Streptococcus pyogenes (Group A Streptococcus)

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Group A Streptococcus (GAS) is synonymous with Streptococcus pyogenes, the only species in this group of β-hemolytic streptococci. GAS is one of the leading pathogenic bacteria that infect children and adolescents, and it is associated with a wide spectrum of infections and diseases. Worldwide more than 600 million cases of GAS pharyngitis ("strep throat") and more than 100 million cases of GAS pyoderma are estimated to occur annually. Although uniformly and exquisitely susceptible to penicillin and many other antimicrobial agents, GAS infections continue to present formidable clinical and public health challenges. The vast majority of GAS infections have a short duration and are relatively benign; however, invasive disease can be fulminant and life-threatening. GAS also differs from other pyogenic bacteria in its potential to produce delayed, nonsuppurative sequelae, such as poststreptococcal acute glomerulonephritis (PSGN) and acute rheumatic fever (ARF), after uncomplicated infections.

The importance of GAS infections in the United States was reinforced at the close of the 20th century by the appearance of severe, invasive GAS infections (e.g., streptococcal toxic shock syndrome [STSS] and necrotizing fasciitis) with high morbidity and mortality. On the global scale, GAS is an important cause of morbidity and mortality primarily in less developed countries, causing more than 500,000 deaths per year.

DESCRIPTION OF THE PATHOGEN

Microbiology

GAS is a gram-positive coccoid-shaped bacterium that grows in chains, producing small white to gray colonies with a clear zone of β-hemolysis on blood agar. It is distinguished from other groups of β-hemolytic streptococci by a group-specific polysaccharide ( Lancefield antigen) in the cell wall. Serologic grouping by the Lancefield method is precise, but group A organisms can be identified more readily by any one of a number of latex agglutination, coagglutination, or enzyme immunassay procedures.

GAS can be subdivided into more than 100 immunologic serotypes by the M-protein antigen on the cell surface and by the fimbriae (hairlike fuzz) that project from the outer edge of the cell. Classically, typing of the surface M protein relied on the available polyclonal antisera, but this technique has been supplanted by a contemporary molecular approach that applies the polymerase chain reaction and deoxyribonucleic acid (DNA) sequencing of the S′ variable region of the EMM gene encoding the M protein (http://www.cdc.gov/nicidin/biotech/strep/strepindex.htm). More than 200 distinct M genotypes have been identified using EMM typing, and a good correlation has been established between known serotypes and EMM types.

M typing or genotyping has been valuable for epidemiologic studies; particular GAS diseases tend to be associated with certain M types. The M types commonly associated with pharyngitis rarely cause skin infections, and the M types commonly associated with skin infections rarely cause pharyngitis. A few of the "pharyngeal" strains (e.g., M type 12) have been associated with PSGN, but far more of the "skin" strains (e.g., M types 49, 55, 57, and 60) have been considered nephrotoxic. A few pharyngeal serotypes, but no skin serotypes, have been associated with ARF. However, evidence suggests that rheumatogenic potential does not depend solely on the serotype, but rather is a characteristic of specific strains within several serotypes. Certain GAS M types are more strongly associated with invasive disease, including M1, M3, M6, M12, M18, and M28. A globally disseminated clone of the M1 serotype has been the leading cause of severe invasive GAS infections, such as necrotizing fasciitis and STSS, over the past 3 decades.

The GAS cell is a complex structure. In rapidly dividing strains (e.g., young cultures, epidemic strains), the cell is covered with a hyaluronic acid capsule that gives the colonies a mucoid or water drop appearance. Microscopic fimbriae protrude from the cell surface into the hyaluronic capsular layer, promoting the adherence of GAS to epithelial cells and extracellular matrix proteins. The fimbriae are composed of a surface-anchored, M protein that adopts a coiled-coil structure, which is closely associated with lipoteichoic acid polymers. GAS are now recognized to express surface pili, corresponding to the classic "T antigen" used in earlier serologic typing schemes. Roughly half of GAS strains display the capacity to opacify mammalian serum, through the activity of the surface-anchored serum opacity factor (SOF) protein, which binds to apolipoproteins to displace high-density lipoprotein (HDL) to form lipid droplets.

The group A carbohydrate, encoded by the cap operon, comprises 40% to 50% of the dry weight of the GAS cell wall. The carbohydrate, a polymer of rhamnose units with side chains of N-acetyl-glucosamine, is responsible for its group (e.g., A) specificity. As with other gram-positive species, a peptidoglycan polymer provides thickness and rigidity for the cell wall, consisting of glycan strands cross-linked by peptide bridges. M protein, pili, antigen, SOF, and other surface proteins are covalently attached to the GAS cell wall by recognition sequences in their C-terminal regions that interact with an anchoring enzyme called sortase.

GAS produces and releases a large number of biologically active extracellular products into the surrounding medium. Some of these are toxic to human and other mammalian cells. Streptolysin S (SLS) is a small, oxygen-stable toxin responsible for β-hemolysis on blood agar; streptolysin O (SLO) is an oxygen-labile, cholesterol-dependent toxin related to staphylococcal β-hemolysin. Both SLS and SLO injure cell membranes, not only lysing red blood cells, but also damaging other eukaryotic cells and membranous subcellular organelles. SLO is antigenic, whereas SLS is not. Streptococcal pyrogenic exotoxins (SPEs) are secreted factors that can act as superantigens and trigger T-lymphocyte proliferation and cytokine release. GAS expresses a broad-spectrum cytotoxic protease, SpeB, which has multiple host targets, various specific peptidases that cleave host chemokines and complement factors, and several nuclease. GAS also produces bacteriocins, which are low molecular weight proteins that can kill a variety of other gram-positive bacteria, and thus may play a role in the promotion of infection or the persistence of colonization.

GAS quorum sensing and virulence gene expression are controlled by the interplay of several transcriptional regulatory systems. These include the two-component control of virulence system (CovRS), which regulates 10% to 15% of the GAS genome, including its hyaluronic acid capsule synthesis operon, and the stand-alone Mgα regulator, which controls expression of M protein and nearby virulence factor genes. Genome sequencing has shown that bacteriophages have played an important role in the evolutionary genetics of GAS, including the transfer of genes that encode antibiotic resistance, SPEs, and other virulence determinants.

PATHOGENESIS AND VIRULENCE

GAS induces serious human disease by at least three mechanisms: suppurative, as in pharyngitis and pyoderma; toxin elaboration, as in STSS and immune-mediated inflammation, as in ARF and PSGN. The complete explanation is available for the predilection of certain body sites for GAS infection, nor for the ability of certain M-type strains to produce pharyngitis and of others to produce pyoderma.

The first step in the pathogenesis of GAS disease in humans is successful colonization of the upper respiratory mucosa or skin. A large
number of adherence factors for epithelial cells and extracellular GAS have been described, including lipoteichoic acid, M protein, pilis, and fibronectin- or laminin-binding proteins, including SfbI, SOF and Lpa. The formation of a GAS biofilm facilitates persistence in humans. Both M protein and fibronectin-binding proteins are important for subsequent uptake of GAS into respiratory epithelial cells. This process of intracellular invasion allows GAS access to a privileged intracellular niche, and it represents a proximal step in the pathogenesis of systemic infection.

The propensity of GAS to produce serious infection in otherwise healthy children and adults defines the pathogen's ability to resist innate immune clearance mechanisms that normally prevent microbial dissemination. For example, when GAS gains access to deeper tissues through cellular invasion or a breakthrough in epithelial integrity, it deploys specific peptides that cleave and inactivates the neutrophil chemotactic interleukin-8 and complement factor 5a. Likewise, SpeB can degrade the host's immunoglobulins and cationic antimicrobial peptides.

M protein is a multifunctional immune resistance factor that promotes GAS resistance to opsonophagocytosis through multiple mechanisms, including the binding of fibrinogen, complement factor H, host antimicrobial peptides, and the Fc region of immunoglobulins. M protein is essential to virulence in animal models, and immunization with M protein provides strong protection against infection with a type-specific GAS strain. During invasive infection, significant quantities of M protein are released from the cell surface by proteolysis; these may form a proinflammatory, clumping complex with human fibrinogen, leading to uncontrolled neutrophil activation, vascular leakage, and toxic shock symptomatology. M protein also collaborates with the GAS virulence factor streptokinase to bind host plasminogen to the GAS surface; this generates plasmin activity, effectively coating the bacterial surface with a powerful protease to facilitate tissue spread.

Most of the more toxic toxins SLS and SLO are toxic to multiple host cell types, including macrophages and neutrophils, and therefore promote GAS tissue damage and resistance to phagocytic clearance. SLO in particular can induce accelerated apoptosis of immune cells and inhibit neutrophil oxidative burst and neutrophil extracellular trap (NET) production. The GAS hyaluronic acid capsule is not immunogenic, mimicking a common human matrix component, and cloaks opsonic targets on the bacterial surface from phagocyte recognition. In the case of the highly invasive, globally disseminated M11T1 GAS clone, hyperinvasive forms bearing mutations in the CovR/S two-component regulatory pathway in vivo under innate immune selection, leading to upregulation of capsule and other key virulence determinants. Specific virulence determinants present in the hyperinvasive M11T1 clone include the phase-encoded DNAse Sla1, which allows GAS to escape killing in DNA-based NETs, and the serum inhibitor of complement (SIC), which binds and inactivates terminal complement components and host defense peptides.

The SPEs are a family of more than 15 bacterial superantigens, including the bacteriophage-encoded SPE A and SPE C. These superantigens induce antigen-non-specific T-lymphocyte activation, suppress antibody synthesis, potentiate endotoxin shock, induce fever, promote the release of proinflammatory cytokines, produce reticulendothelial blockage, and may contribute to the multiorgan failure characteristic of SS.

In the U.S., SS is most commonly associated with infections caused by strains that produce SPE A. Susceptibility to SS appears to be related to the absence of antibodies to both M protein and superantigens, in addition to the presence of specific human leukocyte antigen (HLA) haplotypes. The SPEs share homology with staphylococcal enterotoxins but not with staphylococcal toxic shock syndrome toxin-1. SPE A and SPE C are responsible for the rash of scarlet fever, stimulating the formation of specific antitoxin antibodies that provide immunity against future scarlatiniform rashes, but not against subsequent GAS infections.

Immunologic Response
Although many GAS constituents and extracellular products are antigenic, protective immunity is type specific, mediated by specific anti-M protein and antitoxin antibodies. These antibodies protect against infection with a homologous M type but confer no immunity against other M types. Therefore, multiple GAS infections attributable to different M types are common during childhood and adolescence. Anti-M antibodies persist for years, perhaps for life, protecting against invasive infection but not against pharyngeal carriage. A type-specific antibody may be transferred across the placenta from mother to fetus. A type-specific antibody against M protein usually is not detectable until 5 to 8 weeks after infection, therefore, its primary role may not be in the limitation or termination of active infection, but rather in the prevention of reinfection by the same serologic type. Opsonic type-specific antibodies do not appear after early and effective antimicrobial therapy.

Humoral antibodies to specific streptococcal extracellular products such as antistreptolysin O (ASO) and anti-DNase B can be demonstrated readily by neutralization assays. These assays have been particularly useful in allowing a more precise method of defining GAS infection in clinical and epidemiologic studies and in documenting the occurrence of a preceding GAS infection in patients suspected of having a nonsuppurative complication. The ASO assay is the most commonly used streptococcal antibody test. Because SLO is also produced by group C or group G streptococci, the test is not specific for GAS infections, and the response can be false-positive in patients with streptococcal impetigo.

In contrast, the anti-DNase B response is demonstrable after both skin and throat infections. Neutralizing antibody titers peak at 3 to 6 weeks for SLO and at 6 to 8 weeks for DNase B. Antibody titers against GAS extracellular antigens reported by clinical immunology laboratories may vary. The antibodies are normal for children but for adults, these values, even for the same age group, are higher in some populations than in others.

Epidemiology
GAS has a narrow host range; it is identified almost exclusively in humans and only rarely in other species. GAS is highly communicable and can cause disease in individuals of all ages who do not have type-specific immunity. Disease in neonates is uncommon, probably because of placental transfer of maternal antibody. Significant differences exist between epidemiology of throat and skin infections due to GAS (see chapters 27 and 68).

Severe invasive GAS infections had become uncommon in the U.S. and Western Europe during the second half of the 20th century. However, since the late 1980s a worldwide increase in severe invasive GAS infections has been seen. The incidence of severe invasive GAS disease in industrialized societies (2 to 3 per 100,000 population) is similar in the geographic distinct regions of Europe, North America, and Australia. This rate translates to about 10,000 cases of invasive GAS disease annually in the U.S. However, rates of invasive disease in indigenous populations in Africa, the Asian subcontinent, and the Pacific islands typically are much higher; rates as high as 82.5 per 100,000 have been reported in North Queensland, Australia. Globally it has been estimated that at least 600,000 cases of invasive GAS disease occur each year, resulting in 163,000 deaths.

The stratified squamous epithelium of the oropharynx and skin is the principal barrier against invasive GAS disease. GAS can gain access to sterile sites by means of direct inoculation after an injury that breaches the mucous membranes or skin; however, a substantial number of invasive streptococcal infections have no known site of entry. Epidemiologic data suggest that the oropharynx is the primary site of origin for systemic GAS isolates; therefore, invasive disease is likely to occur as a result of transient bacteremia originating from the oropharynx, possibly as a result of direct tissue penetration by GAS. Varicella is a particularly important risk factor for severe invasive GAS infections in previously healthy children. Other risk factors more common in adults include diabetes mellitus, human immunodeficiency virus infection, intravenous drug use, and chronic pulmonary or cardiac disease.

Clinical Manifestations and Clinical Syndromes
GAS is a common cause of acute pharyngitis (see Chapter 27 [Fig. 118.1]) and puerperal (impetigo) (see Chapter 68) in children and adolescents. GAS also produces a variety of other infections of the respiratory tract, including otitis media, retropharyngeal abscess, perinatal abscess, subcutaneous abscesses, and mastoiditis. Infections of the skin and soft tissues (Figs. 118.2, 118.3, and 118.4), which include cellulitis, erysipelas, peripheral cellulitis, vaginitis, and blistering distal dystrophy (see chapters 68, 74, 84, 85, and 125), are caused by GAS.
**FIGURE 118.1** Typical group A streptococcal pharyngitis showing erythematous soft palate, uvula, and tonsils, with tonsillar exudate. (Courtesy of J.H. Briët®)

**FIGURE 118.2** Young girl with bulous, invasive local infection without trauma or foreign body; the infection was caused by group A streptococcus. (Courtesy of J.H. Briët®)

**FIGURE 118.3** Toddler with Staphylococcus aureus and group A streptococcal infection complicating chickenpox (A). Necrotizing group A streptococcal cellulitis complicating chickenpox (B). (Courtesy of S.S. Long®)

**FIGURE 118.4** Toddler with erysipelas caused by group A streptococcus. (Courtesy of J.H. Briët®)
and 75), and invasive diseases, including STSS (see Chapter 13), necrotizing fasciitis, septicaemia, meningitis, pneumonia, empyema, peritonitis, puerperal sepsis, neonatal sepsis, osteomyelitis, suppurative arthritis, myositis, and surgical wound infections. In addition, GAS is the proven cause of two potentially serious nonsuppurative complications, ARF and PSAGN, and the possible cause of two other potential nonsuppurative complications, poststreptococcal reactive arthritis (PSRA) and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAs) (discussed later in the chapter).

Severe invasive GAS infection is defined as the isolation of GAS from a normally sterile body site; it includes three overlapping clinical syndromes. Cellulitis and bacteremia are the most common GAS invasive diseases, each accounting for about 20% to 40% of invasive GAS disease in published epidemiologic reports. Clinically, cellulitis is characterized by the acute onset of redness and inflammation of the skin, with associated fever, pain, and swelling. GAS bacteremia often triggers a rapid and robust proinflammatory cytokine response that results in a high fever, nausea, and vomiting. Cellulitis and bacteremia also can be preludes to the more serious invasive disease complications of necrotizing fasciitis and STSS.

The GAS “flesh eating disease,” necrotizing fasciitis, is a devastating bacterial infection involving the skin, subcutaneous and deep soft tissues, and muscle. Necrotizing fasciitis involves rapid tissue growth and spread along the fascial sheaths that separate adjacent muscle groups, breach of the fascial sheaths, and necrosis of adjacent tissues. The pathogenesis of necrotizing fasciitis is complex and incompletely understood at the molecular level. However, the rapid tissue destruction and bacterial spread are thought to involve host and bacterial proteases (plasmin, SpeB), GAS pore-forming cytotoxins (e.g., SLO and SIS), and tissue-damaging enzymes released by host neutrophils in response to GAS cell wall components and superantigens. A major risk factor for the development of necrotizing fasciitis is blunt trauma, which is suggested to result in increased vimentin expression that tethers circulating GAS to the injured muscle. Primary varicella (chickenpox) in immunocompetent children is also a well-documented precipitating condition. Invasive GAS infections also can result in STSS, a “cytokine storm” produced in response to GAS superantigens that substantially increases the risk of death. GAS superantigens simultaneously engage major histocompatibility complex (MHC) class II molecules and T-cell receptor (TCR) B-chain variable regions, a molecular “bridging” that results in antigen-independent activation of large numbers of T lymphocytes. The resulting cytokine response by T lymphocytes (lymphotoxin-α, interleukin-2 [IL-2], interferon γ) and antigen-presenting cells (tumor necrosis factor [TNF]-α, IL-1β, IL-6) causes widespread organ dysfunction, disseminated intravascular thrombosis, and tissue injury. The result is an acute, rapidly progressive illness typified by high fever, rapid onset hypotension, and accelerated multisystem failure. The magnitude of the STSS inflammatory response is closely linked to the severity of the disease. The sites where superantigens bind to HLA class II molecules are polymorphic, and strong epidemiologic and genetic evidence indicates that the host’s MHC class II haplotype influences susceptibility to STSS. Specific criteria for the diagnosis of STSS have been established (Box 118.1).  

**Laboratory Findings and Diagnosis**

The clinical course of severe invasive GAS infections often is precipitous, requiring rapid diagnosis and initiation of the appropriate therapy. Although the initial clinical findings of STSS are nonspecific, a high index of suspicion is required, particularly in patients who have an increased risk (e.g., those with varicella). Pain out of proportion to superficial signs of infection can be a clue to underlying necrotizing fasciitis. Cultures of focal lesions are helpful in patients with skin or soft tissue involvement. Blood culture results can be positive in patients with sepsis without an apparent source of infection. A complete blood count can show a relatively normal total leukocyte count, with a marked left shift to immature forms. The patient’s blood pressure should be evaluated frequently. If necrotizing fasciitis is suspected, magnetic resonance imaging may be helpful in confirming the diagnosis; if the disease is present, histologic examination of excised tissue shows extensive necrosis, inflammation, hemorrhage, and thrombosis of small vessels.

**Box 118.1 Definition of Streptococcal Toxic Shock Syndrome**

**CLINICAL CRITERIA**
- Hypotension plus two or more of the following:
  - Renal impairment
  - Coagulopathy
  - Hepatic involvement
  - Acute respiratory distress syndrome
  - Generalized erythematous macular rash
  - Soft tissue necrosis

**DEFINITE CASE**
- Clinical criteria plus isolation of group A streptococci from a normally sterile site

**PROBABLE CASE**
- Clinical criteria plus isolation of group A streptococci from a nonsterile site


**Treatment**

The initial management of a child or an adolescent with a severe invasive GAS infection includes hemodynamic stabilization and specific antimicrobial therapy to eradicate the GAS. When necrotizing fasciitis is suspected, prompt surgical drainage, debridement, fasciotomy, or amputation often is required. Patients with necrotizing fasciitis also need careful fluid and nutritional support and may require extensive skin grafting or other reconstructive surgery, as well as physical therapy. Fluid resuscitation is begun urgently and administered frequently; multiple boluses of fluid are required because of severe volume depletion and ongoing capillary leakage. When fluid resuscitation alone is insufficient to maintain adequate tissue perfusion, inotropic agents (e.g., dobutamine, dopamine, norepinephrine) should be considered.

Parenteral antimicrobial therapy should include agents active against GAS and *Staphylococcus aureus* until the results of bacteriologic studies are available. Once GAS has been identified, intravenously administered penicillin G (200,000 to 400,000 U/kg/day in four to six divided doses) is the drug of choice. A mouse model of streptococcal myositis suggests that clindamycin may be more effective than penicillin in eradicating GAS in severe invasive infections. In addition, clindamycin inhibits protein synthesis and the production of important virulence factors (e.g., M protein, SPEs). Therefore, many experts recommend intravenously administered clindamycin (40 mg/kg/day in three or four divided doses) in addition to penicillin.

Several case reports have described the use of intravenous immunoglobulin (IVIG) therapy in patients with severe invasive GAS infections. An observational cohort study conducted in Canada reported significantly reduced mortality among patients treated with IVIG compared with those who were not treated with IVIG. However, this study had confounding factors that could have affected mortality data, including the use of historical controls and increased use of clindamycin among the patients treated with IVIG. A recent comparative observational study in Europe of 67 patients with streptococcal toxic shock syndrome suggested a therapeutic benefit of both IVIG (odds ratio, 5.6; P = 0.03) and clindamycin (odds ratio, 8.6; P = 0.007) with 28-day survival as the measured end point.

**Prevention**

The only specific indication for long-term use of antibiotics to prevent GAS infection is for patients with a history of ARF or rheumatic heart disease (RHD). Mass prophylaxis generally is not feasible except to reduce the number of infections during epidemics of impetigo and to control epidemics of pharyngitis in military populations and in schools. Measures to prevent the spread of GAS infections have variable effectiveness. The spread of throat or skin infection within a family often
occurs before the index case is identified and isolated or treated. In epidemic situations, especially when cases of ARF or PSSGN occur, a culture survey and treatment of all individuals with positive culture results (mass prophylaxis) may be necessary.

Case reports of clusters of invasive GAS infections within a chronic care facility or among members of a single household have been published. However, given the infrequency of these infections and the lack of a clearly effective chemoprophylactic regimen, the available data currently do not support a recommendation for routine testing for GAS colonization or for routine administration of chemoprophylaxis to otherwise healthy household contacts of people with invasive GAS disease. The Centers for Disease Control and Prevention recommend that healthcare providers inform household contacts of a person with invasive GAS disease about the clinical manifestations of pharyngitis and invasive GAS infections and emphasize the importance of seeking immediate medical attention if contacts develop such symptoms.35

Unfortunately, an effective vaccine to prevent GAS infection has yet to be developed. A major challenge is the great diversity of unique epitopes (more than 100) presented across GAS strains by the hypervariable N termini of the immunodominant surface M proteins. Another challenge is the data suggesting that GAS components, including the coated-coil of the M protein and the GcNac side chain on the cell wall's group A carbohydrate antigen, could elicit antibodies that cross-react with the host's muscle or neural tissues, thereby triggering ARF. Proactive and reverse vaccinology approaches have been used to explore conserved, surface-associated GAS protein antigens (e.g., pilus components, C5a peptidase, and fibrolysin-binding proteins) as potential universal GAS vaccine candidates. Two approaches have been tested in attempts to use the protective immunity of M protein without incurring the risks of molecular mimicry and autoimmune disease. One approach used a conserved, M protein-reactive, C-repeat region found in the cytoplasmic domain of the M protein proximal to the cell wall. In the other approach, molecular techniques have been used to engineer genetically a highly complex multivalent M protein-based vaccine (e.g., 26-variant containing a minimal B-lymphocyte epitope to optimize functional antibody responses.40] Because GAS disease is a major cause of health inequality affecting indigenous children in Australia and New Zealand, the governments of these two countries recently formed the Coalition to Advance New Vaccines for group A Streptococcus (CANSIS) to assess several candidates and to fast-track development of a vaccine most likely to be safe, efficacious, and cost effective.44

Complications

Supportive complications from the spread of GAS to adjacent structures were common before antibiotics became available. Cervical lymphadenitis, perinomillary abscess, retropharyngeal abscess, otitis media, mastoiditis, and sinusitis still occur in children in whom the primary illness has gone unnoted or treatment of pharyngitis has been inadequate. GAS pneumonia occurs occasionally. Nonsuppurative complications are considered in the following sections.

ACUTE RHEUMATIC FEVER

ARF is an inflammatory disorder that commonly involves the joints and heart (and less commonly the brain and skin). It can develop as a complication of an untreated GAS upper respiratory tract infection. The association between GAS and ARF was first postulated based on parallels in peak age (5 to 15 years) and seasonal (winter/spring) incidence, coupled with the observation that outbreaks of GAS pharyngitis in closed communities (e.g., boarding schools and military bases) could be followed by outbreaks of acute ARF. Subsequent serologic studies documenting anti-GAS antibodies in patients with ARF provided further evidence. Clinical studies showed that the antimicrobial therapy that eliminates GAS from the pharynx also prevents initial attacks of ARF, and that long-term, continuous prophylaxis that prevents GAS pharyngitis also prevents recurrences of ARF.

Epidemiology

The incidence of ARF has declined substantially over the past 8 decades in the U.S. and other developed countries, a decline that began even before the advent of penicillin. However, ARF remains a major public health burden in much of the developing world. Currently at least 15.6 million people worldwide have RHD and 282,906 new cases and 233,000 deaths annually are directly attributable to ARF or RHD.7

The incidence of ARF in some developing countries exceeds 50 per 100,000 children. Some of the highest incidence rates reported are in school-aged Pacific Islander children in New Zealand (80 to 100 per 100,000) and in aboriginal children in central and northern Australia (245 to 351 per 100,000).76 In contrast, the most recent ARF incidence data for an industrialized country, obtained from the nonindigenous population of New Zealand, shows a rate of less than 10 per 100,000 children. The prevalence of RHD in children aged 5 to 14 years is highest in sub-Saharan Africa (570 per 100,000), the Pacific Islander and indigenous populations of New Zealand and Australia (350 per 100,000), and south central Asia (220 per 100,000). In contrast, the prevalence in developed countries usually is about 50 per 100,000.68 A dramatic outbreak of acute ARF occurred in the area of Salt Lake City, Utah, beginning early in 1985; more than 200 cases occurred in the first 4 years. Other, smaller U.S. outbreaks have been reported in various communities and among recruits at military training centers, but these resurgences remained localized and did not lead to a nationwide increase in cases. The observation that only a few patients with GAS pharyngitis subsequently experience ARF suggests that specific characteristics of the organisms, the host, and the environment contribute to this complication. Although all the risk factors have yet to be identified, certain potential factors have been described. Experts have long suspected that various strains of GAS differ in the likelihood of subsequent ARF, and a limited number of M serotypes have been linked epidemiologically to outbreaks of ARF. Strains of certain rheumatogenic serotypes (e.g., types 1, 3, 5, 6, and 18), which were isolated infrequently during the 1970s and early 1980s, reappeared dramatically as causes of pharyngitis during the localized outbreaks of ARF in the mid-1980s. The marked decrease in ARF in the U.S. in recent decades has been correlated with replacement of rheumatogenic types by nonrheumatogenic types in childhood acute streptococcal pharyngitis.74

A genetic predisposition to ARF appears to factor.71 Studies in twins have shown a higher concordance rate of ARF in monozygotic than in dizygotic twin pairs. Associations between susceptibility to ARF and HLA class II alleles, the B-lymphocyte alloantigen DR/17, or certain single-nucleotide polymorphisms for TNF-alpha or mannose-binding lectin genes are under investigation; however, such an association has not been noted consistently in various populations. In one highly defined group with mitral valve disease, the collected data suggested that DRB1*0701, DR6, and DQB1*0201 confer susceptibility to ARF.72

Pathogenesis

The pathogenic link between a GAS infection of the upper respiratory tract and an episode of ARF has not yet been established definitively. Most attention has focused on the concept of autoimmune based on molecular mimicry. This theory is supported by the latent period between GAS infection and ARF and by the observations of antigenic similarity between molecular constituents of GAS and several human tissues, including the heart, synovial, and basal ganglia. The sera of patients with ARF contain heart-reactive or myosin-reactive antibodies, frequently in high titers.73 Studies of anti-GAS/anti-heart monoclonal antibodies from RHD have revealed that cardiac myosin, and GcNac, the immunodominant epitope of the group A carbohydrate antigen, are likely cross-reactive antigens involved in antibody deposition on the valve.74 Early work had demonstrated the persistence of increased levels of anti-group A carbohydrate antibody in RHD and an association with a poor prognosis.75 More recently, human T-lymphocyte clones also have confirmed cross-reactivity between cardiac myosin sequences and GAS M proteins.76 Strikingly, immunization with purified recombinant GAS M protein is sufficient to induce autoimmune valvular heart disease in rats.77

Clinical Features

Because no single clinical or laboratory finding is pathognomonic for ARF, in 1944 T. Dukett notes proposed guidelines to aid diagnosis of the disease and to limit overdiagnosis. The Jones criteria, as revised in
BOX 118.2 Jones Criteria for Diagnosis of First Episode of Acute Rheumatic Fever

**DIAGNOSIS**

Diagnosis of acute rheumatic fever requires two major criteria or one major and two minor criteria, plus supporting evidence of antecedent group A streptococcal infection.

**MAJOR CRITERIA**

Carditis
Polyarthritis
Chorea
Erythema marginatum
Subcutaneous nodules

**MINOR CRITERIA**

Clinical findings: Fever, arthralgia
Laboratory findings: Elevated acute phase reactants (erythrocyte sedimentation rate or C-reactive protein); prolonged PR interval

**EVIDENCE SUPPORTING AN ANTECEDENT GROUP A STREPTOCOCCAL INFECTION**

Positive throat culture or rapid antigen test for group A streptococcus
Or
Elevated or rising streptococcal antibody titer (e.g., antistreptolysin O, anti-DNase B)

1992 by the American Heart Association (Box 118.2), provide major criteria and minor criteria, in addition to the requirement for evidence (microbiologic or serologic) of recent GAS infection. The diagnosis of ARF is established according to the Jones criteria when a case fulfills two major criteria or one major plus two minor criteria and meets the absolute requirement of proof of antecedent GAS infection. Nonetheless, ARF can be overdiagnosed even with strict application of the Jones criteria.

Under two circumstances the diagnosis of ARF can be made without strict adherence to the Jones criteria. Chorea may be the only manifestation of ARF. Similarly, indolent carditis may be the only manifestation in patients who first come to medical attention months after onset.

**Minor Manifestations**

The two minor clinical manifestations included in the 1992 revised Jones criteria are (1) arthritis in the absence of the major criterion polyarthritis and (2) fever, typically 38.9°C or higher, that occurs early in the course of the illness. Two minor laboratory manifestations are (1) elevations of acute phase reactants, such as C-reactive protein and/or the erythrocyte sedimentation rate (which is usually >50 mm/hour); and (2) a prolonged PR interval on an electrocardiogram (first-degree heart block). Prospective studies have demonstrated that a prolonged PR interval alone does not constitute evidence of carditis nor predict long-term cardiac sequelae.

**Evidence of Recent Streptococcal Infection**

Supporting evidence of a recent GAS infection is an absolute requirement for the diagnosis of ARF, except with isolated Sydenham chorea. Because ARF develops 2 to 4 weeks after acute GAS pharyngitis, clinical signs of pharyngitis are no longer present, and the throat culture or rapid GAS antigen test result is positive in only 10% to 20% of cases. One third of patients recall no history of previous pharyngitis. Elevated or rising serum antistreptococcal antibody titer are the most reliable basis for diagnosis. If only the ASO level is measured, elevated titers (greater than 500 Told units) are found in 80% to 85% of patients with ARF; 95% to 100% of such patients are identified if two additional antibody levels (e.g., anti-DNase B, antistreptokinase or antihyaluronidase) are measured.

**Differential Diagnosis**

The differential diagnosis of ARF includes many infectious and noninfectious conditions associated with mononuclear or polyarticular arthritis (Table 118.1). Children with juvenile idiopathic arthritis (JIA) tend to be younger and usually have less joint pain relative to their clinical findings that do those with ARF. Spiking fevers, lymphadenopathy, and splenomegaly are more suggestive of JIA. The response to salicylate therapy is
much less dramatic in JIA. Systemic lupus erythematosus (SLE) usually can be distinguished by the presence of antinuclear antibodies.

When carditis is the sole major manifestation of ARF, viral myocarditis, viral pericarditis, Kawasaki disease, and infective endocarditis should be considered. In general, the absence of a significant cardiac murmur excludes the diagnosis of ARF. Echocardiography can distinguish functional murmurs from murmurs caused by congenital heart defects. Patients with infective endocarditis can present with both joint and cardiac manifestations: usually positive blood culture results or associated findings (e.g., hematuria, splenomegaly, splinter hemorrhages) distinguish endocarditis.

**Treatment**

The management of ARF involves antibiotic and anti-inflammatory therapy, symptomatic treatment, and interventions to prevent future GAS infections. When the diagnosis of ARF has been established, a single intramuscular injection of benzathine penicillin G or 10 days of orally administered penicillin or amoxicillin (or a macrolide, in penicillin allergy) is administered to eradicate GAS from the upper respiratory tract, regardless of the throat culture results. For patients who have definite arthritis and those who have carditis without cardiomegaly or congestive heart failure, salicylate therapy (50 to 75 mg/kg/day) should be given for 2 to 4 weeks, then tapered over the next 4 to 6 weeks. The response of ARF arthritis to salicylates is characteristically dramatic; no evidence indicates that other NSAIDs are superior. Patients with carditis and cardiomegaly or congestive heart failure often are prescribed corticosteroid therapy (e.g., 2 mg/kg/day for 2 weeks, with slow taper); a recent meta-analysis suggests that compared with aspirin alone, corticosteroids (or IGV) reduce the risk of heart valve lesions in patients with ARF. Supportive therapies for moderate to severe carditis include oxygen, fluid and salt restriction, diuretics, and angiotensin-converting enzyme inhibitors or digoxin. Bed rest for 2 weeks to 4 months, depending on the degree of carditis, usually is recommended. Because Systenhan chorea often occurs as an isolated manifestation following several courses of ARF, anti-inflammatory agents usually are not indicated. Patients may benefit from rest, limitation of external stimuli, and therapy with phenobarbital, haloperidol, or chlorpromazine as guided by a pediatric neurologist.

**Secondary Prevention and Prognosis**

Because ARF frequently recurs with subsequent GAS infections, secondary prevention is required to avoid recurrences that increase the likelihood and severity of RHD. Secondary prevention requires continuous antibiotic prophylaxis, which should begin immediately after the full course of antibiotic therapy has been completed. Patients with carditis during the initial episode of ARF should receive antibiotic prophylaxis well into adulthood and perhaps for life. Other patients have a relatively low risk of carditis with recurrences, and antibiotic prophylaxis can be discontinued in these patients after 5 years or when they reach the age of 21 (whichever is later). The decision to discontinue antibiotic prophylaxis should be made only after careful consideration of the potential risks and benefits and the epidemiologic factors, such as the risk of exposure to GAS infections.

The regimen of choice for secondary prevention is a single injection of 1.2 million units of benzathine penicillin G every 4 weeks (Table 118.2). Continuous oral antimicrobial prophylaxis can be used in patients likely to adhere to the regimen. Prophylaxis using penicillin given twice daily or sulfadiazine given once daily is equally effective.

The prognosis for patients with ARF depends on the number and severity of clinical manifestations during the initial episode and whether recurrences were allowed to develop. In the absence of recurrent GAS infections, rheumatic fever does not reappear more than 8 weeks after the withdrawal of anti-inflammatory therapy. Approximately 70% of patients with carditis during the initial episode of ARF recover with no residual heart disease if they follow a prophylaxis regimen.

**ACUTE GLOMERULONEPHRITIS**

**Epidemiology**

PSAGN was described by Richard Bright in 1836 as hematuria after scarlet fever. Unlike ARF, PSAGN occurs as a consequence of either GAS pharyngitis or pyoderma. PSAGN is primarily a disease of preschool and school-aged children; approximately 60% of patients are between 2 and 12 years of age. The actual incidence of PSAGN is difficult to determine because many cases are asymptomatic; however, PSAGN is by far the most common form of glomerulonephritis and acute renal insufficiency in children. Certain M types of GAS associated with pharyngitis (e.g., M1, M2, M3, M4, M12, and M15), in addition to certain M types associated with pyoderma (e.g., M49, M52, M55, M59, M60, and M61), are commonly associated with PSAGN and therefore are considered nephritogenic. However, not all strains of a given M type are nephritogenic. Although PSAGN most often is a sporadic disease, it also can occur in epidemic forms. Concomitant presence of ARF and PSAGN is unusual in a population and rare in a patient.

**Pathogenesis and Pathology**

Although the pathogenic link between GAS infections and PSAGN has been clearly established, the mechanisms of renal injury have not been completely defined. However, considerable evidence suggests that PSAGN occurs when soluble immunoglobulin G immune complexes are deposited at the glomerular basement membrane, activating complement and the release of chemotactic factors that lead to infiltration by inflammatory cells. Whether the antigen in these complexes is a GAS antigen or a host-derived antigen that cross-reacts with antistreptococcal antibodies is not clear. Candidate GAS antigens for this process include glycolaldehyde-3-phosphate dehydrogenase (also known as “nephritogenic-associated” streptococcal plasmin receptor) and cysteine protease SplR. Because these proteins are present in virtually all strains of GAS,
BOX 118.3 Signs and Symptoms of Poststreptococcal Acute Glomerulonephritis (PSGN)

COMMON FINDINGS
Hematuria (microscopic or macroscopic)
Edema
Hypertension
Oliguria

VARIABLE FINDINGS
Systemic symptoms (fever, nausea, anorexia, lethargy, abdominal pain)

UNCOMMON FINDINGS
Hypertensive encephalopathy (vomiting, headache, confusion, somnolence, seizures)
Anuria and renal failure
Congestive heart failure

additional host factors are suspected to influence susceptibility, but studies of HLA antigen distribution have failed to identify a specific association with PSGN.\(^\text{33}\)

Although renal biopsy is rarely indicated for patients with PSGN, biopsy can be helpful if hypertension, hematuria, or oliguria, or renal insufficiency persists. The glomerular lesions of PSGN can be proliferative, exudative, or both, especially when the basement membrane is involved diffusely. Electron microscopy reveals deposits consisting of immunoglobulin G and complement component C3, which are found in a subepithelial location during the first 3 to 6 weeks of the disease; the basement membrane usually appears normal.

Clinical Features
PSGN typically occurs about 10 days after the onset of GAS pharyngitis or 3 weeks after the onset of GAS pyoderma. Edema (often periorbital) and hematuria are the clinical findings that usually bring patients with PSGN to medical attention (Box 118.3). Approximately 30% to 50% of children with PSGN have gross hematuria, which is usually described as “cola-colored” urine. Gross hematuria can persist for as little as a few hours or for as long as 2 weeks.

Approximately 50% to 90% of children with PSGN have hypertension. The severity of hypertension is highly variable, but systolic pressures greater than 100 mm Hg and diastolic pressures greater than 120 mm Hg are not unusual. Most children with PSGN also have evidence of circulatory congestion from the expansion of the intravascular fluid volume. Dyspnea, orthopnea, cough, or pulmonary rales may be present. Children with PSGN also have systemic symptoms such as lethargy, anorexia, fever, and abdominal pain, but they seldom appear extremely ill. Occasionally, a fulminant course can evolve, marked by severe oliguria, congestive heart failure, or hypertensive encephalopathy. Rare occurrences of reversible posterior leukoencephalopathy or autoimmune hemolytic anemia have been described.\(^\text{33}\)

Laboratory Findings
Virtually all children with PSGN have microscopic hematuria, and 30% to 50% have gross hematuria. Evaluation of the urine shows pyuria and hyaline, granular, and red blood cell casts. Most children have proteinuria, and approximately 30% are in the nephrotic range, with protein loss greater than 2 g/m² per 24 hours.

During the initial 2 weeks of PSGN, total hemolytic complement activity and C3 levels are depressed in almost all children. About one third of patients have modest elevations of blood urea nitrogen and creatinine. During the first week of PSGN, elevations of circulating immune complexes are seen in most patients, and the quantity of these immune complexes correlates with the severity of the PSGN. Patients with moderate to severe impairment of renal function can demonstrate metabolic acidosis, hyperkalemia, hyperchloremia, hyponatremia, hyperalbuminemia, or dilutional anemia. The best evidence of antecedent streptococcal infection is serologic: 90% to 95% of patients have elevations of ASO and/or anti-DNase B.

Although antibiotic therapy does not affect the clinical course of PSGN, therapy can eradicate the nephritogenic GAS strain that may still be present and thus reduce the risk of transmission to others. Penicillin is the antibiotic of choice for children allergic to penicillin. No immunosuppressants or antiinflammatory therapeutic agent has been shown to accelerate the resolution of renal lesions. Treatment usually consists primarily of supportive measures directed at complications of the disease. Occasionally the associated hypertension is so severe as to cause encephalopathy. Circulatory congestion can be severe and can lead to pulmonary edema and congestive heart failure. Although oliguria often is seen in children with PSGN, anuria and renal failure are uncommon. Overall, the prognosis is favorable. More than 95% of patients with PSGN recover completely without interventions to reduce the severity of the acute episode.\(^\text{34}\)

Prevention
In contrast to ARF, which can be prevented with antibiotic therapy of the antecedent GAS infection, no evidence indicates that PSGN can be prevented once pharyngitis or pyoderma with a nephritogenic strain of GAS has occurred. Antibiotic treatment is given to limit transmission. During outbreaks of GAS pyoderma caused by nephritogenic strains, prophylactic administration of penicillin to children at risk may be beneficial.\(^\text{35}\) Because recurrences of PSGN are rare, long-term antibiotic prophylaxis after an episode is not indicated.

PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDERS ASSOCIATED WITH STREPTOCOCCAL INFECTIONS

In 1998 investigators described a series of 50 patients with childhood onset obsessive-compulsive disorder (OCD) and tic disorders and suggested that these could arise as a result of a poststreptococcal autoimmune process.\(^\text{36}\) The investigators coined the acronym PANDAS to denote pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. They proposed that, in response to GAS infection, this subset of patients with OCD and tic disorders produced autoimmune antibodies that cross-reacted with neuronal tissues in the basal ganglia and associated structures, reminiscent of the autoimmune response implicated in similar clinical manifestations of certain patients with ARF and Sydenham's chorea. Recently two prospective, blinded, multicenter cohort studies of matched pairs found no evidence of a temporal association between GAS infection and OCD/tic symptoms in children who met the published diagnostic criteria for PANDAS.\(^\text{37,38}\) In another study, no correlation was seen between clinical exacerbations of these patients and serum antibodies cross-reactive with brain tissue.\(^\text{39}\) In light of these findings, experts favor a broader concept (i.e., childhood acute neuropsychiatric symptoms [CANS]) and a broader treatment approach.\(^\text{40}\)

Inaccurate diagnosis and treatment of PANDAS is widespread in the pediatric medicine community, and new classification schemes can help delineate the risks for this particular subtype of OCD or tic disorder. Current data indicate that although PANDAS remains a hypothesis (perhaps applicable to a very select subset of patients), complicated interventions such as immune globulin or plasmapheresis may not be warranted.\(^\text{41,42}\)

POSTSTREPTOCOCCAL REACTIVE ARTHRITIS

PSRA describes an entity in patients who had arthritis after an episode of GAS pharyngitis but lacked other major criteria for ARF. ARF peaks in early childhood (4 to 9 years), but PSRA has a bimodal distribution, with a first peak at 8 to 14 years and a second peak in early adulthood.\(^\text{43}\) The arthritis of ARF classically develops 14 to 21 days after an episode of GAS pharyngitis and responds rapidly to NSAID therapy, whereas PSRA occurs about 10 days after GAS pharyngitis and does not respond readily
Key Points: Group A Streptococcus and Clinical Syndromes

EPIDEMIOLOGY, PATHOGENESIS, AND IMMUNITY
- More than 800 million cases of pharyngitis and more than 100 million cases of pyoderma annually worldwide.
- Rheumatic heart disease affects 15.8 million people worldwide.
- Infections can be severe and of short duration or rapidly invasive and fulminating.
- Unique among pyogenic bacteria in causing postinfectious, immunologically mediated diseases (acute rheumatic fever, acute glomerulonephritis).
- More than 100 distinct M-protein genotypes identified, which tend to be associated with infectious and nonsuppurative syndromes.
- Genome sequencing shows that bacteriophages have been important in organism’s evolutionary genetics (e.g., virulence elements, and toxins).
- Pathogenesis of serious disease can occur by three mechanisms: suppurative, toxin elaboration, and immune-mediated inflammation.
- Expression of multiple specific virulence factors can lead to evasion of the patient’s innate clearance response, uncontrollable proinflammatory response, damage to phagocytic cells, acceleration of apoptosis of immune cells, inactivation of terminal complement components, superantigen-induced T-lymphocyte activation, and more.
- Opsonic anti-M-protein antibodies rise 6 to 8 weeks after infection and protect against M type–specific invasive infection.

CLINICAL MANIFESTATIONS
- Causes a wide spectrum of simple and complicated oropharyngeal and respiratory tract infections, skin and soft tissue infections, invasive infections, and toxin-mediated syndromes.
- Necrotizing cellulitis, myositis, and fasciitis can be suspected when a seemingly minor skin or soft tissue infection is associated with disproportionate pain, hyperesthesia or hypoesthesia, local pallor, tenseness, and a blistering lesion.
- Proven cause of nonsuppurative acute rheumatic fever and acute glomerulonephritis (see text).

TREATMENT OF SUPPURATIVE INFECTIONS
- Penicillin retains exquisite activity in vitro; no resistance to β-lactam antibiotics has been seen.
- Clindamycin usually is given in addition to a β-lactam for severe invasive or toxin-mediated disease to overcome the “Eagle effect” (loss of bactericidal capacity of β-lactam at a high density of bacteria/stationary growth phase) and to inhibit protein synthesis and virulence factors.
- Immune globulin intravenous (IGIV) therapy is reserved for severely ill patients with toxic shock syndrome.

PREVENTION
- Vaccine development has been thwarted by the hypervariability and diversity of surface M proteins and by potential immunologic responses that might cross-react with cardiac or neural tissue.
- Novel approaches explore the use of conserved or genetically engineered surface proteins.