first clinical manifestations are defects in urinary concentration that typically present in childhood and are irreversible after the age of 15 years. Tubular damage is also manifested by incomplete distal RTA and relative hyperkalemia, although often only in the setting of a superimposed decrease in GFR. Chronic sickling, anemia, and degeneration of the medullary blood supply all contribute to papillary necrosis. This is usually a progressive asymptomatic process but can present acutely with gross hematuria, renal colic, or passage of sloughed tissue. Compared with an age- and race-matched population, there is typically a much lower incidence of hypertension in individuals with sickle cell nephropathy [59]. When present, however, hypertension, in addition to heavy proteinuria, hematuria, and severe anemia, is a prognostic indicator for progression to ESRD.

The diagnosis of sickle cell nephropathy is made in a patient who has sickle cell disease or a related hemoglobinopathy, with evidence of proteinuria, hematuria, concentrating defects, and renal insufficiency. The glomerular hyperfiltration that occurs early in the disease may initially cause relatively low serum creatinine values, and thus obscure the degree of ongoing renal damage [60]. Mild proteinuria and microscopic hematuria are common. With advancing disease, which is primarily age dependent,
serum creatinine increases to greater than the normal range and renal ultrasound may show increased echogenicity of the renal pyramids. Clubbing of the calyces on intravenous pyelography was once a useful sign of papillary necrosis; however, it is becoming increasingly difficult to find centers that continue to perform this test. Contrast-enhanced CT urography may be an acceptable alternative.

There is no known treatment to reverse the microvascular changes once they have irreversibly occurred in early adolescence, and, unfortunately, the evidence for specific treatment for sickle cell nephropathy is lacking. Avoidance of sickle crises as far as possible is paramount for preventing such changes. Once they have occurred, treatment with an ACEI has been shown to reduce proteinuria in several studies [61, 62], and it is anticipated that this may slow the rate of renal deterioration as with other proteinuric diseases, although this has not been formally studied. It is recommended that all proteinuric patients who have sickle cell disease and can safely tolerate an ACEI be maintained on as high a dose as possible to limit proteinuria.

Cystic disorders

Inherited cystic disorders of the kidney arise in the tubulointerstitial compartment, and most progress to ESRD at rates inherent to the given disease mutation. Autosomal dominant polycystic kidney disease, although generally not considered a tubulointerstitial disease, is one of the most common inherited human diseases, occurring in approximately 1 in 500 live births, and is a leading cause of ESRD. Its appearance on renal ultrasound in an affected adult is diagnostic and reveals innumerable bilateral renal cysts causing massive kidney enlargement. A spectrum of much less common autosomal recessive inherited diseases known collectively as nephronophthisis causes CIN in childhood that almost universally leads to ESRD by early adolescence. Cysts are typically not seen on ultrasound, although the kidney has an echogenic texture. An even rarer autosomal dominant disorder known as medullary cystic kidney disease leads to the same process in adults, as manifested by elevated serum creatinine, hypertension, gout, anemia, and progression to ESRD. This rare disease needs to be distinguished from the much more common disorder of medullary sponge kidney (MSK) that seems to be a developmental malformation leading to relatively small medullary cysts. Although it commonly causes microscopic hematuria and a propensity to form kidney stones, MSK is relatively benign unless complications occur from urinary tract infections or nephrolithiasis.

Multiple myeloma

Multiple myeloma is generally a disease of the elderly, and the possibility of this malignancy should not be ignored in an elderly patient with new-onset renal failure [63]. Whereas filtered monoclonal light chains, also known as Bence-Jones proteins, can cause subtle tubular toxicity manifested
by aminoaciduria, glycosuria, phosphaturia, and RTA (Fanconi’s syndrome), the most serious outcome is the development of an often irreversible form of tubulointerstitial disease called light chain cast nephropathy (LCCN) or “myeloma kidney.” It is associated with increased tumor burden and light chain excretion and is the result of the accretion of filtered light chains and Tamm-Horsfall protein in the distal tubule, often presenting acutely in the setting of extracellular volume depletion, infection, or hypercalcemia [64]. Casts, in addition to obstructing the tubular flow in affected nephrons, tend to incite a giant cell or foreign body reaction and can lead to tubular rupture, resulting in interstitial fibrosis. LCCN should also be considered as a possible diagnosis in patients who have known MGUS or “smoldering myeloma” and develop worsening renal function, because this may be an indication of progression to frank myeloma [65,66].

The possibility of myeloma or a related disorder should be suspected in any elderly patient presenting with unexplained renal failure. Clues to the diagnosis include anemia, bone pain, and hypercalcemia. It is important to emphasize that urinary dipsticks are insensitive to excreted light chains. Therefore, a negative urinalysis result for protein simply excludes albuminuria. Conversely, a positive test result for protein in a spot or a 24-hour collection and a negative dipstick result are highly suggestive of Bence-Jones proteinuria. Serum and urine should both be sent for protein electrophoresis and for immunofixation for the detection and identification of a potential monoclonal band. A sensitive method is now clinically available to detect urine and serum free light chains.

The initial goal of treatment of cast nephropathy is to correct factors, such as volume depletion or hypercalcemia, that may have precipitated the event. Definitive treatment of the underlying malignancy is ultimately required, however, and often involves a chemotherapeutic regimen followed by autologous stem cell replacement. Plasmapheresis was once considered a viable strategy to reduce circulating light chains in those patients presenting with acute renal failure from cast nephropathy. A recent randomized study, however, has shown no benefit of this adjunctive therapy to the standard treatment, and it is no longer recommended [67].

Immune-mediated tubulointerstitial nephritis

There are several immune-mediated tubulointerstitial conditions that should be identified by the primary care physician, because renal function can often be improved with corticosteroids. Sjögren’s syndrome is a systemic autoimmune disorder that primarily targets the exocrine glands, especially the lacrimal and salivary glands, and thus results in symptoms, such as dry eyes and mouth, that constitute the “sicca syndrome.” Several nonexocrine organs, such as the kidney, skin, lung, gastrointestinal, and nervous systems, can also be affected by focal or diffuse lymphocytic infiltration. Tubulointerstitial nephritis is the most common renal manifestation of
Sjögren's syndrome and can be associated with distal RTA, nephrogenic diabetes insipidus, and moderate renal failure. Serologic features may include hypergammaglobulinemia and positive anti-Ro (SS-A) and anti-La (SS-B) antibodies. Treatment of the interstitial nephritis with prednisone is usually effective, but maintenance therapy with an immunosuppressive agent may be required to prevent relapse.

A related disorder that is defined by its effects on the eyes and renal interstitium is termed *tubulointerstitial nephritis with uveitis (TINU)*. It is not frequently encountered but seems to affect children, whose renal disease is typically self-limited, in addition to adults, whose disease may follow a relapsing course and be more steroid dependent. Clinical extrarenal features include fever, anorexia, abdominal pain, arthralgia, and eye pain and

### Table 3

<table>
<thead>
<tr>
<th>Element of encounter</th>
<th>Symptom, sign, or historical clue</th>
<th>Potential diagnoses</th>
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<tbody>
<tr>
<td>HPI</td>
<td>Red or smoky urine, especially after a URI</td>
<td>IgAN, PSGN</td>
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<td>Foaming of urine (bubbles) with increase in weight or leg swelling</td>
<td>Any disorder causing the nephrotic syndrome</td>
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<td>Hemoptysis</td>
<td>Pulmonary-renal syndrome, such as WG, MPA, or Goodpasture's syndrome</td>
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<td>Past history</td>
<td>Bedwetting into late childhood or adolescence</td>
<td>Reflux nephropathy</td>
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<td>Childhood urinary infections</td>
<td>MN, MPGN, MCD, amyloidosis, LCDD, cast nephropathy</td>
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<td>Malignancy</td>
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<td>Occupational history</td>
<td>Exposure to heavy metals (eg, batteries, alloys)</td>
<td>Goodpasture's syndrome</td>
</tr>
<tr>
<td></td>
<td>Exposure to volatile hydrocarbons</td>
<td>Lead nephropathy</td>
</tr>
<tr>
<td></td>
<td>History of moonshine ingestion</td>
<td>MPGN (with HCV), MN (with HBV), collapsing GN (with HIV)</td>
</tr>
<tr>
<td></td>
<td>Intravenous drug use</td>
<td></td>
</tr>
<tr>
<td>Social history</td>
<td>Country of origin</td>
<td>Balkan nephropathy</td>
</tr>
<tr>
<td>Medication</td>
<td>Prescribed</td>
<td>CIN or AIN</td>
</tr>
<tr>
<td></td>
<td>Over-the-counter (NSAIDs)</td>
<td>Analgesic nephropathy, MCD</td>
</tr>
<tr>
<td></td>
<td>Alternative/herbal</td>
<td>Chinese herbal nephropathy</td>
</tr>
<tr>
<td></td>
<td>Recent oral phosphate bowel preparation</td>
<td>Phosphate nephropathy</td>
</tr>
<tr>
<td>Family history</td>
<td>ESRD and deafness in male patients, microscopic hematuria</td>
<td>Hereditary nephritis (Alport’s syndrome)</td>
</tr>
<tr>
<td></td>
<td>Early-onset proteinuria, ESRD</td>
<td>Hereditary FSGS</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Purpura lesions</td>
<td>HSP, cryoglobulinemia, vasculitis</td>
</tr>
<tr>
<td></td>
<td>Eye pain or dryness</td>
<td>TINU, Sjögren's syndrome</td>
</tr>
<tr>
<td></td>
<td>Proliferative retinopathy on funduscopy</td>
<td>Diabetic nephropathy</td>
</tr>
</tbody>
</table>

*Abbreviations.* AIN, acute interstitial nephritis; HBV, hepatitis B virus; HPI, history of present illness.
redness with blurred vision and photophobia. The uveitis can occur before, concurrent with, or, more commonly, after the initiation of the interstitial nephritis. Typical of many tubulointerstitial diseases, there is mild proteinuria, elevated creatinine, and anemia. In TINU, the ESR is usually elevated as well. The renal and ocular manifestations generally respond well to prednisone but may require maintenance therapy with an agent like azathioprine or mycophenolate to prevent recurrences. Systemic lupus erythematosus, in similar fashion, can rarely cause a tubulointerstitial disorder in the absence of glomerular disease and should be suspected in a patient with clinical and laboratory features of interstitial nephritis, other systemic features suggestive of lupus, and positive lupus serology. Finally, immune-mediated tubulointerstitial nephritis may be idiopathic in nature, indicated only by positive staining of the tubular basement membrane for immunoglobulin.

Included in the differential diagnosis with Sjögren’s syndrome, TINU, and lupus interstitial nephritis is sarcoidosis [68,69]. Sarcoidosis is a disease of the reticuloendothelial system and is marked by granulomatous inflammation in affected organs, such as the lung and hilar lymph nodes, kidney, and skin. The granulomatous renal interstitial process is usually not clinically significant but may cause renal insufficiency. Hypercalcemia attributable to extrarenal production of 1,25-OH-vitamin D can lead to nephrocalcinosis or vasoconstriction-mediated renal failure, however. Renal dysfunction is an indication for treatment with corticosteroids in patients who have sarcoidosis.

Summary

The spectrum of glomerular and tubulointerstitial diseases covered in this article is by no means exhaustive but is rather intended to give the primary care physician (PCP) a general overview of some of the more common or illustrative renal disorders encountered in clinical practice. Elements of the past history, including detailed family, medication, and social histories, in addition to recent symptoms and physical examination findings (Table 3) are as much a part of the diagnostic workup as are urinary and blood tests. Division into nephrotic, nephritic, and tubulointerstitial processes based on all these findings is useful for narrowing the differential diagnosis and deciding on further testing. Critically, the rapidity of renal deterioration must be assessed, when appropriate, with serial measurements of serum blood urea nitrogen (BUN) and creatinine, and cases of RPGN and pulmonary-renal syndrome should receive immediate attention. The PCP is a welcome and much needed partner to the nephrologist in the initial diagnosis and long-term management of patients who have renal disease.

References


