Acute Poststreptococcal Glomerulonephritis: The Most Common Acute Glomerulonephritis

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Educational Gaps

1. If a patient is symptomatic with infectious symptoms and glomerulonephritis simultaneously, other infectious causes besides streptococcus or other causes of nephritis, such as IgA nephropathy, should be considered.
2. A single antistreptolysin O titer value is not as specific for poststreptococcal glomerulonephritis as a depressed C3 level, although an increase in serial antistreptolysin O titers is more so.

Objectives After completing this article, readers should be able to:

1. Recognize the complications of poststreptococcal glomerulonephritis.
2. Order an appropriate laboratory evaluation of poststreptococcal glomerulonephritis.
3. Differentiate poststreptococcal glomerulonephritis from other forms of glomerulonephritis.
4. Know the time sequence of resolution of hypocomplementemia and urinary findings in poststreptococcal glomerulonephritis.
5. Plan the initial management of poststreptococcal glomerulonephritis.
6. Understand that poststreptococcal glomerulonephritis rarely progresses to chronic kidney disease.

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ABBREVIATIONS

ASO	antistreptolysin O
BP	blood pressure
GAS	group A *Streptococcus*
PSGN	poststreptococcal glomerulonephritis

CASE STUDY

A 5-year-old boy with a history of autism spectrum disorder was seen in his pediatrician's office approximately 3 weeks ago for a honey-crusted rash on his face, the dorsal aspect of his hands, and his legs. At that time, he was diagnosed as having impetigo and given a prescription for triple antibiotic cream to place on the skin lesions for the next 2 weeks. The lesions improved, but several weeks after the impetigo was diagnosed, the boy became less active and developed swelling of his eyelids, face, and hands. His condition culminated with notably decreased oral

intake for a few days and the appearance of coffee-colored urine noted in the toilet, prompting the family to bring the boy to the local emergency department.

On examination, the child is not toxic appearing and does not engage the physician but will interact with his parents. He is afebrile, with a heart rate of 92 beats per minute and a blood pressure (BP) at rest of 138/87 mm Hg. There is slight fullness to his eyelids, but he appears otherwise normocephalic. His lung, heart, and abdominal examination findings are normal, but he has leg edema (1+). His genitourinary examination findings are normal, although the physician notes that the patient pauses from playing when percussing over his costovertebral angles. His skin lesions have healed.

Laboratory evaluation reveals red urine with large amounts of blood, 0.1 g/dL (1 g/L) of protein, and small amounts of leukocyte esterase, but no nitrites apparent on dipstick testing. Microscopic examination reveals 30 to 49 red blood cells, 5 to 9 white blood cells, and 3 to 4 hyaline casts per high-powered field. A complete blood cell count reveals 13,600 white blood cells, a hemoglobin level of 8.2 g/dL (82 g/L) (reference range, 11.5–13.5 g/dL [115–135 g/L]), and 278,000 platelets. Renal function test results are normal, with a serum creatinine level of 0.47 mg/dL (42 μmol/L) (reference range, 0.29–0.48 mg/dL [26–42 μmol/L]), but the serum albumin level is decreased at 2.7 g/dL (27 g/L) (reference range, 3.5–4.7 gm/dL [35–47 g/L]). The emergency department physician is considering next steps in this child's evaluation and treatment.

DEFINITION

One of the oldest clinical observations in nephrology is the association of dark and scanty urine after scarlet fever, which was first documented in the medical literature more than 200 years ago. This postscarlatinal disorder was termed *acute glomerulonephritis*. Because it was later discovered in the 1920s that scarlet fever was caused by an infection with β-hemolytic streptococcus, the etiologically correct term *poststreptococcal glomerulonephritis* (PSGN) became synonymous with acute glomerulonephritis, and the 2 terms are often used interchangeably even today.

However, acute glomerulonephritis technically describes the pathologic process characterized by inflammation and/or cellular proliferation of the glomeruli not caused by direct infection of the kidneys. It classically manifests as an acute nephritic syndrome with hematuria, proteinuria, and evidence of volume overload. However, it may also present as nephrotic syndrome (severe proteinuria, hypoalbuminemia, and edema) or as a disorder characterized by particularly rapidly progressive acute kidney injury. Of note, and much beyond streptococcal infection, there are numerous different causes of glomerulonephritis, some being primary disorders only of the kidneys and others representing multiorgan conditions with secondary renal involvement.

For clarity purposes, this review focuses on PSGN. It is a primary disorder of the kidneys with extrarenal manifestations being secondary to renal dysfunction. It is also the prototypical and most widely known form of *postinfectious glomerulonephritis*, a term that is also used indiscriminately and interchangeably with PSGN, even though PSGN is really a subset of it.

EPIDEMIOLOGY

PSGN remains by far the most common glomerulonephritis in children worldwide. Its global burden has been estimated at well more than 450,000 cases annually, with most cases occurring in children. Most of these cases (97% in previous estimates) occur in developing countries, where pyodermal infections, such as impetigo, are common. Despite a lower incidence in developed countries, PSGN is still the most common glomerulonephritis in children in the United States, and its epidemiology offers interesting insights into its prevention.

Group A *Streptococcus* (GAS) has commonly been subtyped by its surface M proteins, which help determine its virulence. Since the 1970s, however, it has been known that another protein, serum opacity factor, may be a determinant of secondary sequelae of GAS infection. Opacity factor–positive strains, which consist of a certain subset of M subtypes, have been associated with causing glomerulonephritis, explaining their classification as so-called nephritogenic strains. Interestingly, opacity factor–negative strains include those that may be rheumatogenic. Thus, the epidemiologic features of PSGN and acute rheumatic fever, the other significant complication of GAS, are not perfectly in parallel to each other because they are caused by different GAS strains but share many similarities.

Nephritogenic strains of GAS may also be further subdivided into those that primarily cause pharyngitis and those that primarily cause pyoderma. The serotypes most associated with pharyngitis are M types 12, followed by 1, 4, and 25, whereas types 49, 2, 42, 56, 57, and 60 cause skin infections.

Epidemics of nephritogenic GAS skin infections in the mid-20th century, including domestic outbreaks on American Indian reservations, led to some of the advances in our understanding of the epidemiology of the disease. PSGN secondary to pyodermal infections tends to peak in the summer and fall in temperate locales, whereas PSGN secondary to

pharyngitis more often occurs in the winter and spring. In more tropical climates, including much of the developing world, there is less seasonal variation of pyodermal infections and, hence, of PSGN. Generally, and similar to acute rheumatic fever, PSGN still causes a disproportionate burden of disease in poorer, rural, and indigenous communities of the world.

Comparison studies of different eras in various countries indicate that the overall incidence of PSGN has decreased significantly in the developed and developing worlds. Much of this decline is related to the overall reduction of GAS pyoderma, especially in developed countries. This near eradication is likely secondary to increased overall and earlier use of antibiotics with skin infections, leading to decreased transmission of these virulent strains. The same may be said for pharyngitis-associated PSGN because streptococcal pharyngitis has been aggressively treated in the past few decades. However, other interventions, such as more readily available access to health care and more widespread fluoridation of the water, which has been found to be bactericidal to GAS, have also been speculated to have effects. (1)

The reported annual incidence of PSGN in developing countries has been estimated at 9.3 cases per 100,000 persons, with rates as high as 93 per 100,000 among Aboriginal Australian children. (2) This finding contrasts with Italian biopsy data that report an annual incidence of 0.3 cases per 100,000 persons. A more recent reported local incidence in the United States from the early 2000s was 0.64 cases for every 100,000 persons, decreased from 2.18 cases from 40 years earlier. (3)

This much lower incidence in developed regions is not solely due to improved medical conditions, although this likely contributed to the greater reduction in incidence seen during the past half century. It is more likely due to an underestimation of the true incidence of PSGN. Most cases in developed countries may not be referred for subspecialty care or remain subclinical if no medical attention is sought. Studies in siblings and close contacts of PSGN patients have found that the rate of subclinical disease is 3 to 4 times that of symptomatic cases. Hence, isolated microscopic hematuria in some children may actually represent the resolving sequela of such subclinical cases.

PATHOGENESIS

Like the epidemiology of GAS infection, the pathogenesis of PSGN has been well researched throughout the years. In fact, it was correctly speculated that the glomerular injury in what came to be known as PSGN was caused by immune complexes as far back as the early 1910s, noting similarities between it and serum sickness. Subsequently, it was confirmed that immune complexes induce the pathologic changes of PSGN, but uncertainty persists as to the exact GAS antigens that cause the formation of these complexes and precisely how they come to be present in the glomeruli.

There are 3 prevailing theories about the mechanism of immune complex injury to the glomeruli. The first theory is that there is formation of GAS antigen and antibody complexes in the circulation with subsequent trapping in the glomeruli. The second theory is that there is first deposition of GAS antigens into glomerular components with subsequent antibody binding in situ, resulting in immune complex formation. The third theory is that some GAS antigens in the serum resemble components of the glomerular basement membrane, commonly referred to as molecular mimicry, leading to the generation of cross-reacting antibodies and the formation of complexes in the glomeruli. Evidence supporting and contradicting each of these theories has included the patterns of complement pathway activation (contrary to the first theory) and similarities to other GAS-induced diseases (supporting the third theory), but it is currently thought that GAS antigen deposition with in situ immune complex formation is most likely.

Similarly, the exact GAS antigen(s) leading to immune complex formation also remains somewhat elusive. Two of the leading candidate antigens are nephritis-associated plasmin receptor and streptococcal pyrogenic exotoxin B. Studies from different areas of the world have offered strong evidence for each antigen in evaluations of PSGN histopathology, showing the presence of antigen within the immune complexes seen in kidney biopsy samples and, serologically, elevation of antibody titers against each in PSGN patients. With strong evidence for both antigens from differing parts of the world, there may not be a single antigen that causes PSGN. Rather, several different antigens may well trigger disease in different populations, with the risk for disease development being more host related.

Regardless of the exact mechanisms leading to immune complex formation and deposition, there is a common pathway of inflammatory response in the glomerulus, which results in many of the clinical signs and symptoms of the disease. The presence of immune complexes leads to complement deposition, leukocyte infiltration, and proliferation of the structural mesangial cells of the glomerulus. This, in turn, diffusely impairs capillary perfusion, resulting in a reduction of glomerular filtration, although not always to the degree that is detectable by an increase in serum creatinine level. With this decrease in filtration, water and sodium are retained, leading to an increase in extracellular volume and

fluid overload. In addition, by-products of metabolism normally filtered in the urine, such as potassium, urea, and organic acids, may also accumulate.

CLINICAL ASPECTS

As noted historically, PSGN typically presents with symptoms of nephritis after a latency period after the instigating GAS infection. It typically affects children between 4 and 12 years of age and is rarely seen in individuals younger than 2 years or older than 18 years. The latency period after infection may vary from 1 to 2 weeks after pharyngitis to 3 to 6 weeks after skin infections.

The most common presenting symptoms are the classic triad of glomerulonephritis: gross hematuria, edema, and hypertension. However, a number of patients may have only subclinical involvement with microscopic hematuria, normal to just mildly elevated BP, and no obvious edema, and these patients may accordingly never come to medical attention.

Hematuria is seen in virtually all patients with PSGN, but only one-third of them may note gross hematuria. In these patients, their dark urine may be better described as tea or coke colored because hemoglobin in the urine oxidizes and turns brown after a prolonged time in that acidic environment. The initial gross hematuria may last up to 10 days. Although the gross hematuria can recur with febrile illnesses in the subsequent weeks after acute presentation, these reexacerbations are uncommon and should raise suspicion about other causes of gross hematuria, especially other glomerulonephritides, and prompt a subspecialty referral. Microscopic hematuria will often persist for months and even up to a few years after presentation. As mentioned, subclinical PSGN may actually be the cause of a fair percentage of isolated asymptomatic microhematuria that is later detected serendipitously by routine urinalysis screening.

Edema is described as being present in 65% to 90% of all patients. Because the cause of edema is excessive fluid and sodium retention and not massive protein losses in the urine, ascites is not typically present. Pulmonary edema is also uncommon but may be seen in more severe cases. Evidence of congestive heart failure has also been described in up to 50% of cases when being sought. Like gross hematuria, edema also tends to be short-lived, lasting only 7 to 10 days.

Hypertension often mirrors edema because they share the same origin: excessive fluid and salt retention. It occurs in 60% to 80% of patients with PSGN and requires treatment in approximately half of all cases. Hypertension tends also to be very acute in duration, typically resolving after approximately 10 days. However, it can be fairly severe during this short duration. Cerebral symptoms, such as headache or visual disturbance, have been described in up to one-third of all PSGN patients, and hypertensive encephalopathy has been reported in up to 11% of nontreated patients in developing nations.

Scanty urine, or oliguria, may be seen in less than half of all patients, although a disproportionate number of hospitalized patients seem to have this symptom. Other common symptoms presenting with PSGN, likely secondary to some degree of uremia or generalized inflammation, include malaise, weakness, nausea, and dull flank pain.

LABORATORY TESTING

The diagnosis of PSGN is strongly suggested by clinical findings, especially when there is a history of recent GAS infection, and only a few laboratory tests are needed for confirmation. Ideally, confirmation of GAS pharyngitis at the time of acute infection is obtained by throat culture or rapid streptococcal antigen testing because culture results are only positive 20% to 25% of the time when checked at the later onset of nephritic symptoms. In addition, culture-proven GAS pharyngitis is seen in only 10% to 20% of patients presenting with a sore throat, adding value to confirmation testing to avoid overdiagnosis, and thus overtreatment, of patients who actually have other causes, likely viral, of pharyngitis. Alternately, the diagnosis of impetigo is often made clinically and without obtaining a wound culture, so the need for a positive GAS culture result is not an absolute requirement to diagnose PSGN.

Fortunately, there are other ways to potentially confirm a recent GAS infection in the absence of a recent positive culture result. Elevated serum titers against GAS proteins have long been used to indicate possible infection, with antistreptolysin O (ASO) titers being the most commonly used. ASO titers typically will peak approximately 2 to 4 weeks after an episode of pharyngitis and remain elevated for several months (Figure 1). Therefore, detecting a rise in titers over time may be diagnostic.

However, there are limitations of using ASO titers in common clinical practice. ASO titers are often not checked serially to document an increase but almost universally obtained only once, at the time of presentation with nephritic symptoms. This timing may be early in the PSGN course, potentially before the increase and peak in ASO titers, and could thus lead to a false-negative result. It has also been reported that ASO titer peaks may be blunted in patients who have been treated with antistreptococcal antibiotics, making them less sensitive tests. ASO titers also do not typically rise in GAS skin infections because streptolysin

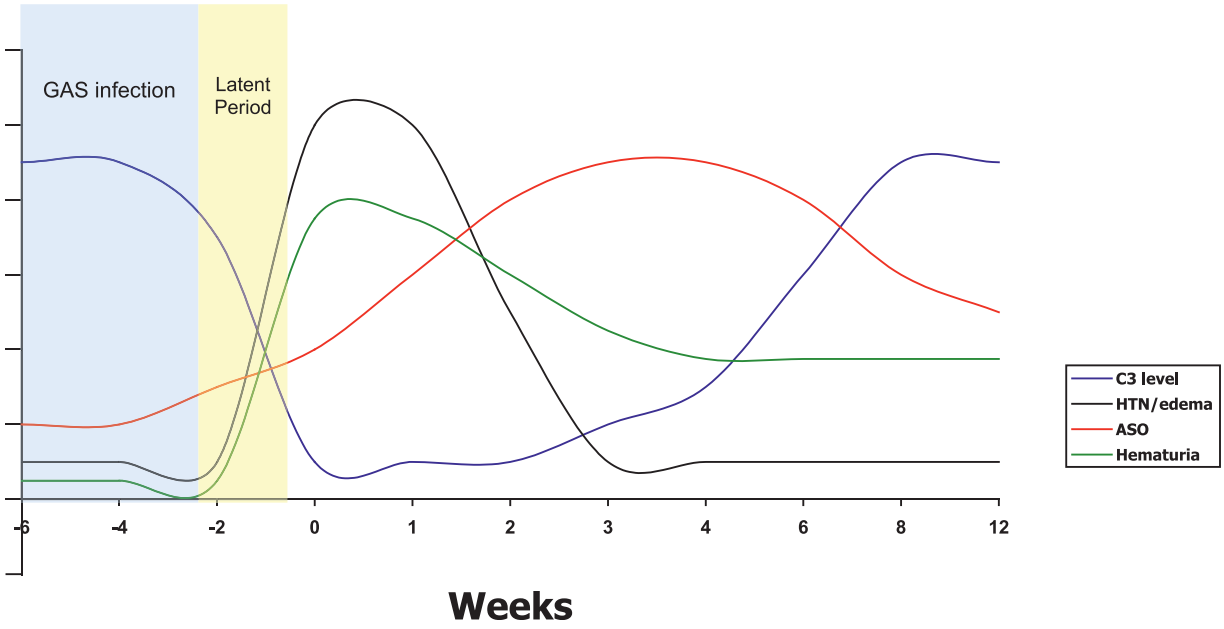

Figure 1. Typical course of symptoms and laboratory changes in poststreptococcal glomerulonephritis. ASO=antistreptolysin O; GAS=group A *Streptococcus*; HTN=hypertension.

may be bound by lipids in the skin. Finally, elevated ASO titers may persist in a convalescent phase for up to 6 months in some individuals and could be potentially misleading in someone much further removed from their GAS infection.

Titers against other GAS antigens may also be used to make the diagnosis, especially when checked in combination with ASO titers. Elevated DNAse B levels may also be seen with GAS pharyngitis, but, unlike ASO, they become elevated with pyodermal infections as well. Checking more than one GAS antigen titer has greater specificity than a single antigen test. There are several commercially available tests that check multiple antigen titers (eg, LeapStrep, CheckSpectra-ASO and DNAse B, Streptozyme-ASO, DNAse B, streptokinase, and hyaluronidase), but they also have high (25%–50%) false-negative rates.

Perhaps the test of greatest diagnostic value in the diagnosis of PSGN, as well as in most other postinfectious glomerulonephritides, is serum C3, especially because C3 is a component of the actual pathogenesis of the disease. C3 levels are decreased in more than 90% of all cases of PSGN. This decrease tends to occur even before the development of nephritis symptoms (Figure 1) and persists for up to 8 weeks. Accordingly, a low C3 level is often concomitant with new-onset nephritic symptoms, which leads to medical evaluation. Hypocomplementemia (ie, low C3 levels) alone is not diagnostic of PSGN because several other glomerulonephritides may also be associated with hypocomplementemia (Table 1). However, transient hypocomplementemia, as seen in PSGN, is virtually diagnostic of the disease. Of course, it is simply not known at the time of presentation if the hypocomplementemia is going to be transient.

Another advantage of checking serum C3 levels in patients with acute nephritis symptoms is that this test is helpful in evaluating other possible causes of glomerulonephritis. In PSGN, the alternate complement pathway is activated, but other total pathway components, such as C4, are typically not consumed. Therefore, checking both C3 and C4 levels may help differentiate some of the other possible diagnoses (Table 1). Some centers may measure total complement activity as a proxy for C3 levels, with low total complement activity levels equating to decreased C3 levels. Interestingly, and despite the diagnostic utility of these laboratory tests, neither the depth of C3 depression nor the height of ASO titers correlate with disease severity of PSGN.

Other recommended testing, as should be performed in any renal disease, includes urinalysis with microscopy, complete blood cell count, electrolyte levels, and renal function testing. Urine dipstick test results will often reveal large amounts of blood and protein, whereas leukocyte esterase test results may also be positive. Microscopic examination of the urine often yields some leukocytes being present and at times even white blood cell casts. In a freshly voided specimen, visualized red blood cells in the urine may appear dysmorphic, and red blood cell casts may also be seen. The presence of red blood cell casts is not specific for PSGN but is pathognomonic of glomerular disease in general.

TABLE 1. **Glomerulonephritides With Normal and Low Complement Levels**

Normocomplementemia (C3)
ANCA-positive vasculitides
Microscopic polyangiitis
Wegener granulomatosis
Diarrheal-associated HUS
Goodpasture disease
Hereditary nephritis (Alport syndrome)
HSP nephritis
IgA nephropathy
Hypocomplementemia (C3) with low C4 levels
Chronic bacteremia (endocarditis, shunt nephritis)
MPGN type 1 (70% of cases)
SLE nephritis
Hypocomplementemia (C3) with normal C4 levels
MPGN types 2 and 3 (60%)
Other postinfectious glomerulonephritis
PSGN

ANCA=antineutrophil cytoplasmic antibody; HSP=Henoch-Schönlein purpura; HUS=hemolytic uremic syndrome; MPGN=membranoproliferative glomerulonephritis; PSGN=poststreptococcal glomerulonephritis; SLE=systemic lupus erythematosus.

The blood cell count may reveal leukocytosis and somewhat decreased platelet and hemoglobin levels. Elevated white blood cell counts may be seen secondary to the recent GAS infection or the generalized inflammation with PSGN. Platelet counts may be mildly decreased from serum dilution, but extremely low levels ($<50 \times 10^3/\mu L$ [50×10^9/L]) may prompt concern about other pathologic mechanisms causing platelet consumption or destruction. Hemoglobin levels may be mildly or moderately low, with almost one-third of patients having a hemoglobin level less than 10 g/dL (<100 g/L). Levels less than 8 g/dL (<80 g/L) should also prompt concern about other conditions.

Electrolyte levels are often normal, but hyponatremia may be seen from dilution with total body fluid overload. Hyperkalemia and anion gap acidosis could be seen if renal function is significantly impaired. An increase in blood urea nitrogen level can be seen in up to two-thirds of patients, although elevation in serum creatinine levels occurs in only 20% of patients. However, if there is a significant elevation in creatinine (rise of >50% above normal), serial monitoring of creatinine every 12 hours is indicated because there are rapidly progressive forms of nephritis that may require emergency interventions. Interestingly, the fractional excretion of sodium is often low (<1%) in PSGN patients, indicating that their kidneys are behaving more as if intravascular volume depletion has occurred by holding onto sodium somewhat inappropriately.

Renal biopsy is typically not necessary to make the diagnosis of PSGN. A biopsy would only be indicated if there are features that are not typical of PSGN, such as normal complement levels or nephrotic syndrome. More importantly, a biopsy is needed immediately if there is rapid progression of disease, indicated by a sustained rapid increase in serum creatinine or severe oliguria. Typical PSGN biopsy findings include those expected from the pathogenesis of the disease: enlarged glomeruli with increased cellularity and infiltration of leukocytes, including neutrophils. Immunofluorescence will be positive for C3, IgG, and/or IgM, indicative of immune complex deposition. However, the hallmark finding of PSGN is seen on electron microscopic views in which immune deposits are seen in the subepithelial space as large "humps" or "haystacks."

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of PSGN includes most other types of childhood glomerulonephritides, which also tend to present acutely (Table 2), including primary glomerular diseases, such as IgA nephropathy, membranoproliferative glomerulonephritis, hereditary nephritis (commonly called Alport syndrome), and, importantly, other forms of postinfectious glomerulonephritis. Also on the list of differential diagnoses are secondary glomerulonephritides, such as systemic lupus erythematosus nephritis, Henoch-Schönlein purpura nephritis, Goodpasture disease, and glomerulonephritis as part of antineutrophil cytoplasmic antibody–associated vasculitides, as well as hemolytic uremic syndrome, all conditions in which the kidneys are only one organ system that may be involved.

Like most diseases, a thorough history and physical examination may help differentiate among some of these diagnoses. One of the first questions should be about recent illnesses in the past month preceding the onset of nephritis to establish whether the patient had a recent GAS infection, which ideally was, but may not have been, diagnosed. Of note, a history of preceding but non-GAS infection would be present for other postinfectious glomerulonephritides but also for a number of the other differential diagnoses because they are immune-mediated disorders that can be triggered by acute illnesses. Other symptoms of interest include

TABLE 2. **Distinguishing Clinical Features of Other Glomerulonephritides and Glomerular Diseases**

DIAGNOSIS	HISTORY	SIGNS, SYMPTOMS, AND PHYSICAL EXAMINATION FINDINGS	LABORATORY FINDINGS
ANCA-associated vasculitis (WG, MPA)	Female-male ratio of 4:1 in WG Middle-aged adults Flulike symptoms presenting for 2 months	Fever, weight loss, arthralgia Purpuric rash (MPA) Mononeuritis (MPA) Chronic sinusitis, epistaxis (WG) Dyspnea, cough (WG) Saddle nose deformity (WG)	Pulmonary infiltrates on radiograph Positive ANCA (c-ANCA with WG and p-ANCA with MPA)
Goodpasture disease	Typically young men aged 20–30 years	Hemoptysis Chest pain	Anti–glomerular basement membrane antibodies
Hereditary nephritis (Alport syndrome)	Family history in males of hearing loss and renal dysfunction	High-frequency hearing loss Anterior lenticonus of the eyes	
HSP		Palpable purpura (buttocks, extensor surfaces of legs) Colicky abdominal pain Joint pain or swelling Orchitis in boys	
HUS	Exposure to undercooked meat, animal feces (petting zoo, farm)	Bloody diarrhea Vomiting Pallor	Hemolytic anemia (schistocytes on blood smear, LDH level elevated, low haptoglobin level) Thrombocytopenia Stool culture positive for *Escherichia* coli O157:H7
IgA nephropathy	Typically manifests in preadolescents to young adults (second or third decade of life)	Synpharyngitic simultaneous with URI (or GI) symptoms	
MPGN	Associated with chronic hepatitis B infection	Asymptomatic 50% of cases	Persistent decrease in serum C3
SLE	Female-male ratio of 4:1 in children Family history of lupus or autoimmune disorders Preponderance in African American and Hispanic females	Discoid or malar rash Photosensitivity Arthralgias Oral or nasal ulcers Serositis	Cytopenias (anemia, leukopenia, and/or thrombocytopenia) Antinuclear antibody titer Anti–double-stranded DNA titer

ANCA=antineutrophil cytoplasmic antibody; GI=gastrointestinal; c-ANCA=cytoplasmic antineutrophil cytoplasmic antibody; HUS=hemolytic uremic syndrome; LDH=lactate dehydrogenase; MPA=microscopic polyangiitis; MPGN=membranoproliferative glomerulonephritis; SLE=systemic lupus erythematosus; p-ANCA=perinuclear antineutrophil cytoplasmic antibody; URI=upper respiratory tract infection; WG=Wegener granulomatosis.

otolaryngologic (sinusitis and oral ulcers), respiratory (chronic cough, hemoptysis, and epistaxis), abdominal (pain, cramping, and bloody diarrhea), musculoskeletal (joint swelling, stiffness, and redness), and dermatologic (rash) symptoms. A family history should inquire about relatives with hearing loss, autoimmune disorders, or dialysis or kidney transplantation. Distinguishing physical examination findings include the presence of a malar rash, purpura on the buttocks or lower extremities, or joint redness and swelling (Table 2).

One of the first diagnostic evaluations to determine the cause of glomerulonephritis is measuring serum levels of C3 and C4. There are a limited number of diagnoses that are associated with hypocomplementemia and specifically low C3 levels (Table 1). Of note, patients with non-GAS postinfectious glomerulonephritis may also present with a history of infectious symptoms and similar findings of hypocomplementemia, but one of the distinguishing features of PSGN is the latency period in which there is

resolution of infectious symptoms before the development of nephritis. In contrast, many of the other postinfectious glomerulonephritides (Table 3) tend to concur with persistent symptoms of infection, such as fever. Likewise, with some active infections and continued antigen exposure, there is ongoing activation of the classic complement pathway and consumption of C_3 and C_4, which may set these infections apart from PSGN. In these cases, a blood culture or other evaluations for active infection, such as inflammatory markers or echocardiography, may be warranted.

Outside the possible lack of preceding GAS infection, membranoproliferative glomerulonephritis is often indistinguishable clinically from PSGN. However, low C_3 levels will often persist beyond 8 weeks in membranoproliferative glomerulonephritis. Other laboratory results, which may assist with diagnostic options, include a complete blood cell count, antinuclear antibody titer, and antineutrophil cytoplasmic antibody testing. If these results do not help in pinpointing the diagnosis, and sometimes even if they do, a renal biopsy may be needed.

MANAGEMENT

Prior prompt antibiotic therapy of the initial GAS infection may help abate nephritis development and prevent the spread of infection to susceptible individuals. In developing nations where PSGN is more prevalent, prophylactic antibiotic use in at-risk individuals has effectively contained the spread of nephritogenic GAS strains during the endemic and epidemic periods.

Although early antibiotic treatment would theoretically reduce the total time of GAS antigen exposure and thus,

TABLE 3. **Various Infections and Agents Associated With Acute Postinfectious Glomerulonephritis**

BACTERIA	VIRUSES	FUNGI	PARASITES
Pharyngitis or skin infections	Hepatitis B[a]	*Coccidioides immitis*	Malaria
Group A *Streptococcus* (*pyogenes*)	Hepatitis C[a]	Histoplasmosis	*Plasmodium malariae*[a]
Group C and G *Streptococcus*	Human immunodeficiency virus[a]		*Plasmodium falciparum*
Endocarditis	Cytomegalovirus[b]		*Plasmodium vivax*
Streptococcus viridans	Varicella		Leishmaniasis (*Leishmania donovani*)
Staphylococcus aureus	Epstein-Barr[b]		Toxoplasmosis[a]
Staphylococcus epidermidis	Parvovirus B19		Schistosomiasis (*Schistosoma mansoni*)
Abscess	Enteroviruses		Filariasis (*Wuchereria bancrofti*)
Streptococcus viridans	Echovirus		
Staphylococcus aureus	Coxsackievirus		
Gram-negative bacilli	Paramyxoviruses		
Intraventricular shunt infections	Measles		
Staph epidermidis	Mumps		
Staph aureus			
Diphtheroids			
Pneumonia			
Streptococcus pneumoniae			
Mycoplasma			
Legionella			
Enterocolitis			
Yersinia enterocolitica			
Salmonella Typhi			
Campylobacter jejuni			
Rickettsial disease			
Rocky Mountain spotted fever			
Q fever (*Coxiella*)			
Ehrlichiosis			
Others			
Neisseria meningitides			
Syphilis (*Treponema pallidum*)[a]			

[a]*Often may be associated with nephrotic syndrome rather than acute nephritis.*
[b]*Often more associated with tubulointerstitial disease than glomerular injury.*

teleologically, the degree of immunologic response, it has not been proven to prevent PSGN. A Cochrane review of 27 trials of sore throat management found a trend toward antibiotic treatment protecting against the development of nephritis, but there were too few cases of PSGN for this to be statistically significant. (4) Similarly, trials comparing different cephalosporins given during a 5-day course compared with the traditional 10-day course of penicillin found no difference in the rates of developing PSGN. Therefore, although GAS infections should still be treated in a timely manner, unlike what has been observed for other GAS complications, it is not apparent that prompt antibiotic therapy is critical for the prevention of PSGN.

The primary management of PSGN, once it sets in, is supportive in treating the main sequelae of the disease (ie, edema, hypertension, hyperkalemia, and impaired renal clearance). As mentioned earlier, these sequelae present early in the disease course and tend to be short-lived but can vary in intensity, so patients may require frequent (daily or every other day) reevaluations to monitor their progression. Immediate referral to a pediatric nephrologist is warranted in patients whose creatinine level is increased 50% over normal or continues to increase, whose BP is greater than 99th percentile for age and height, or who have accompanying neurologic symptoms with their hypertension. Similarly, these same patients will likely require hospitalization for more acute interventions for these symptoms or more frequent monitoring of their renal function.

Because the edema and hypertension of PSGN share a common origin, their initial management should include some degree of restricted fluid and sodium intake along with enhanced diuresis. Thiazide diuretics may be effective first-line agents, whereas loop diuretics should be considered in those with more significant edema or some degree of renal dysfunction to ensure potency of action because thiazides are not as effective when renal function is less than 30 mL/min/1.73 m^2. The 2 may be paired as well, but potassium-sparing diuretics should be avoided because of the existing risk of hyperkalemia in PSGN. Loop diuretics alone have been proven to be more effective than other single antihypertensive agents. (5)

If greater hypertension control is needed, then the addition of a calcium channel or β-blocker may be considered. Calcium channel blockers have been associated with fluid retention and edema and thus should not be the sole agent used, but they are likely to be effective when used in combination with a diuretic. β-Blockers can contribute to hyperkalemia and should therefore be used with vigilant laboratory monitoring.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are often viewed warily in the setting of PSGN. Theoretically, they may not be as effective with fluid overload because these patients have low serum renin and aldosterone levels. However, intrarenal renin levels are likely to be elevated in patients with PSGN who have decreased glomerular capillary perfusion. In fact, studies have found better BP control and cardiac outcomes in PSGN patients treated with an angiotensin-converting enzyme inhibitor than with other antihypertensives, including loop diuretics. (5) However, the concern with the use of these agents remains the potential for further worsened glomerular filtration and hyperkalemia, so caution is warranted.

Therefore, thiazide and/or loop diuretics remain mainstays for BP control in PSGN. If poorly controlled hypertension continues to be an issue, a subspecialist should be consulted.

Hyperkalemia can typically be controlled with limiting dietary intake in the short term, along with the use of diuretics. Potassium-binding exchange resins, such as sodium polystyrene, can be considered, but they are a source of added sodium to the patient. Uncontrollable hyperkalemia, fluid overload that compromises respiratory function, or rapidly increasing blood urea nitrogen levels (>100 mg/dL [>35.7 mmol/L]) are all indications for dialysis in these patients. When dialysis is required, it fortunately is often only needed acutely until the glomerular inflammation begins to resolve and some kidney function has been recovered.

In patients whose symptoms are severe enough to prompt a renal biopsy, high-dose intravenous corticosteroids may be prescribed by the treating nephrologist, especially if there is histologic evidence of crescents, which indicate a greater degree of acute inflammation. However, there is no evidence that corticosteroid immunosuppression is beneficial in treating PSGN, even in more severe cases; therefore, this treatment may be more panacea to the prescriber than to the patient.

PROGNOSIS

Despite limited treatment options for PSGN, its overall prognosis is good. Volume overload resolves rapidly, typically within 10 days, and serum creatinine levels return to baseline within 3 to 4 weeks. Any associated proteinuria often tends to resolve shortly after this, whereas microscopic hematuria can linger for several months to a few years. Fortunately, recurrence of PSGN is extremely rare, although there have been case reports of this occurring, mainly with pyoderma from different nephritogenic strains. Fatality rates attributable to PSGN range from 0.02 to 0.4 deaths per 100,000 population from reports from developing nations, whereas fatalities in developed nations are extremely

rare. The causes of mortality in these patients tend to be complications related to volume overload, such as heart failure, or to critical care interventions, such as mechanical ventilation and dialysis, necessary in more severe cases.

Longer-term outcomes of PSGN were initially reported as excellent, with a very small fraction of patients having any persistent sequelae for 5 to 10 years. However, within the last decade, more studies have examined outcomes beyond 10 years, with somewhat different results. Persistent urinary findings, either hematuria or proteinuria, have been reported in as few as 5% but up to 20% of PSGN patients after 10 years. Hypertension is less prevalent but seen in 3% of patients, whereas azotemia from chronic kidney disease is noted in less than 1% in several cohorts. Normal complement levels, the findings of nephrotic syndrome, and biopsy findings of crescent formation are all predictors of worse long-term prognosis.

For patients with a fairly typical disease course, screening urinalysis and BP measurement may be performed quarterly for the first year and annually thereafter. If proteinuria or hypertension persists after that first year, then referral to a pediatric nephrologist is warranted.

- On the basis of primarily consensus because of a lack of relevant clinical studies, the main sequelae of PSGN (hypertension, edema, gross hematuria, and impaired renal function) are greatest in the first 7 to 10 days of disease. Therefore, this period requires the most vigilance for adverse effects.
- On the basis of some research evidence and consensus, the most effective treatment of hypertension and edema in PSGN is loop or thiazide diuretics, which may also address hyperkalemia. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may be effective in hypertension control but carry the risk of hyperkalemia and temporarily impairing recovery of renal function.
- On the basis of some research evidence and consensus, the prognosis for PSGN, even long term, is good. Despite being the most prevalent of the childhood glomerulonephritides, it often does not cause chronic kidney disease, but persistent microscopic hematuria and proteinuria may be seen in less than 10% of patients.

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Summary

- On the basis of strong research evidence, the prevalence of poststreptococcal glomerulonephritis (PSGN) is decreasing worldwide, although it still remains the leading cause of glomerulonephritis in children. The overall decrease in prevalence of PSGN has been mainly driven by a significant decrease in pyoderma seen in the last half-century, such that postpharyngitic PSGN is most commonly seen in developed nations.
- On the basis of primarily consensus because of a lack of relevant clinical studies, the latency period between streptococcal infection and the development of nephritis is a hallmark of PSGN, with this period lasting 1 to 2 weeks with pharyngeal infections or 2 to 6 weeks with skin infections. Concurrent infectious and nephritis symptoms should elicit further suspicion of other causes of glomerulonephritis.
- On the basis of expert opinion, PSGN is one of a handful of nephritic disorders with hypocomplementemia (low C3 level). The decrease in C3 is found in more than 90% of PSGN cases and is typically seen earlier than an increase in antistreptolysin O titers. Measuring C3 and C4 may also be helpful in the evaluation of other causes of acute nephritis.

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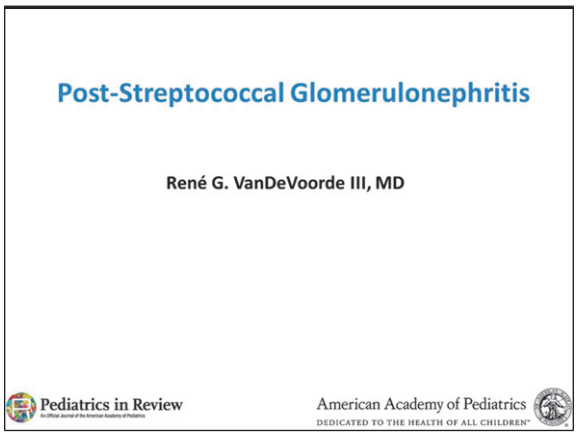

PIR Quiz

1. A 4-year-old girl developed a rash on her hands that was diagnosed as impetigo. She was prescribed a topical cream for treatment. Four weeks later she develops red urine and is brought to the local emergency center for evaluation. Urinalysis reveals proteinuria (4+) and increased red blood cells (2+). Her mother, a microbiologist at the local university, questions the factors that determine the virulence of the organism. Which of the following statements is accurate regarding group A *Streptococcus* (GAS) infections?
    A. GAS is subtyped by its surface M proteins, and the proteins dictate its virulence.
    B. Opacity factor–positive strains of GAS are associated with rheumatologic illnesses.
    C. Poststreptococcal glomerulonephritis (PSGN) closely mimics acute rheumatic fever because they share the same GAS strains.
    D. The serotypes of GAS most associated with pharyngitis are M types 2, 42, and 49.
    E. The virulence of GAS is attributed to serum opacity factor.
2. What are the most common age and period for the development of PSGN?
    A. 2 years old and 4 weeks after diagnosis of impetigo.
    B. 8 years old and 1 week after an episode of pharyngitis.
    C. 10 years old and 4 weeks after an episode of pharyngitis.
    D. 12 years old and 1 week after diagnosis of impetigo.
    E. 14 years old and 6 weeks after an episode of pharyngitis.
3. A 12-year-old boy presents with a 2-day history of dark urine. He has no pain or fever but reports recently completing a course of oral antibiotics for streptococcal pharyngitis. You suspect glomerulonephritis. Which of the following symptoms best characterizes the classic triad of glomerulonephritis in pediatric patients?
    A. Hematuria, edema, and hypertension.
    B. Hematuria, hypertension, and ascites.
    C. Hematuria, hypertension, and oliguria.
    D. Proteinuria, edema, and hypoalbuminemia.
    E. Proteinuria, hypertension, and volume overload.
4. A 6-year-old boy presents with a history of red urine in the past 2 days. On examination, he has edema of his feet. His mother states that he was diagnosed as having streptococcal pharyngitis 2 weeks ago. You diagnose him as having PSGN. Which of the following laboratory scenarios is most likely associated with PSGN?
    A. Antistreptolysin O titer elevation during an acute skin infection.
    B. Antistreptolysin O titer elevation early in the course of pharyngitis.
    C. Elevated C3 and total complement activity.
    D. Elevated DNAse B levels.
    E. Low level of serum C3.
5. You are the attending pediatrician in the acute care unit of a regional children's hospital. One of your patients is an 8-year-old girl who has been admitted with hematuria and proteinuria. As you discuss PSGN with the medical students, they ask you at what point a pediatric nephrology consultation would be appropriate. You answer that a pediatric nephrology consultation should *initially* be considered in the setting of PSGN:
    A. When creatinine levels are increased 50% above normal.
    B. When dialysis is being considered.
    C. When the blood urea nitrogen level increases to twice the baseline value.
    D. With the development of any degree of hypotension.
    E. With the onset of hypokalemia.

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