

## Glomerulonephritis

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Early diagnosis of glomerulonephritis (GN) in the adolescent is important in initiating appropriate treatment and controlling chronic glomerular injury that may eventually lead to end-stage renal disease (ESRD). The spectrum of GN in adolescents is more similar to that seen in young and middle-aged adults than to that observed in prepubertal children. In this article, the authors discuss the clinical features associated with GN and the diagnostic evaluation required to determine the specific type of GN. With the exception of hereditary nephritis (Alport's disease), virtually all types of GN are immunologically mediated with glomerular deposition of immunoglobulins and complement proteins. The inflammatory events leading to GN may be triggered by a number of factors. Most commonly, immune complexes deposit in the glomeruli or are formed in situ with the antigen as a structural component of the glomerulus. The immune complexes then initiate the production of proinflammatory mediators, such as complement proteins and cytokines. Subsequently, the processes of sclerosis within the glomeruli and fibrosis in the tubulointerstitial cells lead to chronic or even irreversible renal injury [1]. Less commonly, these processes occur without involvement of immune complexes—so-called “pauci-immune GN.”

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## Presentation and diagnostic evaluation

The hallmark of GN is inflammation within the glomeruli that typically manifests as hematuria and proteinuria (Box 1). Renal function may be normal or reduced, depending on the severity of the acute condition or the presence of chronic glomerular injury. Patients often have a normal physical examination and blood pressure. However, sometimes they may present with any combination of oliguria, hypertension, and edema. Some types of GN have other associated findings, such as a vasculitic rash, arthritis, or even pulmonary hemorrhage.

The hematuria can be macroscopic (visible) or microscopic. Microscopic examination of the urinary sediment characteristically shows dysmorphic red blood cells (RBCs) and often RBC casts. Dysmorphic RBCs can be detected with routine microscopy but are best detected by phase contrast microscopy. Greater than 30% of RBCs exhibiting dysmorphic features, such as doughnut shape and blebs, is a highly sensitive indicator of glomerular disease [2,3]. The degree of proteinuria may vary from normal ( $< 4 \text{ mg/m}^2/\text{h}$ ) to nephrotic range ( $> 40 \text{ mg/m}^2/\text{h}$ ). A random urine protein-to-creatinine ratio provides information as acceptable as that of a timed (usually 24-hour) collection, with normal being less than 0.2 and nephrotic range being greater than 2.0.

Except in the typical case of poststreptococcal acute glomerulonephritis (PSAGN) with normal or transiently decreased renal function, renal biopsy is required to determine the precise diagnosis and severity of the glomerular involvement. Either consultation or referral to a nephrologist is necessary when the primary care physician suspects GN other than mild or typical cases of PSAGN. Certain blood tests will provide clues to the diagnosis and, in some instances, become markers for response to treatment. Baseline blood tests include complete blood count, creatinine, complement (C3 and C4), and streptococcal serology (antistreptolysin O and Streptozyme). Among all types of GN (Box 2), the ones associated with significant depression of serum C3 concentration are PSAGN, membranoproliferative glomerulonephritis (MPGN), systemic lupus erythematosus (SLE), nephritis of chronic bacteremia (ventriculo-atrial shunt and

### Box 1. Presenting signs and symptoms of glomerulonephritis

#### *Hematuria*

- Macroscopic (visible) or microscopic
- Dysmorphic RBCs and RBC casts

#### *Proteinuria*

#### *Hypertension*

#### *Edema*

#### *Renal insufficiency*

- Transient
- Progressive

**Box 2. Differential diagnosis of glomerulonephritis***Poststreptococcal acute glomerulonephritis**IgA nephropathies*

IgA nephropathy (Berger's disease)

Henoch-Schönlein

*Membranoproliferative glomerulonephritis*

Idiopathic—types I, II, III

Secondary—nephritis of chronic bacteremia, hepatitis B and C, alpha-1 antitrypsin deficiency, etc.

*C1q nephropathy**Membranous nephropathy—typically presents with nephrotic syndrome**Alport syndrome**Antiglomerular basement membrane disease**Antineutrophil cytoplasmic autoantibody (ANCA) glomerulonephritis**Pauci-immune ANCA-negative glomerulonephritis**Systemic lupus erythematosus*

subacute bacterial endocarditis), and hepatitis B GN. Significant C4 activation manifested by depression of serum C4 concentration is typically seen in SLE and sometimes in type I MPGN. The presence of systemic manifestations warrants a more extensive battery of diagnostic tests based on the diseases in the differential diagnosis (discussed later in this article for each specific disease).

**Principles of therapy**

Current treatment of GN has two main objectives: control of inflammation and inhibition of fibrosis. Anti-inflammatory agents include intravenous or oral corticosteroids, cyclophosphamide, azathioprine, mycophenolate mofetil, and fish-oil supplements containing omega-3 fatty acids. Drugs that reduce proteinuria will inhibit tubular injury and fibrosis [1]. These may include angiotensin-converting enzyme inhibitors (ACEi), angiotensin 2 receptor blockers (ARB), and perhaps statins and anti-oxidants. Specific treatments will be discussed in each section.

**Acute glomerulonephritis**

An adolescent with GN may present with signs and symptoms that require immediate intervention. One scenario is a presentation of renal insufficiency that

worsens daily, as evidence accumulates that the patient does not have PSAGN. Such patients may have rapidly progressive GN (RPGN) that is characterized pathologically by crescents forming from the cells of Bowman's capsule. If the process progresses, the crescent will irreversibly destroy the glomerular tuft. ESRD may occur within weeks of the onset of this process. This process is a true emergency that requires prompt referral to a nephrologist. Treatment with high-dose intravenous methylprednisolone and, in some cases, plasmapheresis may halt the process [4–7]. Another scenario is the occurrence of hypertensive encephalopathy or pulmonary edema at the onset of PSAGN. Adolescents who present with hypertension should be admitted to control the blood pressure and prevent these complications.

### *Rapidly progressive glomerulonephritis*

RPGN may be diagnosed in the adolescent who presents with macroscopic hematuria and is found to have an elevated serum creatinine that continues to rise on a daily basis. Nonspecific symptoms such as fatigue and lethargy are common. Often the macroscopic hematuria persists until well after the initiation of treatment with intravenous methylprednisolone. Typically, more than 50% of the glomeruli should be affected with crescents for a case to be classified as RPGN [8]. All of the immunologically mediated types of GN may present as RPGN, but the types most frequently associated with it are antiglomerular basement membrane (anti-GBM) disease, antineutrophil cytoplasmic autoantibodies (ANCA) GN, and Henoch-Schönlein purpura nephritis (HSPN). PSAGN may also have crescent formation and in some cases will fit the definition of RPGN. The rarity of RPGN in children and adolescents is illustrated by a pediatric series that found crescents in 56 of 372 biopsy specimens, with only two meeting criteria for classification as RPGN [9]. Often pediatric nephrologists will treat patients with fewer than 50% of glomeruli affected with crescents as if they had RPGN. Despite aggressive therapy, the outcome is often progression to ESRD. Early diagnosis and aggressive treatment are the most important factors in preservation of renal function.

### *Poststreptococcal acute glomerulonephritis*

Early descriptions of PSAGN were based on the description of epidemics or clusters of cases usually related to pyoderma, with many cases being asymptomatic [10–12]. The peak age at occurrence was 4 to 5 years; few cases were diagnosed in adolescents. In the latest pediatric series from Memphis, only 11% were age 13 or older (S. Roy, personal communication, 2004). At the present time, cases tend to occur more sporadically, with more due to pharyngitis than to pyoderma, and the incidence in both the United States and other countries is declining [13–15].

The diagnosis of PSAGN is based on clinical features, depression of serum C3 concentrations, and the presence of streptococcal antibodies or enzymes in-

dicative of a recent infection with group A  $\beta$ -hemolytic streptococcus. At the time of clinical presentation, the throat culture is often negative. The anti-streptolysin O titer is significantly elevated in 50% to 80% of pharyngitis-associated cases. Antihyaluronidase and antideoxyribonuclease-B titers are elevated in pyoderma-associated cases [11]. Ninety percent of patients have decreased serum C3 concentration acutely [16], with the level returning to normal within 4 to 8 weeks [17,18]. Renal biopsy is rarely required in patients with PSAGN. However, a renal biopsy is indicated in atypical situations, such as prolonged decrease in C3, recurrence of gross hematuria, progressive increase in proteinuria, and progressive deterioration in renal function.

The clinical presentation of PSAGN is quite variable. Mild cases may have microscopic hematuria with no other symptoms, whereas severe cases can present with acute renal failure or hypertension, often accompanied by pulmonary edema [19]. Infection with a nephritogenic strain of group A  $\beta$ -hemolytic streptococcus occurs over a week before the clinical onset of GN. The latent period is 1 to 2 weeks after pharyngitis and 3 to 6 weeks after onset of pyoderma. The typical presentation is hematuria, mild edema, and hypertension. Macroscopic hematuria occurs in over half of patients and may last for 1 to 2 weeks [20]. In addition to dysmorphic RBCs and RBC casts, the urine sediment often has significant pyuria, with white blood cells seen within casts. Although proteinuria is usually found, it is not generally in the nephrotic range; less than 5% of patients with PSAGN have the nephrotic syndrome. Transient oliguria occurs in half of the patients, but renal failure requiring dialysis is unusual. Edema and hypertension are related to sodium retention and increased intravascular volume and generally respond to salt restriction and diuretic therapy. Hypertension usually resolves after several weeks. However, some patients may present with hypertensive encephalopathy manifested by some combination of headache, nausea, blurring of vision, seizures, and coma. Mild anemia due to hemodilution and leucocytosis is common, and the sedimentation rate is usually increased. The mainstay of treatment is still supportive. A low-salt diet is advised, but if significant edema and hypertension are present, a loop diuretic such as furosemide should be added.

Only certain subtypes of the group A  $\beta$ -hemolytic streptococci are associated with GN. Pharyngitis-associated types are 1, 3, 4, 12, 25, and 49; pyoderma-associated types are 2, 49, 55, 57, and 60 [21]. Pharyngitis-associated PSAGN usually occurs in winter and early spring, whereas pyogenic-related PSAGN often happens in late summer [20].

The typical histologic features are endocapillary proliferation with neutrophil infiltration. The glomeruli appear larger than normal, with capillary lumens that often are narrowed. Immunofluorescent stains show granular deposits of immune complex along the capillary wall and in the mesangium. These deposits are typically composed of IgG, C3, and properdin, with occasional IgM and IgA. Electron microscopy shows large electron-dense "humps" in a subepithelial location [22]. The humps and immune deposits disappear after resolution of the acute phase of PSAGN [23]. It is still not clear whether the inflammation is caused by circulating immune complexes, complexes formed in situ, or both. The antigen or antigens

that trigger the nephritogenic response and activate the alternative complement pathway are most likely related to specific nephritogenic M proteins [24].

With the rare exception of severe crescentic PSAGN, which potentially may progress to ESRD, the outcome of PSAGN is excellent. The clinical signs usually resolve within several weeks, followed by cessation of proteinuria and hematuria. Microscopic hematuria may persist for several months, but the urinalysis is usually normal by 6 to 12 months. The occurrence of a second new case of PSAGN in the same child is well documented [25].

### **Chronic or persistent glomerulonephritis**

Most types of GN will enter a chronic or persistent phase. Often such patients are at risk for continued glomerular injury that potentially could result in ESRD. Commonly, patients with GN that began in childhood or adolescence do not reach ESRD until adulthood. Progression to ESRD in adolescents with chronic GN may be delayed or even avoided with attention to the principles of renal protection [26]. This attention involves aggressive control of hypertension and treatment of proteinuria for both normotensive and hypertensive patients with an ACEi or an ARB. These agents are effective in reducing proteinuria in virtually all forms of chronic GN. Many adolescents and young adults exhibit poor compliance with regard to taking their medications. The primary care physician plays an important role in monitoring control of hypertension, encouraging compliance with medications, and stressing the importance of regular follow-up by the nephrologist. In addition, the physician should be aware of ACEi fetopathy as a major risk for pregnant adolescents so that the drug may be stopped immediately if the patient becomes pregnant. ACEi and ARB therapy should be used cautiously in adolescents at risk for dehydration, particularly in the football player involved in summer practice who has an increased risk for development of prerenal azotemia.

#### *IgA nephropathy*

IgA nephropathy (IgAN) is the most commonly diagnosed type of glomerulonephritis in the adolescent. Sixty-two percent of 47 patients at the authors' institution were age 13 or older at the time of biopsy [27]. In 1969 Jean Berger [28] reported the finding of deposition of IgA in the mesangium of the glomerulus in children and adults who experienced an episode of macroscopic hematuria during an episode of pharyngitis. This classic presentation of macroscopic hematuria at the time of a respiratory infection is the event that usually results in the referral of the adolescent to a nephrologist who performs the biopsy necessary for diagnosis. At the authors' institution, they recommend a biopsy when the urine protein-creatinine ratio is more than 0.5. They sometimes

perform a biopsy with a lower degree of proteinuria when the child has recurrent macroscopic hematuria or when there is high parental anxiety and the urine sediment is consistent with GN (dysmorphic RBCs and RBC casts). IgAN differs from PSAGN in that the patient may be febrile at the time the hematuria begins, is normotensive or only mildly hypertensive, usually has normal renal function, and almost always has a normal or increased serum C3 concentration. However, in Japan, only one third of patients with IgAN present with macroscopic hematuria; the others have asymptomatic microscopic hematuria or proteinuria [29]. Some individuals with this presentation will have one or more episodes of macroscopic hematuria after diagnosis [29].

Although severe hypertension is unusual early in the course of pediatric IgAN, according to norms based on age, gender, and height, about 20% of pediatric patients with IgAN are hypertensive at the time of diagnosis [27]. A mild and transient reduction in renal function may occur either at presentation or during an episode of macroscopic hematuria [30,31]. However, in the United States, adolescents do not present with ESRD or chronic renal insufficiency (CRI) as frequently as adults. In the authors' recent series, 2 of 29 adolescents presented with ESRD and one with mild CRI [27], as compared with over 40% of United States adult patients who had CRI at diagnosis [32,33].

The diagnosis of IgAN is based on the demonstration on renal biopsy of IgA as the dominant or codominant immunoglobulin in a predominantly mesangial deposition and on the absence of clinical evidence for any systemic disease, such as HSP or SLE [30]. The immune deposits may also contain IgG or IgM and usually contain C3 and the alternative complement pathway protein, properdin. Evidence for classic complement pathway involvement with deposition of C1q or C4 appears in fewer than 10% of patients [34].

No serologic test is specific for IgAN. Serum C3 and C4 levels are usually normal, and serum IgA level may be elevated in patients with the condition [35].

The clinical course and eventual outcome of IgAN are quite variable [29,31]. Many adolescents have recurrent episodes of macroscopic hematuria during viral respiratory illnesses. These episodes may subside after several years. Long-term follow-up of patients diagnosed with IgAN in childhood and adolescence indicates that between 25% and 50% will enter a remission phase in which the renal function and urinalysis are normal [27,29,36]. In contrast, life-table analysis of data from over 100 pediatric patients followed in Lexington, Kentucky and Memphis predicted that 15% would progress to ESRD 10 years from onset and 30% after 20 years [31].

Patients should be followed particularly closely if they have prognostic markers associated with progression to ESRD. These markers include severe biopsy findings such as sclerotic lesions within the glomeruli, a urine protein-to-creatinine ratio persistently greater than 1.0, and hypertension [29,31,32]. African American children and adolescents were previously thought to have worse outcomes than white children [31,37], but since 1990 the authors have diagnosed more African Americans and find no difference in progression to ESRD based on race [27].

Currently, treatment of IgAN in adolescents is not guided by results of well-designed randomized control trials (RCTs) that employ appropriate outcome measures [38]. The first choice for treatment of hypertension is an ACEi. Adolescents with a urine protein-to-creatinine ratio greater than 1.0 after 3 months of ACEi therapy may benefit from additional therapy. Several regimens of daily, alternate-day, and even intravenous steroids have been used to treat children and adults with IgAN. This treatment is problematic, because adolescents have a low tolerance for the side effects of Cushingoid facies, weight gain, and exacerbation of acne. Fish oil supplements (FOS) have been widely used in adults with IgAN and appear to slow the progression to ESRD in both patients with normal renal function and CRI [39]. The North American IgAN Study Group [40] examined FOS versus alternate-day prednisone versus placebo in patients under age 40 with the primary endpoint of decline in kidney function. This study found no significant difference with regard to decline in renal function among the alternate-day prednisone, FOS, and placebo groups [41]. However, proteinuria declined significantly after 2 years of treatment for both the prednisone and FOS groups as compared with the placebo group.

Mycophenolate mofetil (MMF) suppresses antibody formation by B cells through impairment of de novo purine synthesis [42]. Case series suggested that MMF may reduce proteinuria in a variety of glomerular diseases, including IgAN [43,44]. The North American IgAN Study Group recently began a multicenter RCT designed to test the hypothesis that treatment with MMF improves proteinuria in patients with IgAN who were pretreated and continued to be treated with ACEi and FOS, as compared with a placebo control group of patients receiving comparable doses of ACEi and FOS without MMF [45].

Although the pathogenetic mechanisms involved in the development and clinical expression of IgAN have yet to be fully elucidated, there appears to be a primary event involving aberrantly glycosylated IgA1 molecules (deficient in galactose in *O*-linked glycans of the hinge regions). These deposit are found in the glomeruli [46,47] and in circulating immune complexes [48] of patients with IgAN.

Most patients with IgAN do not have a familial history of kidney disease. However, familial occurrences of IgAN have been described in Kentucky [49,50] and in northern Italy [51]. Numerous pedigrees with first-, second-, and third-degree relatives having IgAN or HSPN have also been reported [52]. Studies in the pedigrees from Italy and Kentucky showed that half of them had linkage between probable and biopsy-proven cases and a locus on chromosome 6 [53]. This finding provides hope that further investigation will find a gene or genes associated with IgAN.

Deposits of IgA frequently recur in the allograft soon after transplant into a patient with IgAN. Clinically important recurrence of IgAN is unusual within several years of transplant. However, there is a significant late risk of graft loss, often in the second decade after transplant [54]. Transplantation is still recommended for adolescents with ESRD due to IgAN. However, care should be taken to exclude mild or subclinical IgAN in potential living donors.



*Henoch-Schönlein purpura nephritis*

HSP is a vasculitic disease with typical petechial and purpuric lesions that occur predominantly on the lower extremities and buttocks. Other symptoms commonly seen at presentation are abdominal pain and arthritis or arthralgia, particularly in the knees and ankles. Often the urinalysis is normal at presentation, with microscopic hematuria and proteinuria developing within the subsequent 3 months [36]. Adolescents with a normal urinalysis at diagnosis should have a urinalysis performed at weekly intervals for 4 weeks and again at months 2 and 3 from onset. The development of microscopic hematuria or proteinuria warrants referral to a nephrologist.

The peak age for development of HSP is early childhood (age 4–6 years), with onset in adolescence and adulthood being less common. Many children with HSP never develop clinically apparent GN. Early experience suggested that presentation in late childhood and adolescence was related to the severity of GN at presentation [55], but subsequent reports found no correlation between age at presentation and outcome [56,57].

HSPN and IgAN share common pathogenetic factors. The renal biopsy findings are indistinguishable, with both conditions having prominent mesangial deposition of IgA [58]. However, HSPN is more likely than IgAN to have capillary loop immune deposits and significant crescentic involvement. After simultaneous adenovirus infections in previously healthy identical twins, one had the clinical phenotype of HSP and the other had only macroscopic hematuria, but both had mesangial IgA deposits [59]. As mentioned previously, IgAN and HSPN sometimes occur in closely related individuals [52]. HSPN has developed in children previously proved or suspected to have IgAN based on episodes of isolated macroscopic hematuria [60]. Some children being followed for HSPN will experience one or more episodes of macroscopic hematuria at the time of an upper respiratory illness in the absence of rash, joint, or abdominal symptoms [61]. The aberrantly glycosylated IgA1 molecules found in IgAN are also present in patients with HSPN [46].

Virtually all data on treatment of HSPN derive from case series [38]. Crescentic or RPGN is usually treated with high-dose methylprednisolone, often with the addition of other immunosuppressive medications such as cyclophosphamide. In many instances HSPN will resolve over time. However, some patients will have persistence of microscopic hematuria and proteinuria. Treatment in such cases should be similar to that of IgAN, with ACEi or ARB and consideration of other agents, such as FOS or alternate-day prednisone.

*Membranoproliferative glomerulonephritis*

MPGN, also known as mesangiocapillary GN, was first described in 1965 when West et al [62] made the association between persistent hypocomplementemia (low C3 concentration) and light microscopic features of severe mesangial proliferation with thickening of the capillary walls. Because the hypo-

complementemia occurs in only 75% of patients with MPGN, normal serum levels of complement proteins cannot exclude the diagnosis. Based upon glomerular morphology, MPGN can be divided into three types that may represent distinct disorders [63].

MPGN is an infrequently occurring form of GN; in most parts of the world its incidence appears to be declining. However, the peak age for onset of the disease is in the adolescent years. The three most common clinical presentations of MPGN are asymptomatic proteinuria with microscopic hematuria, acute nephritic onset, and the nephrotic syndrome [63–65]. Patients detected in the earliest stages of MPGN are most likely to present with asymptomatic proteinuria and hematuria. An acute nephritic onset may mimic PSAGN, but MPGN should be suspected in patients whose serum C3 concentration does not return to normal within 6 weeks of onset. Adolescents with macroscopic hematuria, hypertension, and the nephrotic syndrome are more likely to have MPGN than PSAGN and should have a renal biopsy at presentation. MPGN is the likely diagnosis for an adolescent with new-onset nephrotic syndrome, a low serum C3, and no evidence of SLE. Nephrotic syndrome at presentation is a marker of poor prognosis [64,65]. Most adolescents with MPGN are hypertensive at presentation, but severe hypertension is unusual.

Type I MPGN is characterized by granular immune complex deposition in the mesangium capillary loops with interposition of the mesangium between the endothelium and the basement membrane; it resembles a duplication of the membrane. The immune deposits seen on electron microscopy are in a sub-endothelial location and usually can be shown to contain IgG, IgM, C1q, C4, and C3 by immunofluorescent staining [66]. The serum C4 concentration may be mildly depressed, but usually not to the extent seen in active SLE. These findings suggest that, in MPGN, immune complexes activate the classic complement pathway.

Type II MPGN is characterized by activation of the alternative complement pathway by C3 nephritic factor (C3Nef), an autoantibody to the C3 convertase (C3b, Bb) [67,68]. The presence of C3Nef leads to continuous consumption of C3 that appears to precede the development of GN. Other conditions associated with the presence of C3Nef, such as partial lipodystrophy, place an affected individual at risk for developing type II MPGN [69]. Electron microscopy shows electron-dense deposits within the glomerular basement membrane; some investigators believe that these represent an alteration of the basement membrane rather than true immune deposits [70]. Immunofluorescent studies show that these basement membranes stain for C3, with or without IgG or IgM staining. Typically, serum levels of C3 are markedly depressed, with levels of C4 and C5 remaining normal [63].

Type III MPGN is characterized by electron-dense deposits that are within and on both sides of the basement membrane (subendothelial and subepithelial). A C3Nef that converts C3 more slowly and activates the terminal complement components has been found in patients with type III MPGN [71]. Serum C3 levels are typically decreased, with C4 level normal. Type III MPGN has been

linked to chromosome 1q31–32 in a four-generation Irish pedigree containing eight affected individuals [72].

Secondary MPGN has occurred in association with such conditions as nephritis of chronic bacteremia, hepatitis B, hepatitis C, and alpha-1 antitrypsin deficiency [73]. In such instances, treatment should be directed, if possible, toward the primary disease.

The outcome is not good for all three types of MPGN, with perhaps 50% of patients reaching ESRD within 10 years of diagnosis. Furthermore, few treatment data from RCTs are available. Uncontrolled experience at Cincinnati Children's Hospital has been used to advocate long-term alternate-day prednisone for treatment of all three types of MPGN [74]. Data from the International Study of Kidney Diseases in Childhood trial of alternate-day prednisone compared with placebo showed significantly better survival for steroid-treated patients with types I and III MPGN, but not type II [75]. These studies were performed long before the routine administration of ACEi or ARB for control of hypertension and treatment of proteinuria. Currently it is difficult, if not impossible, to provide strong evidence-based recommendations for treatment of adolescents with MPGN [76]. However, ACEi or ARB for all types and a course of alternate-day prednisone, particularly for patients with type I MPGN, appear prudent. MPGN, particularly types I and II, often recurs after a renal transplant and may lead to loss of the allograft [77,78]. Newer immunosuppressive agents such as MMF may assume a role in the treatment of MPGN [43], but the apparent decline in the incidence of MPGN makes it unlikely that RCTs will be organized in the near future.

### *C1q nephropathy*

Jennette and Hippe [79] described C1q nephropathy in 1985 as a distinct pathologic entity in which patients with steroid-resistant nephrotic syndrome had mesangial deposits where C1q was the dominant or codominant reactant. Electron-dense deposits that appear similar to those seen in IgAN are also found in the mesangium. No clinical or pathologic evidence of MPGN, membranous nephropathy, or SLE is seen. At the authors' center, only 57% of the 21 cases had nephrotic syndrome at presentation [80]. The majority (62%) of their patients were adolescents, with 57% being African American and 57% male. Nephrotic-range proteinuria in the absence of the nephrotic syndrome was found in another 29%. The remaining 14% had only proteinuria or hematuria at presentation. Patients with C1q nephropathy often progress to ESRD, particularly when the nephrotic syndrome persists. Treatment with corticosteroids and other immunosuppressant agents such as cyclosporine A has been attempted.

### *Membranous nephropathy*

The majority of pediatric patients with idiopathic membranous nephropathy present with nephrotic syndrome. The Southwest Pediatric Nephrology Study

Group found that only 15% of 54 patients were not nephrotic at presentation [81]. Presumably, some of these nonnephrotic patients had microscopic hematuria. Hence, membranous GN should be considered in the differential diagnosis of GN in the adolescent.

### *Alport syndrome*

Alport syndrome is a hereditary defect of glomerular basement membranes that results in hematuria and may progress to ESRD [82]. Diagnosis is often made after examination of the urinalysis in a child from a family with multiple cases of hereditary nephritis. Thus, most adolescents with the condition are now diagnosed early. Children may initially present with heavy microscopic hematuria (large blood on dipstick), followed by the development of proteinuria. Adolescents with Alport syndrome may have persistent macroscopic hematuria or even episodic occurrences, as seen in IgAN, at the time of intercurrent infection. Many, but not all, individuals with Alport's syndrome also have sensorineural deafness and ocular defects. The hearing loss is bilateral and often first detected during adolescence. Conical protrusion on the anterior aspect of the lens (anterior lenticonus) is the most common manifestation of the eye defect. Cataracts may develop after a minor traumatic event.

About 80% of patients are from kindreds with an X-linked dominant pattern of inheritance, whereas others have autosomal recessive or autosomal dominant patterns [82]. In the X-linked pedigrees, usually the males have more severe disease than the females. Affected males usually progress to ESRD as adults, but progression sometimes occurs during adolescence. Because of X-chromosome inactivation, many females will never have more than microscopic hematuria with or without mild proteinuria. However, some females do have more significant clinical disease and may even progress to ESRD.

Renal biopsy is often nondiagnostic in the young child. At a later stage of the disease, light microscopic examination of the kidney tissue may show mesangial enlargement, glomerulosclerosis, tubulo-interstitial fibrosis, and prominent interstitial foam cells. The diagnostic pathologic lesion is the electron microscopic demonstration of irregular thinned and thickened areas of the basement membrane, with splitting and splintering. However, only the thinning of the basement membrane may be seen at early stages, and some patients with typical clinical Alport's syndrome have only basement-membrane thinning, even at advanced stages [82].

The underlying defect in Alport's syndrome is in type IV collagen [83]. Unique mutations are found in different families with Alport's and may partially explain the observed heterogeneity in presentation and progression. The X-linked form of Alport's syndrome has the mutation in the COL4A5 gene. Families with the autosomal recessive form of Alport's syndrome have mutations in COL4A3 or COL4A4 on chromosome two [84].

Progression to ESRD in patients with Alport's syndrome is difficult if not impossible to prevent [82]. Proteinuria may be reduced and renal function

stabilized by treatment with either cyclosporine A [85] or ACEi [86]. Patients with Alport's syndrome who progress to ESRD are usually good candidates for renal transplant, although there is a small risk of developing anti-GBM GN in the allograft [87].

### *Antiglomerular basement membrane disease*

Anti-GBM (Goodpasture's) disease usually presents as RPGN; 60% of cases have pulmonary hemorrhage [88]. Although anti-GBM disease is very rare, the ability to diagnose and aggressively treat the condition may prevent fatal complications. The incidence of anti-GBM disease in Europe was 0.5 cases per 1 million persons per year [88]. Only one adolescent with anti-GBM disease has been diagnosed at the authors' center in the past 20 years.

Anti-GBM disease may be first diagnosed by a renal biopsy that shows linear deposition of IgG along the glomerular capillary loop. Specific anti-GBM antibodies are found in the serum but do not always correlate with disease activity. These antibodies react against an epitope in the NC-1 domain of the alpha-3 chain of type IV collagen [89]. Some patients may have a negative serology, and the diagnosis is made by biopsy alone.

When anti-GBM disease is diagnosed, treatment is begun with intravenous corticosteroids and plasma exchange, followed by oral corticosteroids and cyclophosphamide. The goal of treatment is removal of anti-GBM antibodies and suppression of antibody formation. If the disease is diagnosed early, patients may be able to maintain normal renal function. Patients with more advanced disease may receive a renal transplant after anti-GBM antibodies become negative [90].

### *Antineutrophil cytoplasmic autoantibody glomerulonephritis*

ANCA GN was first described in 1982 in adults with necrotizing GN [91]. ANCA represents a family of autoantibodies against constituents in the neutrophil cytoplasm [92]. The primary antigens for these autoantibodies are proteinase 3 (anti-PR3) and myeloperoxidase (anti-MPO). ANCA GN is characterized by a vasculitis affecting renal arterioles and glomerular capillaries. The vasculitis may be limited to the kidney or include other organ systems, particularly the skin and lungs.

Adolescents may present with various symptoms, such as malaise, sinusitis, myalgia, arthralgia, and rash [93,94]. The rash may mimic the palpable purpura of HSP [95] or be more extensive, with ecchymoses and ulcerations. The systemic vasculitis may also manifest as abdominal pain with intestinal bleeding and peripheral neuropathy.

In a recent pediatric series of 31 Japanese children with ANCA GN, almost half were over age 13 and most were female [93]. The morbidity of pediatric ANCA-GN is high, particularly if the patient has renal insufficiency at diagnosis [94]. In the Japanese report, almost 50% had ESRD or CRI with a mean follow-up of 42 months. No evidence-based guidelines are available for treatment of

children with ANCA GN. Treatment in children with or without other systemic involvement usually consists of intravenous methylprednisone, followed by oral prednisone and additional immunosuppression with cyclophosphamide or azathioprine [94]. Prolonged maintenance treatment with these agents is indicated until long after remission has been achieved with negative ANCA.

### *Pauci-immune glomerulonephritis*

Before the development of a classification system for ANCA-associated GN [92], most cases of ANCA GN were classified as pauci-immune GN or idiopathic crescentic GN. Some adolescents with crescentic GN will have negative or sparse glomerular deposits of immunoglobulins or complement components, as well as negative anti-PR3 and anti-MPO antibodies. As in ANCA GN, serum C3 concentration is normal. The approach to treatment of such patients is similar to that of ANCA GN, but without the benefit of a serologic marker to assess response to treatment. Thus, treatment must be guided by improvement in proteinuria and systemic markers of inflammation such as erythrocyte sedimentation rate and C reactive protein.

### *Systemic lupus erythematosus*

SLE is an important cause of GN in the adolescent, with females affected much more frequently than males. Discussion of the diagnosis and clinical course of SLE in the adolescent is beyond the scope of this review. SLE will occasionally present in the adolescent as GN without other clinical SLE features, such as malar rash and arthritis. Marked depression of serum C4 and C3 concentrations in a patient with GN is highly suggestive of SLE, because extremely low levels of C4 are unusual for other types of GN. Renal biopsy is recommended for patients with SLE who have an abnormal urinalysis and significant urinary protein excretion. This measure makes it possible to determine the renal histologic class that is used to guide the initial treatment.

The 2003 classification of lupus nephritis by the International Society of Nephrology and Renal Pathology Society is based on the original World Health Organization system. This system uses the following major headings: Class I—minimal mesangial lupus nephritis, Class II—mesangial proliferative lupus nephritis, Class III—focal lupus nephritis, Class IV—diffuse lupus nephritis, Class V—membranous lupus nephritis, and Class VI—advanced sclerosis lupus nephritis [96]. GN is the major cause of long-term morbidity in SLE and, if not controlled, may lead to ESRD. Prognostic indicators for progression to ESRD include severity of the renal histologic involvement and black race [97–99].

Oral corticosteroids and ACEi may be sufficient therapy for mild GN (Classes I and II). For many patients with Class III and IV histology, treatment protocols involve such immunosuppressive agents as intravenous cyclophosphamide or oral MMF [100–103]. Clinicians caring for adolescents with SLE GN

should be aware of the potential complications of these immunosuppressive agents, such as bone marrow depression and opportunistic infections.

## Summary

GN in the adolescent requires prompt diagnosis. When even mild degrees of renal insufficiency are documented, immediate referral to a nephrologist is necessary to ensure that serious conditions, such as RPGN, are correctly diagnosed and aggressively managed. In an adolescent with macroscopic hematuria, the demonstration of dysmorphic RBCs, RBC casts, and proteinuria indicates that the bleeding is of glomerular origin. Physicians caring for adolescents with chronic GN should have a basic understanding of the specific disorders. They may be involved in blood pressure monitoring and should be aware of the potential side effects of the antihypertensive and immunosuppressive medications used in patients with GN.

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