CHAPTER

# 46 Acute Infectious Glomerulonephritis Including Poststreptococcal and Other Bacterial Infection–Related Glomerulonephritis

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Acute glomerulonephritis is characterized by the sudden appearance of hematuria, proteinuria, and red blood cell (RBC) casts. The differential diagnosis of this syndrome is listed in Table 46.1. The initial diagnostic approach includes clinical evaluation and serologic determinations, which can be classified as those diseases associated with a low versus a normal serum complement level. Histologic evaluation is very useful in confirming the diagnosis and defining the extent of inflammation and fibrosis. This chapter considers glomerulonephritis associated with bacterial infections. Glomerular diseases associated with other organisms are covered in subsequent chapters. Acute poststreptococcal glomerulonephritis (APSGN) is the prototype; however, the incidence has declined in industrialized countries over the last 50 years.[1] Furthermore, because other bacterial, viral, and parasitic organisms can be associated with acute glomerulonephritis, the term "acute postinfectious glomerulonephritis" (APIGN) is more appropriate.[2] The disease spectrum is also changing, involving more adults and fewer children.[3] The prevalence has also increased in diabetics, intravenous drug abusers, and alcoholics.[4]

The initial discussion focuses on APSGN, followed by consideration of other bacterial infections, with particular emphasis of APIGN associated with staphylococci. APSGN is distinguished from the other causes of acute glomerulonephritis by its characteristic serologic, histologic, and chronologic features. A link between streptococci and acute glomerulonephritis can be traced to epidemics of scarlet fever in the 18th century.[5] During the earlier part of the 20th century, it was recognized that infection with $\beta$-hemolytic streptococci could lead to glomerulonephritis.[5–8] Since this discovery, the clinical presentation and histologic features of the disease have been carefully documented, and considerable progress has been made in identifying the pathogenic mechanisms involved.

## ACUTE POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

### Epidemiology and Incidence

APSGN is most prevalent in developing countries,[9] and it may occur sporadically or in epidemic form. Although the sporadic form is more common, analysis of epidemics has been particularly revealing.[10–25] It affects children more than adults, with peak age from 2 to 6 years (Table 46.2). Approximately 5% of cases are found among children younger than 2 years, with a slightly greater incidence (5%–10%) in adults older than 40. Spread between family members is common, and nephritogenic streptococci have been isolated from household pets.[26] Males have overt nephritis more commonly, and females tend to have more subclinical disease.[15,27] Cases of subclinical nephritis outnumber those of overt nephritis (4:1 to 10:1).[2,28] In temperate zones, APSGN occurs more commonly in winter months, and typically after pharyngitis; whereas in the tropics, skin infections during the summer are the initiating event.[29] Cyclical outbreaks of epidemic forms have been observed, although the reason for these cycles has not been fully explained.[21,30,31]

APSGN follows infection with only certain groups of streptococci, termed "nephritogenic." Group A streptococci are responsible for the majority of cases, and certain types predominate.[5,32,33] Nephritogenic group A streptococci have been characterized serologically by their cell wall proteins, M and T.[5,34–40] The risk of nephritis following infection with nephritogenic strains depends on the location of infection. For example, with type-49 streptococci, the risk of nephritis is five times greater with skin infections than with pharyngitis.

Nephritis following pyoderma with types 47, 55, 57, and 60 is also common.[5,15] The identification of nephritogenic strains suggests that there are factors unique to these

## 46.1 Major Causes of Acute Nephritis

| Low Serum Complement Level[a] | Normal Serum Complement Level |
|---|---|
| **Systemic Diseases** | **Systemic Diseases** |
| Systemic lupus erythematosus (focal ~75%, diffuse ~90%)[a] | Polyarteritis nodosa |
| | Wegener granulomatosis |
| Cryoglobulinemia (~85%) | Hypersensitivity vasculitis |
| Subacute bacterial endocarditis (~90%) | Henoch-Schönlein purpura |
| | Goodpasture syndrome |
| "Shunt" nephritis (~90%) | Visceral abscess |
| **Renal Diseases** | **Renal Diseases** |
| Acute poststreptococcal glomerulonephritis (~90%) | IgG-IgA nephropathy |
| | Idiopathic rapidly progressive glomerulonephritis |
| Membranoproliferative glomerulonephritis | Anti-glomerular basement membrane disease |
| Type I (~50%–80%)[b] | Pauci-immune[c] (no immune deposits) |
| Type II (~80%–90%) | Immune-deposit disease |

Normal serum complement levels indicate that production of complement components is keeping up with consumption; it does not exclude participation of complement in the inflammatory process. Repeat measurements useful (2 to 3 × 1 week apart). Consistently normal serum levels are useful in narrowing the diagnostic possibilities.

[a]Percentages indicate the approximate frequencies of depressed C3 or hemolytic complement levels during the course of disease.

[b]Most common pathologic findings associated with hepatitis C infection.

[c]Pauci-immune indicates lack of significant glomerular deposition of immunoglobulin by direct immunofluorescence. Many patients have circulating ANCA.

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strains that are pathogenically relevant (see later). However, host factors also play a role, as only approximately 10% of patients infected with nephritogenic strains develop overt disease. ASPGN has been reported following renal transplantation, although these patients are at no greater risk for the disease.[41]

### Pathology (Table 46.3, Fig. 46.1)

Typically there is diffuse glomerulonephritis, with variable severity.[41,44,56,60–62] On light microscopy, there is cellular infiltration and glomerular cellular proliferation.[63] The predominant cell types depend on the timing of the biopsy. Within the first 2 weeks of disease, neutrophils, eosinophils, lymphocytes, and monocytes are present in the capillary lumen and in the mesangium, and endothelial and mesangial cell proliferation is prominent.[5,35,42] CD4 T cells usually exceed CD8 cells early on, whereas later CD8 cells predominate. Periglomerular accumulation of T cells may also be observed.[45] Occlusion of capillary lumen is not unusual, and mesangial expansion is typical.[44] Intracapillary fibrin thrombi and deposits and/or necrosis are observed in some cases. This pattern characterizes the so-called "exudative phase." During this period, intermittent thickening of capillary walls, corresponding to large subepithelial immune deposits, or "humps," are often observed (i.e., by trichrome staining). Focal capsular adhesions or segmental crescents are relatively common. Abundant crescent formation is unusual, but has been seen in more severe situations.[5,46] Over 4 to 6 weeks, polymorphonuclear neutrophils (PMNs) are no longer present, and hypercellularity with mononuclear cells (mesangial cells and/or infiltrating monocytes) predominates. During this latter phase, capillary lumens are usually patent. Glomerular hypercellularity usually slowly resolves, although mesangial hypercellularity may persist for months. Extraglomerular abnormalities are usually not as prominent

## 46.2 General Characteristics Of APSGN

Age: Children > adults (5% <2 years; 5% to 10% >40 years)
Sex: Male > Female
Clinical manifestations: subclinical 4–10 × > overt nephritis
Site of infection: pharynx (temperate zones), skin (tropics)

## 46.3 Pathology of APSGN

**Light Microscopy**

Diffuse proliferative glomerulonephritis

First 2 weeks (Exudative phase)

- Capillary lume: neutrophils, eosinophils, lymphocytes, monocytes
- Mesangial, endothelial cell, mesangial cell proliferation[5,35 42,43]
- Mesangial expansion typical; occasional occlusion of capillary lumen[44]
- CD4 T cells > CD8; occasional peri-glomerular[45]

Intracapillary fibrin thrombi and/or necrosis (less common)

Focal capsular adhesions or segmental crescents (relatively common; abundant crescents unusual[5,46,47])

Capillary wall thickening (second to subepithelial immune deposits, "humps")

Interstitial edema, ATN

Late phase (4 to 6 weeks)

Glomerular hypercellularity (second mesangial cells and monocytes) slowly resolves

- Interstitial infiltrates, and/or mild arteriolitis may be observed in either phase.[48] Severe vasculitis has been reported but is unusual.[49–51]

**Immunofluorescence**

- IgG, C3 diffuse granular/mesangial and capillary walls
- IgG disappears before C3
- IgM early, resolves slowly
- Properdin, (C5b-9) granular pattern, fibrin in severe cases
- Starry sky pattern of deposits associated with hypercellularity[52–55]
- Rope or garlandlike pattern: mesangial deposits with disease resolution[53–55]; persistent deposits associated with proteinuria and glomulerulosclerosis
- Significant IgA suggests IgAN or HSP
- Deposits in small vessels associated with vasculitis

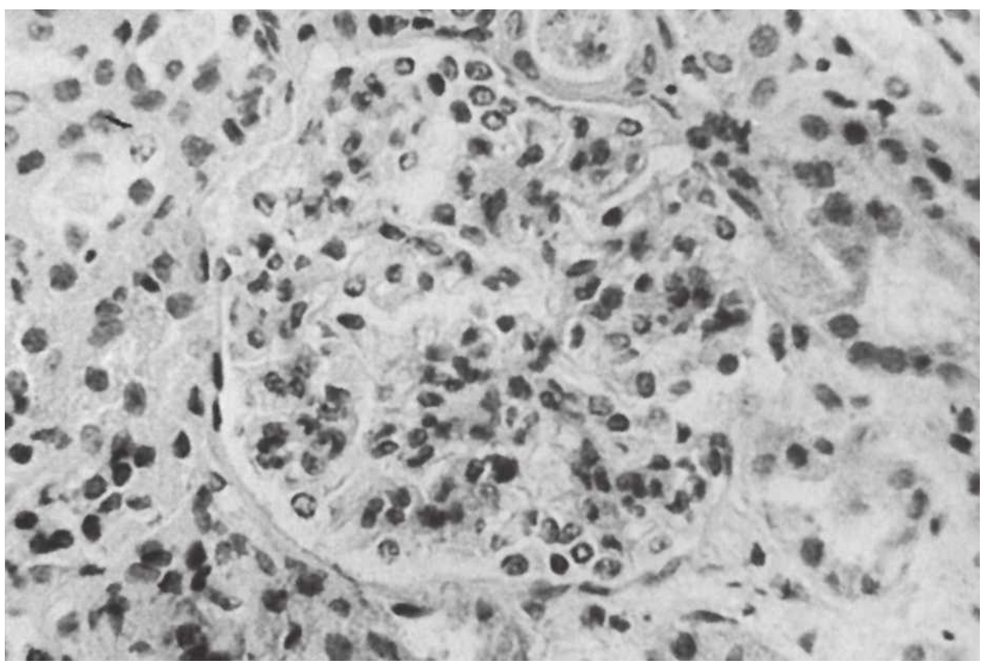
**Electron Microscopy**

- Dome-shaped subepithelial electron-dense deposits resemble camel "humps"; (hallmark)[42]
- Most abundant in first month near slit pores[12,55–57] with proteinuria
- Remnant electron-lucent areas provide diagnostic clues[58]
- Subendothelial, mesangial, intramembranous deposits and smaller subepithelial deposits variably present and persist after resolution of subepithelial humps[58]
- Large subendothelial deposits associated with proteinuria and edema[59]
- Large intramembranous deposits associated with garlandlike pattern[55]
- GBM typically normal thickness[48]

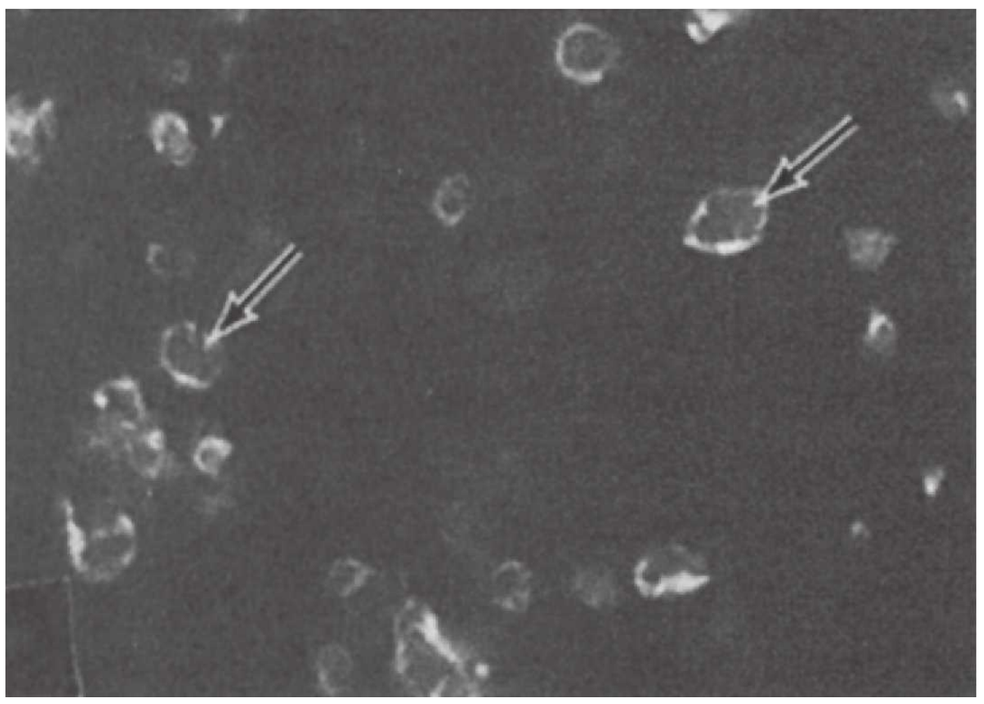
ATN, acute tubular necrosis; GBM, glomerular basement membrane; HSP, Henoch-Schönlein purpura.

during either phase; however, interstitial edema, tubular necrosis, scattered mononuclear interstitial infiltrates, and/or mild arteriolitis have been observed.[48] Severe vasculitis has been reported but is unusual.[49–51]

By immunofluorescence microscopy, deposits of immunoglobulin G (IgG) and C3 are distributed in a diffuse granular pattern within the mesangium and capillary walls.[44,53–55,64] C3 is invariably present, whereas the quantity of IgG depends on the timing of the biopsy, and it is not uncommon to see only C3 deposits very early or late in disease. IgM can be present early in disease but may also be observed in smaller amounts later on. Significant amounts of IgA suggest an alternative diagnosis (e.g., IgA nephropathy or Henoch-Schönlein purpura). C1q and C4 are not usually detected; however, properdin and terminal complement components (C5b-9) are often present and in a granular pattern. Fibrin deposits can be detected in more severe cases. Different patterns of immune deposition have been observed, usually related to the timing of the renal biopsy. Early in the disease (the first few weeks), the fine granular appearance of immune deposits resemble a "starry-sky" appearance; this pattern is associated with glomerular hypercellularity.[53–55] With resolution of the disease (after 4–6 weeks), the immune deposits take on a more mesangial pattern, prior to



A



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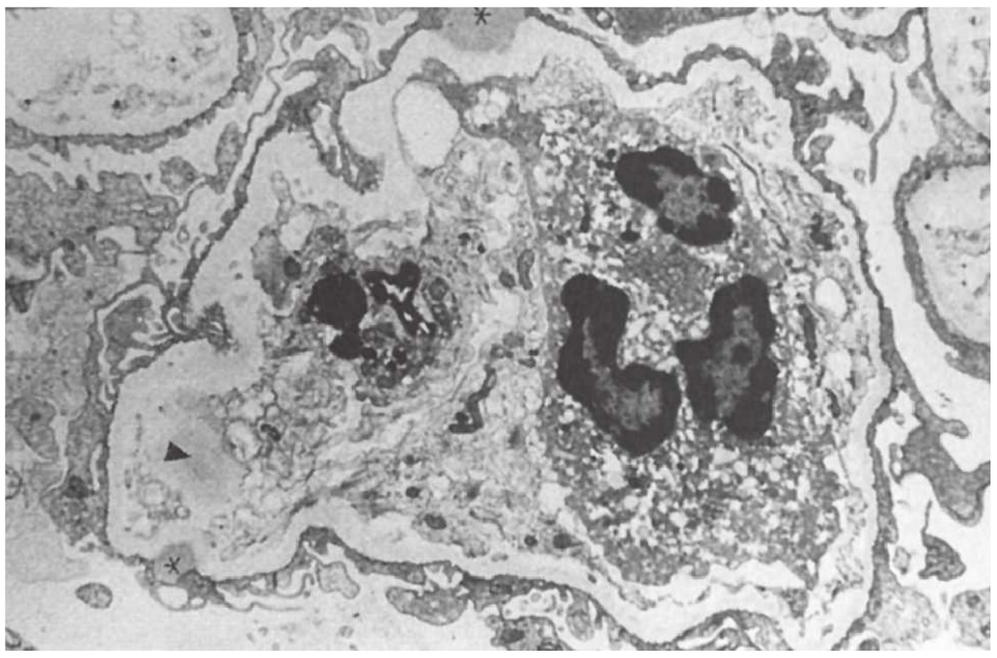

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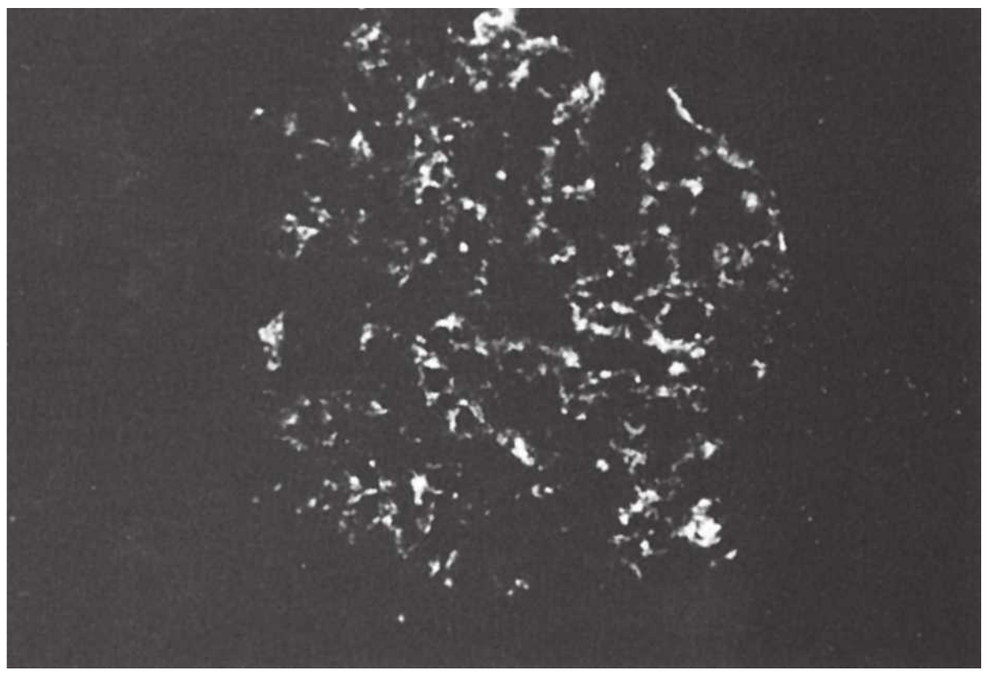

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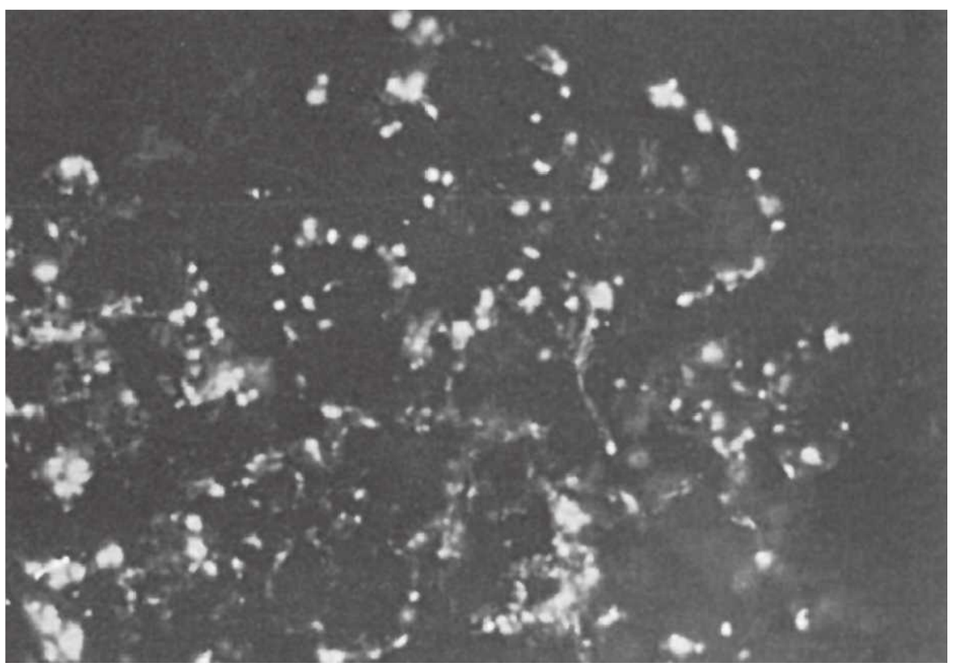

E

**FIGURE 46.1** Pathology of poststreptococcal glomerulonephritis. **A:** Endocapillary proliferation with increased number of mesangial cells and glomerular infiltration with neutrophils (PMN). Biopsy specimen taken 10 days after the beginning of symptoms. (Hematoxylin &eosin ×500.) **B:** Intraglomerular cells reactive with OKM1 monoclonal antibody (*arrows*) in a biopsy specimen obtained 14 days after the initial symptoms. Monocytes and neutrophils are recognized by the antibody, and reactivity with antihuman lactoferrin (which identifies PMN) in serial sections was used to define glomerular monocyte infiltration. **C:** Glomerular capillary loop with PMNs in the lumen. Electron-dense deposits are present in subepithelial ("humps") (*) and subendothelial (<) locations. (×12,000). **D:** C3 deposits (+1) in the glomerular basement membranes and mesangium. (FITC-labeled antihuman ×500.) **E:** Glomerular deposition of the membrane attack complex of complement in a biopsy specimen obtained 16 days after onset identified with monoclonal poly-C9 antibody, which recognizes a neoantigen on C9. Pattern and localization of deposits is similar to the one found for C3 and C5. (**B** and **E** reproduced with permission from Parra G, Platt JL, Falk RJ, et al. Cell populations and membrane attack complex in glomeruli of patients with post streptococcal glomerulonephritis: identification using monoclonal antibodies by indirect immunofluorescence. *Clin Immunol Immunopathol.* 1984;33:324.)

disappearing. C3 may be present in the absence of detectable Ig, either very early in the disease (less than 2 weeks) or with disease resolution (i.e., with resolution of the IgG deposits). In about one fourth of cases, the deposits are large, and they aggregate in a rope or garlandlike pattern, and this pattern may be associated with persistent mesangial hypercellularity on light microscopy. When these type deposits are present, they may last for months and be associated with heavy proteinuria and development of glomerulosclerosis.[52–55] By contrast, transition to a mesangial pattern is usually associated with clinical and pathologic resolution. Immune deposits in small vessels may occur in the setting of vasculitis.

Dome-shaped subepithelial electron-dense Ig deposits, which resemble camel "humps," are the hallmark feature on electron microscopy.[42] These humps are most abundant within the first month, and frequently observed near epithelial slit pores.[12,55–57] They have been associated with heavy proteinuria, and resolve within 4 to 8 weeks. In later stages of the disease, they may be absent; however, remnant electron-lucent areas are occasionally observed and provide diagnostic clues.[58] Subendothelial, mesangial, and intramembranous deposits (along with smaller subepithelial deposits) are often present in variable amounts, and they usually persist after resolution of subepithelial humps.[58] Patients with large subendothelial deposits, without mesangial deposits, were found to have more proteinuria and edema.[59] Large intramembranous deposits are associated with the garlandlike pattern of immune deposits.[55] The basement membrane is usually of normal diameter, although thickening has occasionally been observed.[48] Cellular infiltration and proliferation relates to the timing of the biopsy, as described.

## Pathophysiology

The association of APSGN with streptococcal infections from nephritogenic group A $\beta$-hemolytic streptococcus (GAS) implies that there are unique properties of these bacterial strains. Nevertheless, not all individuals infected with nephritogenic streptococci develop disease, suggesting that host factors are also important for disease expression. Four major mechanisms pertaining to the pathogenesis have been proposed, and they may be operative to varying degrees in individual patients. These mechanisms are summarized in Table 46.4.

Other factors may also contribute to disease susceptibility. Outbreaks among families during epidemics provide clues[27,61,83]; however, in contrast to rheumatic fever,[84] studies have thus far failed to support linkage. Nevertheless, bacterial systemic and host factors likely influence the specific characteristics and severity of disease,[45,55,85–87] and

### 46.4 Pathogenesis of APSGN

1. **In situ immune complex formation.** Cell wall antigens (i.e., M proteins) from nephritogenic strains bind directly to glomeruli and activate the alternative complement pathway to initiate injury. Subsequently, antistreptococcal antibodies bind to glomerular-bound streptococcal antigens, leading to recruitment of polymorphonuclear leukocytes and mononuclear cells to amplify local inflammation via FcR engagement and classical complement activation. Candidate streptococcal antigens include: nephritis-associated plasmin receptor a glycolytic enzyme with glyceraldehyde-3–phosphate dehydrogenase (NAPIr-GAPDH) activity and streptococcal pyrogenic exotoxin B (SPE B) nephritis plasmin binding protein (NPBP), streptococcal pyrogenic exotoxin B precursor (SPE B), cationic proteinase produced by nephritogenic streptococci (related to an erythrogenic toxin),[65] heparin-inhabitable basement membrane binding protein,[66] streptococcal-derived kidney binding proteins,[67] and streptokinase.[43,67,68]
2. **Molecular Mimicry.** Antistreptococcal antibodies react with glomerular antigens,[36,69–71] including matrix and cell wall antigens.[36] Through either shared primary sequence homology or tertiary structure.[72–75]
3. **Altered IgG.** Streptococcal enzymes modify normal IgG; subsequently the altered IgG (a) elicits an immune response and (b) localizes in glomeruli (e.g., through charge-charge interactions).[76] Antibodies versus the deposited/altered IgG bind to the fixed or "planted" glomerular antigen to initiate inflammation.[77,78] In support of this mechanism: neuraminidase-producing streptococci desialate of IgG (making it more cationic),[79,80] elevated levels of serum rheumatoid factor, neuraminidase activity and free sialic acid are often present in patients with APSGN, and anti-Ig antibodies have been eluted from the kidney of a patient with this disease.[79,80] However, neuraminidase-producing streptococci are not unique to APSGN patients, and rheumatoid factor activity is present in many individuals with streptococcal infection who do not develop glomerulonephritis.
4. **Deposition of circulating streptococcal antigen-anti-streptococcal antibody immune complexes** (i.e., deposition based on affinity of exposed and complexed streptococcal protein fragments for glomeruli). Likely has a role in amplifying local inflammatory response, once disease is established.[81,82]

the relative role of host factors in glomerulonephritis is discussed in Chapter 48.

## Clinical Manifestations (Table 46.5)

The symptoms of the disease are characteristic; however, most patients present with only a few features of the acute nephritic syndrome.[88] Typical presentations include edema, gross hematuria, and hypertension.[5,11,12,14,15,17,21,25,61,64,89] Anasarca is more common among children.[5] Occasionally, patients with gross hematuria will complain of dysuria. Hypertensive encephalopathy is unusual, but if untreated may be associated with seizures.[5,12] Encephalopathy may occur in the absence of significant hypertension due to cerebral vasculitis.[90] Some patients present with signs and symptoms of congestive heart failure; however, coexistence of rheumatic fever is rare.[15] Rapidly progressive glomerulonephritis with acute renal failure is unusual but well documented.[91] Hypertension and heart failure usually resolve after diuresis.

Children are more frequently affected than adults, although diagnosis may be delayed in the elderly.[5,15,21,27,31] During epidemics, most infected individuals develop only subclinical evidence of nephritis.[27,29,61,92] Nephrotic syndrome occurs in 5% to 10% of children and ~20% of adults,[5] and may occur either initially or later with improvement in glomerular filtration rate (GFR). Rapidly progressive glomerulonephritis occurs infrequently in children (~2%), and it is slightly more common in adults. In children, the clinical symptoms of acute glomerulonephritis usually resolve within 1 to 2 weeks; in adults, resolution may be more prolonged with a higher incidence of progressive renal disease.

The latent period between infection and nephritis depends on the site of infection: typically 1 to 3 weeks following pharyngitis, and 3 to 6 weeks after skin infection.[15] Shorter latent periods of days suggest an alternative diagnosis such as IgA nephropathy. The preceding infection may be accompanied by severe symptoms or be asymptomatic. In many cases, it is not possible to identify an antecedent infection. Regional lymphadenopathy may be present, even after other symptoms and signs of the primary infection have resolved. The acute nephritic syndrome usually lasts 4 to 7 days; however, it may be more prolonged in adults, especially in those with crescentic glomerulonephritis.[25] Coincident rheumatic fever or arthritis is unusual.[93,94] Recurrent episodes are uncommon, but repeated bouts of hematuria may occur during the initial episode. Although de novo disease involving transplanted kidneys is unusual, it may be associated with deterioration of graft function.[95] Extrarenal manifestations are uncommon but include arthritis and choroiditis.[96]

**46.5 Clinical and Laboratory Manifestations of APSGN[2,118]**

| | |
|---|---|
| **Clinical** | |
| Edema | 85% |
| Gross hematuria | 30% |
| Back pain | 5% |
| Oliguria (transient) | 50% |
| Hypertension | 60%–80% |
| Nephrotic syndrome | 5% |
| **Laboratory** | |
| Urinalysis: proteinuria, hematuria, casts | 100% |
| Nephrotic range proteinuria | 10% |
| Serum creatinine ≥2 mg/dL | 25% |
| Streptococcal antibody profile (streptozyme) | |
| In patients with pharyngitis | >95% |
| In patients with skin infections | 80% |
| False-positive rate | 5% |
| Early abic Rx prevents antibody response | |
| C3, C4, and/or CH50 depressed | >90% |
| Hypergammaglobulinemia | 90% |
| Cryoglobulinemia | 75% |
| Rheumatoid factor | 33% |

## Laboratory Findings (Table 46.5) and Diagnosis

Hematuria and proteinuria are invariably present, RBC casts and dysmorphic RBCs are common, and white blood cells often present. Proteinuria is characteristic, but nephrotic syndrome occurs in only 5% of patients at initial presentation.[60,97] Occasionally, there may be a transient increase in proteinuria to the nephrotic range with improvement in GFR, as the disease resolves.

At onset, the GFR is reduced and the serum creatinine is usually elevated, but may remain within the upper limits of the normal laboratory range; 25% of patients have a serum creatinine greater than 2 mg/dL.[2] Anemia may be present during the acute illness and early recovery period.[98] About 25% of patients will have a positive throat or skin culture,[99] although there is a greater yield of obtaining a positive skin culture in patients with impetigo.[100]

In the first 2 weeks of active nephritis C3 and CH50 levels are significantly depressed whereas C4 and C2 levels are usually normal or only mildly decreased—marked depression suggests another diagnosis.[5,88,101–103] Properdin levels are decreased in over 50% of patients, reflecting activation of the alternate complement pathway,[104] whereas increased plasma levels of C5b–9 reflect contribution of the membrane attack complex to pathogenesis.[105] Complement levels typically return to normal by 1 month, so they may be normal at initial presentation in some patients.[106] Persistent depression

suggests another diagnosis.[101] C3 nephritic factor may be present in low amounts, but marked and/or persistent elevations are more typical of MPGN.[86]

Elevated titers of antibodies to extracellular products of streptococci, as measured in the streptozyme test, are positive in more than 95% of patients with pharyngitis and 80% of patients with skin infections.[5,15,40,107] This test measures five different streptococcal antibodies: antistreptolysin (ASO), antihyaluronidase (AHase), antistreptokinase (ASKase), antinicotinamide-adenine dinucleotidase (anti-NAD), and anti-DNAse B antibodies. The ASO, anti-DNAse B, anti-NAD, and AHase are more commonly positive after pharyngeal infections, whereas anti-DNAse B and AHase are more often positive following skin infections.[108–110] Overall, these tests are relatively specific for streptococcal infections, with a 5% false-positive rate. However, because the incidence of streptococcal infections in the general population is relatively high (especially in young children), they may be elevated in patients with unrelated streptococcal infection and glomerulonephritis. Antibody titers are elevated at 1 week, peak at 1 month, and fall toward their preinfection level after many months.[111,112] An increasing antibody titer is indicative of recent infection. Antibodies against M proteins are type-specific and confer strain-specific immunity.[39] They are detectable at 4 weeks following infection and persist for years; however, they are unrelated to the severity of disease. Early treatment with antibiotic therapy may prevent the antibody response to both extracellular products and M proteins but not nephritis; therefore, negative results in a patient who previously received antibiotics do not exclude the diagnosis.

### Natural History and Prognosis

The overall prognosis is very good (<0.5% mortality; <5% end-stage renal disease [ESRD]).[13,16,18,19,21,23,24,60,113–116] Children have a better prognosis than adults whereas patients older than 40 years with rapidly progressing glomerulonephritis (RPGN) have a worse prognosis,[13,21,31,117] although RPGN associated with APSGN has a better prognosis than other forms of RPGN. Recovery after short-term dialysis dependence is not atypical, although renal function may not return to normal. Persistent urinary and histologic abnormalities are common in both adults and children and may last for years.[10,13,118] The persistence of proteinuria at 3 and 10 years is approximately 15% and 2%, respectively.[118] Patients with prolonged nephrotic syndrome or persistence of heavy proteinuria have a worse prognosis,[23,53–55,118] and persistent hypertension may contribute to progressive renal failure.[60,119]

### Treatment and Prevention

Therapy is symptomatic with aims to control blood pressure and volume overload (e.g., with antihypertensives and overdiuretics). Dialysis may be necessary to treat hyperkalemia, volume overload, or uremia. Restriction of physical activity is appropriate during the first few days of the illness but is unnecessary once the patient feels well. The acute phase of the illness usually resolves within a week, and most patients undergo spontaneous diuresis after that interval.

Steroids, immunosuppressive agents, and/or plasmapheresis are generally not indicated. In adults with rapidly progressive renal failure with crescentic glomerulonephritis; however, treatment with a short course of intravenous pulse steroid therapy may be beneficial (500 mg to 1000 mg per 1.73 $m^2$ of intravenous methylprednisolone daily, for 3 days). More prolonged treatment with steroids or other immunosuppressive therapy is not recommended. Long-term antihypertensive therapy in patients with hypertension and chronic kidney disease is essential to limit progressive renal failure.

Specific therapy for streptococcal infections is important and includes treatment of the patient, family members, and close personal contacts.[120] Throat cultures should be performed on all these individuals and treatment with penicillin G (250 mg four times a day, for 7 to 10 days), or erythromycin (250 mg four times a day, for 7 to 10 days) in patients allergic to penicillin, is indicated to prevent both the development of nephritis in carriers and the spread of infection to others. Whether or not early treatment of infected patients prevents nephritis is not known. For patients with skin infections, attention to personal hygiene is also essential.

## ACUTE POSTINFECTIOUS GLOMERULONEPHRITIS

### Epidemiology and Changing Prognosis

As indicated, although the incidence of APSGN has declined over the over the past few decades, other infections (e.g., staphylococcal) have become more frequent causes of acute postinfectious glomerulonephritis.[4] For example, a retrospective review found Staphylococcus as the infectious agent in 60% of the cases of PIGN in adults in Taiwan. Of particular relevance, the patients were older (mean age 61 years) with male predominance, and there was an increased risk for developing chronic kidney disease.[121,122] A large review of APIGN in North America supported these observations, and almost 40% of the patients were immunocompromised with diabetes (~1/3), cancer, alcoholism, AIDS, and intravenous drug use as the most frequent associations.[2,123] The most common sites of primary infection were upper respiratory tract (24%), skin (17%), lung (17%), and heart (i.e., endocarditis, 12%).[4] Impaired overall health, immunity, poor hygiene, cutaneous ulcers, and poor dentition likely contribute to risk.[124,125] Alcoholism has been associated with a poor prognosis. APIGN may complicate diabetic glomerulosclerosis, because underlying staphylococcal infections are common in this group.[126,127] Complete remission rates are lower (25–50%) with an increased short-term mortality.[2,4,24,97,122,128,129]

## Pathology

Although an array of lesions have been reported, three patterns dominate: diffuse endocapillary proliferation (70%–82%), focal proliferative, and exudative glomerulonephritis (8%–12%) or focal mesangial proliferative glomerulonephritis (<10%), whereas MPGN is observed in less than 10% of patients.[2–4] When APIGN and DGS coexist, mesangial and subendothelial deposits predominate with few small subepithelial deposits, IgA (vs. IgG) may predominate, and subepithelial humps are less frequently observed[4] or IF C3 deposits predominate with focal IgG deposition.[130]

## Clinical Features

Most patients are male and elderly, with immunocompromised background. Classic features of AGN may not be present, and some present insidiously with the nephrotic syndrome. Overt history of infection is atypical.[2] Recurrent episodes are uncommon,[131] and PIGN is an uncommon etiology of de novo glomerulonephritis after renal transplantation.[132]

## Therapy

Indications for immunosuppressive therapy over supportive care and antimicrobial therapy have included acute renal failure with/without crescents on renal biopsy. Corticosteroids have been most commonly used, although there is no clear evidence of benefit.[4] Treatment of the underlying conditions, strict control of blood pressure, and abstinence from alcohol may help overall outcome.

# BACTERIAL ENDOCARDITIS

## Epidemiology

Investigations to define the incidence of this complication have the typical limitations of retrospective studies and/or lacked histologic confirmation,[133,134] and effective antibiotic therapy may underestimate its frequency. Additionally, early and more effective therapies along with changes in the causative organisms have influenced the incidence of glomerulonephritis over recent years. Nevertheless, the incidence of glomerulonephritis associated with Streptococcus viridans–induced endocarditis has declined, and glomerulonephritis associated with acute bacterial endocarditis, particularly involving Staphylococcus aureus, has increased. Other organisms (e.g., Bartonella henselae, brucellosis, Actinobacillus) have also been linked.[133,134] The evolutionary trend with S. viridans and S. aureus is reviewed here.

In the preantibiotic era, glomerulonephritis was documented in a majority of patients dying from subacute bacterial endocarditis (SBE),[135–138] but with antibiotics, the prevalence decreased precipitously.[134–138] Early reports associated glomerulonephritis less frequently with acute bacterial endocarditis.[136] It was postulated that infection with less virulent organisms led to a more indolent and prolonged course, resulting in a greater antibody response that led to a higher incidence of immunologically mediated events.[119,134,139–141] More recent studies, however, suggest that either strain or host-dependent factors are operative.[134] Several factors contribute to this changing epidemiologic pattern, including use of prophylactic antibiotic regimens in patients with known valvular lesions, earlier recognition of bacteremia, and more effective antibiotics, among others.[138]

Coincident with this decline, there has been an increase in acute endocarditis in intravenous drug abusers. This is often due to S. aureus with infection of normal heart valves, and clinical evidence of glomerulonephritis has been found in 40% to 78% of patients with this condition.[134,142,143] Particularly noteworthy, the mean duration of clinical illness prior to the onset of glomerulonephritis is less than 10 days, and many patients are treated with antibiotics prior to overt disease.

## Pathologic Features

Although, like ASPGN, many patterns have been reported, a few are more common. In general, the pathology can be divided into subacute and acute forms. Glomerular changes occurring with subacute endocarditis are usually less severe, with focal and segmental glomerulonephritis.[136,144] By contrast, patients with acute disease often have diffuse proliferative glomerulonephritis,[133] and crescents may be observed.[134,145] Rarely, features typical of membranoproliferative glomerulonephritis have been reported (e.g., double contours).[134,146,147] Edema and leukocyte infiltration are typical interstitial findings,[133,134,138,148] and they may be either immune-, infection-, or drug- (e.g., due to antibiotics) mediated.[133,149] Renal embolization has been reported in 30% to 60% of patients with fatal bacterial endocarditis and should be considered in the context of unexplained renal failure,[150] because peripheral manifestations of embolization are infrequent.[134] Mesangial and subendothelial capillary wall deposits of IgG, IgM, and complement (C3 > C1q) predominate,[133,148,151] with subendothelial and mesangial deposits.[148,151] Patients with acute S. aureus endocarditis often have subepithelial and intramembranous deposits.[151]

## Clinical Features

The manifestations depend on the duration and severity of disease but are typical of acute glomerulonephritis,[152] hematuria is common,[134,148] and heavy proteinuria (nephrotic syndrome ~15%), hypertension, and renal dysfunction may develop, especially with delayed or ineffective therapy.[134,148,153–155] Gross hematuria should raise suspicion of either renal infarction or drug-induced interstitial nephritis[156]; pyuria is common (~2/3), and positive urine cultures are present in 15% to 30%.[157,158] Hypertension occurs infrequently (perhaps due to cardiac involvement),[134,159] and reduced GFR is variable, but may be a presenting symptom.[150]

## Laboratory Findings (Table 46.6)

In general, laboratory findings do not correlate with disease activity. Primarily alternative pathway activation, particularly in patients with S. aureus endocarditis and glomerulonephritis, have been reported, suggesting that the bacterial wall antigens are capable of direct activation of either the alternative or mannose complement activation pathways, leading to nephritis prior to IgG deposition.[134,160] Normalization of complement levels usually occurs with bacteriologic cure and resolution of glomerulonephritis, whereas persistent hypocomplementemia suggests failure to control infection, which in turn may lead to progressive renal failure.[9]

## Differential Diagnosis

In this setting, other considerations include renal emboli, drug-induced interstitial nephritis, and acute tubular necrosis and they are especially relevant in patients with deteriorating renal function.[9,47,169] Embolization of valvular vegetations to the kidney can result in infarction, producing the gross pathologic appearance of "flea-bitten" kidneys.[170] The clinical presentation is gross hematuria, sometimes associated with flank pain. Septic emboli may lead to renal abscesses, and endocarditis should always be considered in patients with multiple renal abscesses. The presence of heavy proteinuria, RBC casts, and dysmorphic RBCs suggests glomerulonephritis. Other considerations include drug-induced interstitial[134] and acute tubular necrosis and, occasionally, renal pathology is necessary to distinguish these entities.[62]

## Treatment and Outcome

Eradication of infection with antibiotic and valve replacement (when appropriate) remain the mainstays of therapy.[9] The severity of the glomerulonephritis is related to the duration of infection prior to the initiation of antibiotic therapy.[134] Proteinuria and microscopic hematuria can persist for months after bacteriologic cure. The outcome of patients with severe renal dysfunction is variable, ranging from continued improvement over weeks to months in some, to persistent and progressive renal failure requiring dialysis in others, despite bacteriologic cure. Patients with a high proportion of glomerular crescents in renal biopsy specimens are more likely to have irreversible disease or progressive renal insufficiency.[9,134] With early and appropriate antibiotic therapy, mortality is less than 5%,[159] and GFR usually improves.[134] However, patients with advanced renal dysfunction at presentation may have further deterioration of the GFR, requiring dialysis. The mortality rate is high in this population, and this is most likely related to the combination of severe infection and renal failure.

The role of immunosuppressive therapy in patients with progressive renal failure, despite optimal antibiotic and surgical treatment, remains controversial. Anecdotal case reports suggested that plasmapheresis, corticosteroids, and cytotoxic agents, alone or in combination, may be useful in this situation.[145,163,171–175] However, in addition to the usual adverse effects of these agents, this therapy poses the risk of exacerbating the underlying infectious process. Therefore, these agents should only be considered under very specific circumstances, and there should be definitive clinical and laboratory evidence of bacteriologic cure. In one series, in 204 consecutive episodes of bacterial endocarditis, one third developed an elevated serum creatinine (≥2 mg/dL), and there was a fivefold increase in mortality in this subgroup.[176] Factors associated with an increased risk of acute renal failure included increased age, hypertension, thrombocytopenia, S. aureus infection, and prosthetic valve involvement.

**46.6 Laboratory Findings of Glomerulonephritis Associated with Bacterial Endocarditis**

- Rheumatoid factor: variable (10% to 70%)[161,162]
- Circulating immune complexes (~90% nondiagnostic)[117,134,163–165]
- Cryoglobulins (mixed >90%)[142,164]
- ANCA + in patients with vasculitis[166–168]
- Hypocomplementemia[134]
  - Depressed C3, C4[117,143,153,154,159,164]
  - Alternative pathway less commonly
  - Acute ~ 66%
  - Subacute 90%

## Shunt Nephritis

### Epidemiologic Patterns

Surgically implanted ventriculoatrial, ventriculojugular, and ventriculo-venal caval shunts have been commonly used to treat hydrocephalus.[169] Overall, infection occurs in 6% to 27% of patients with these ventriculovascular shunts,[169] with nephritis in 1% to 4% of those infected.[177] Staphylococcus epidermidis accounts for 75% of infections,[133,178] although other organisms have been isolated (e.g., S. aureus, diphtheroids, Listeria monocytogenes, Peptococcus species, Serratia species, Bacillus subtilis, Corynebacterium bovis, Gemella morbillorum, Propionibacterium acnes, fungi).[177,179–187] Ventriculoperitoneal devices are more resistant to colonization and infection, and associated glomerulonephritis is rare.[68,188] Most cases have been reported in children.[169,180,185] Recurrence of shunt nephritis in a transplanted kidney has not been reported.[47]

### Clinical Manifestations

Symptoms may develop within weeks to years after the shunt placement. Fever is present in nearly all patients[169]; arthralgias, malaise, and weight loss suggest infection,[144,169]

and purpura, lymphadenopathy, and hepatosplenomegaly is typical.[133,144] Hematuria (gross hematuria, ~50%), proteinuria (nephrotic syndrome, 28% to 43%), and renal failure (46% to 62%) are common at initial presentation.[133,169]

### Laboratory Findings

C3 and C4 is low with active nephritis,[189] with normalization after treatment of the infection and resolution of glomerulonephritis. Persistently depressed levels suggest either inadequate therapy or another cause of glomerulonephritis.[190] Cryoglobulinemia may be present.[169,180,187,191] Blood cultures are often positive. However, sometimes the organisms are difficult to grow, with identification after culture of the removed shunt.

### Pathologic Features

The typical lesions resemble MPGN type I[144,151,169] and, less commonly, diffuse proliferative changes similar to PIGN may be present.[192] Granular IgM (84%), IgG, (66%), and C3 (94%) deposits by IF and subendothelial and mesangial electron-dense deposits are typical.

### Treatment and Outcome

Because antibiotic therapy alone is usually unsuccessful, treatment should include prompt removal of the infected shunt with external drainage and intravenous/intraventricular antibiotics.[193] Full recovery of renal function has been reported in two thirds of patients after eradication of infection,[178,181,189,194] whereas others observed either chronic kidney disease (CKD) or persistent urinary abnormalities.[133,169] Rarely, progression to ESRD has been reported.[169] Immunosuppressive therapy is not effective in these patients.[186]

## Visceral Sepsis-Associated Glomerulonephritis

### Epidemiology

Subacute or chronic infections including intrathoracic and intraabdominal abscesses, osteomyelitis, dental and maxillary sinus abscesses, septic abortions, and aortofemoral bypass graft infections have been associated with glomerulonephritis.[195–198] Glomerulonephritis has also been reported coincident with tuberculosis, pneumococcal pneumonia, Campylobacter (Helicobacter) jejuni enteritis, Salmonella-Schistosoma mansoni infections, and typhoid fever.[195–198]

### Clinical Manifestations

Most patients have signs and symptoms associated with the underlying infection, typically with high fever and weight loss. The interval between the onset of infection and diagnosis of glomerulonephritis is variable (e.g., 2 weeks to 3 years).[195] Common manifestations include purpura, arthralgias (i.e., related to cryoglobulinemia),[195,199] hematuria, and proteinuria ± acute renal failure (with oliguria and hypertension).[195,199]

### Laboratory Findings

Blood cultures are frequently negative, usually due to antecedent antibiotic administration. Mixed cryoglobulins are usually present at the time of diagnosis and disappear with eradication of infection.[195,199] The serum C3, C4, and CH50 levels are typically normal, unless there is an associated endovasculitis. C3 nephritic factor has occasionally been identified[144,200,201]; however, rheumatoid factor is usually absent.[200]

### Pathologic Features

Proliferative glomerulonephritis is typical; however, a diverse group of lesions have been reported, including MPGN and[144,197,200] immune deposits consisting primarily of C3 (with/without IgG, IgM) in mesangial, subendothelial, or subepithelial locations. Subepithelial humps have been observed on occasion.[133]

### Treatment and Outcome

Complete remission of glomerulonephritis is usually achievable with early and complete eradication of the underlying infection[196,197,200]; however, delayed and inadequate treatment may result in irreversible loss of renal function.[200]

## Methicillin-Resistant Staphylococcus–Associated Glomerulonephritis

Methicillin-resistant Staphylococcus (MRSA)-associated glomerulonephritis differs from staphylococcal endocarditis-induced glomerulonephritis[202,203] in that serum complement levels are usually normal, there is polyclonal elevation of serum IgA and IgG levels, and IgA is often present within glomerular deposits with IgG and C3.[204,205] On average, glomerulonephritis occurs 5 to 6 weeks following the onset of MRSA infection and approximately 50% of infections are associated with pleural or abdominal abscesses. RPGN and/or the nephrotic syndrome is typical.[202] One third of patients have leukocytoclastic vasculitis and thrombocytosis occurs in three quarters. Renal pathology shows variable degrees of mesangial and/or endocapillary proliferation and crescents. IgA, IgG, and C3 deposit along with mesangial and capillary wall deposits on EM.

MRSA-associated glomerulonephritis often improves with effective eradication of infection[206]; however, some patients do not respond to antibiotic therapy and progress to ESRD.[207] Anecdotal experience with corticosteroids following apparent successful treatment of the underlying MRSA infection[206] led to relapse of the infection, with death from sepsis, raising concern over use prior to eradication.

Hemoperfusion with polymyxin B–immobilized fiber may be a useful therapy to reduce proteinuria in patients' refractory to antibiotic therapy.[208]

Reports of MRSA infections associated with renal amyloidosis, Henoch-Schönlein purpura, IgA nephropathy, and diabetic nephropathy underscore the importance of renal biopsy in distinguishing the underlying cause of disease,[209–211] and serum IgA subclass distribution may provide clues.[212] Overall, the incidence of MRSA-associated glomerulonephritis may be declining with better control of hospital-acquired MRSA infections.[205,213]

## Syphilitic Glomerulopathy

### Epidemiologic Patterns

The association between syphilis and renal disease has been known for more than a century.[214] Proteinuria is the most common manifestation. Nephrotic syndrome is more common with congenital syphilis (up to 8%) than in secondary forms (<1%).[209–212] Since the advent of mass screening and treatment campaigns, these forms of syphilis are now seen less commonly in developed countries. Primary syphilis is rarely a diagnostic dilemma, but secondary syphilis can be more difficult to diagnose, especially in homosexual males where no primary chancre develops.[215]

### Pathology/Pathogenesis

The most common lesion resembles membranous nephropathy.[216] In some patients, mild mesangial and endothelial cell proliferation, associated with mesangial deposits of IgG and IgM, may be present.[144] Electron microscopy usually consists of variable thickening of the glomerular basement membrane (GBM) with subepithelial and occasional subendothelial dense deposits. Rarely, the histology resembles lesions associated with APSGN. Treponemes have been found in some cases within glomeruli, although other mechanisms may be operative.[217–219]

### Clinical Manifestations

Affected children with congenital syphilis usually present at 1 to 4 months with edema and hypertension.[216,220,221] Rash and hepatosplenomegaly are common, and the typical radiologic findings associated with congenital syphilis are often present. Adults present with features of the nephrotic syndrome during active secondary syphilis.[216,220,221] Less commonly, AGN is the principal manifestation.[222]

### Laboratory Findings

Positive results on serologic testing for syphilis in the appropriate clinical setting, in association with renal histologic findings, support the diagnosis. Serum complement levels (C3 and C4) are depressed in congenital syphilis, but normal in adults with secondary syphilis and nephropathy.[144]

### Treatment

Penicillin is the treatment of choice.[144] For congenital syphilis, aqueous crystalline penicillin G, 50,000 units/kg/day, intravenously in divided doses for 10 days, or penicillin G procaine, 50,000 units/kg/day, intramuscularly for 10 days. For secondary syphilis, penicillin benzathine, 2.4 million units, intramuscularly (one dose), or penicillin G procaine, 600,000 units/day, intramuscularly for 8 days. Proteinuria subsides within 6 weeks of successful therapy in most patients. The prognosis is excellent with rapid recovery as the rule. CKD in treated patients has not been reported.[215]

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