

Group A Streptococcal Toxic Shock Syndrome

Classification and structure

Streptococcus pyogenes (group A streptococcus) is one of the most important bacterial pathogens in humans. All group A streptococci are beta-hemolytic, with certain strains producing toxins capable of causing streptococcal toxic shock-like syndrome (STSLS) or scarlet fever, while other strains produce less severe diseases such as rheumatic fever or post-streptococcal glomerulonephritis. Group A streptococcal (GAS) organisms are gram-positive, catalase-negative, and facultatively anaerobic. In clinical specimens, they occur as short and long chains on Gram stain. They are nutritionally fastidious and are usually cultivated in complex media, often supplemented with blood or serum. When cultured on sheep blood-agar plates, *S. pyogenes* appears as white to gray colonies surrounded by zones of complete (β) hemolysis.

The cell wall of *S. pyogenes* is a complex structure containing many different antigenic substances. It is enveloped in a non-immunogenic, hyaluronic acid capsule that facilitates cell invasion and retards phagocytosis by polymorphonuclear leukocytes (PMN) and macrophages of the host.^{1,2} The serogroup-specific carbohydrate of group A strains is a dimer of rhamnose and N-acetylglucosamine. The M protein is a cell wall surface protein as well as the major virulence factor of group A streptococci. Strains rich in this protein are resistant to phagocytosis by PMN and capable of initiating disease. Group A streptococci are divided into serotypes on the basis of antigenic differences in M-protein molecules as well as nucleotide differences in the *emm* gene encoding the molecule.³ Acquired human immunity to streptococcal infections is based on the development of antibodies directed against the antiphagocytic moiety of M protein. M proteins analogous to those of group A streptococci are present in many strains of groups C and G streptococci.^{4,5} Non-M-typeable strains may frequently be identified by a subsidiary typing system using slide agglutination reactions and based on the antigenic differences in T proteins. Although the T protein has proved to be a useful epidemiologic marker, it has no known role in streptococcal virulence.

In addition to its somatic constituents, group A streptococci elaborate numerous extracellular products, including DNases, streptolysin O and S, hyaluronidase, streptokinase, and streptococcal pyrogenic exotoxins which are responsible for the rash of scarlet fever.

Historical perspective

GAS causes a variety of illnesses ranging from very common and mild conditions such as pharyngitis and soft tissue infections (impetigo and cellulitis), to less common but severe invasive infections including scarlet fever, septicemia, pneumonia, meningitis, puerperal sepsis, and necrotizing fasciitis. Beginning as early as 1515, descriptions of epidemic pharyngitis with or without scarlatinal symptoms appeared in European medical literature.⁶ In the 1700s, scarlet fever was extensively documented throughout Europe. It probably arrived in North America in about 1735, allegedly first noted in Massachusetts at the same time as a highly fatal diphtheria epidemic. The scarlet fever pandemic of 1825-1885 killed hundreds of thousands in Europe and North America, with 25-30% mortality rate in children who were afflicted by this disease. By the mid-1950s, GAS infections were considered fairly mild with mortality rate dropping to under 2%.

However, in 1987, a report was published describing two patients in the U.S. with aggressive group A streptococcal infections having clinical features of shock similar to the staphylococcal toxic shock syndrome described a decade earlier.⁷ This syndrome was further characterized in a subsequent report describing 20 patients, most were younger than 50 years old and otherwise healthy, who had invasive group

A streptococcal infections. Shock, multi-organ system involvement, and rapidly destructive soft-tissue infection were the predominant clinical findings.⁸ In this series, the case-fatality rate was 30% even though most patients received appropriate antibiotics, supportive care and, where necessary, surgical debridement. Between 1981 and 1993, additional cases of the streptococcal toxic shock-like syndrome were reported in the U.S., Europe, Canada, Japan.^{9, 10, 11, 12} In addition, outbreaks of invasive group A streptococcal infections were reported in closed environments such as nursing homes and hospital environments. Secondary cases of STSS are rare, but transmission to family members or health care workers has been documented.^{13,14,15} At that time, this dramatic clinical presentation was one not typically associated with group A streptococcal infections or bacteremia. The striking difference was that these patients had early onset of shock and organ failure, with some exhibiting no apparent site of infection at presentation. In a retrospective population-based study surveying hospitals in Pima County, Arizona, a toxic shock-like syndrome occurred in 8% of GAS infections from 1988-1990, compared with none of the infections between 1985-1987.¹⁶ This further signaled a shift in the epidemiology of GAS infections and the emergence of streptococcal toxic shock syndrome (STSS).

In recognition of a worldwide increase in the occurrence of severe group A streptococcal infections and the streptococcal toxic shock-like syndrome, a consensus definition and diagnostic criteria were formulated in 1993.¹⁷

Table 1. Proposed Case Definition for the Streptococcal Toxic Shock Syndrome

<p>I. Isolation of group A streptococci (<i>Streptococcus pyogenes</i>)</p> <p>A. From a normally sterile site (e.g. blood, cerebrospinal, pleural, or peritoneal fluid, tissue biopsy, surgical wound, etc.)</p> <p>B. From a nonsterile site (e.g., throat, sputum, vagina, superficial skin lesion, etc.)</p> <p>II. Clinical signs of severity</p> <p>A. Hypotension: systolic blood pressure \leq 90 mm Hg in adults or $<5^{\text{th}}$ percentile for age in children</p> <p style="text-align: center;">AND</p> <p>B. ≥ 2 of the following signs:</p> <ol style="list-style-type: none"> 1. Renal impairment: creatinine $>2\text{mg/dL}$ for adults or greater than or equal to twice the upper limit of normal for age 2. Coagulopathy: platelets $<100,000/\text{mm}^3$ or DIC defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products 3. Liver involvement: transaminases or total bilirubin levels $>$ twice the upper limit of normal 4. ARDS defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in the absence of cardiac failure, or evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia 5. A generalized erythematous macular rash that may desquamate 6. Soft-tissue necrosis, including necrotizing fasciitis or myositis or gangrene
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Clinical manifestations

Most invasive GAS and STSS infections are community-acquired. Persons of all ages may be afflicted with STSS and most are not immunosuppressed, although some have diabetes and alcoholism. This is in sharp contrast to the previous reports of GAS bacteremia in which most patients were either less than 10 or greater than 60 years of age and had underlying diseases such as cancer, renal failure, leukemia, and severe burns, or were receiving corticosteroids or other immunosuppressive drugs.^{18,19,20,21} Primary varicella is a major risk factor for fulminant GAS infection in children, while exposure to children with sore throats, minor trauma, surgical procedures, childbirth, diabetes, cardiac disease, malignancy, and intravenous drug abuse are definable risk factors in adults.²² Nonsteroidal anti-inflammatory agents, taken for muscle strain, trauma, or chickenpox may mask the early signs and symptoms of streptococcal infection.²³ But various

studies in last few years did not find that NSAID use increased the risk of more severe infections such as necrotizing fasciitis or STSS.^{21,24}

The initial site of streptococcal infection cannot be ascertained in 45% of cases⁷, but the most common portals of entry are the skin, vagina or pharynx. In the remaining cases, pneumonia, meningitis, and joint infection have been described.²⁵ Twenty percent of patients have an influenza-like syndrome characterized by fever, chills, myalgia, and diarrhea that precedes hypotension by 24 to 48 hours. In phase 1 of STSS, confusion or combativeness is reported in 55% of patients on presentation. In patients who have associated necrotizing fasciitis, postpartum infection, or myositis, progressive pain is the most common initial symptom and usually precedes any localized evidence of infection. A diffuse, scarlatina-like erythema occurs in about 10% of patients, in contrast to those afflicted by staphylococcal toxic shock syndrome who uniformly have a rash. Phase 2 of STSS is characterized by fever (70-80%), tachycardia (80%), hypotension (35-65%), and pain if necrotizing fasciitis or myositis are present (44-85%). In phase 3 of STSS, renal failure is common (80%) with ARDS occurring in 60% of these patients.⁷ The progression of necrotizing fasciitis from normal-appearing skin to purple bullae in modern times may take place within a 24-hour period of time, whereas that described by Meleney in 1924 took 7 to 10 days.²⁶

Pneumonia due to *S. pyogenes* is frequently associated with preceding viral infections such as influenza, measles, or varicella or with chronic pulmonary disease. Numerous epidemics have been described in military recruit populations.²⁷ The onset is typically abrupt and characterized by chills, fever, dyspnea, productive cough, and pleuritic chest pain. The pulmonary picture is that of bronchopneumonia with consolidation being uncommon. Pleural effusion develops early in 30 to 40% of the cases and typically consists of copious amounts of thin serosanguineous fluid. Complications include mediastinitis, pericarditis, pneumothorax, and bronchiectasis. Mortality is low with penicillin therapy and adequate drainage of empyema, but the clinical course of the disease is often prolonged.

Laboratory tests are useful because they show evidence of renal impairment even before hypotension is apparent in 40-50% of STSS cases.⁵⁹ Creatine phosphokinase levels in serum are markedly elevated in those with necrotizing fasciitis and myonecrosis. The white blood count is usually normal or elevated at admission but with a profound left shift. Bacteremia is documented in 60% of the cases, compared to rarity of positive blood cultures in staphylococcal toxic shock syndrome. Blood cultures are positive in only 60% of cases. Finally, serum albumin and calcium levels are usually low on admission and drop precipitously as a diffuse capillary leak syndrome develops and can be associated with higher mortality.²⁸

Pathogenesis

Unlike most cases of staphylococcal toxic shock syndrome, the organisms must invade tissue and/or the bloodstream in streptococcal TSS. The M protein contributes to invasiveness through its ability to impede phagocytosis and inhibit activation of the alternate complement pathway on the cell surface.^{2,3,29} Following infection with a particular M type of GAS, specific antibody confers resistance to challenge with viable GAS of that M type. The entry of group A streptococci into the deeper tissues and blood stream may occur as a result of a breach of a barrier, or the organism itself may penetrate intact mucous membranes such as the pharyngeal mucosa. Within the deeper tissue and blood stream, the induction of cytokine synthesis by various virulence proteins plays a critically important role in the production of shock and organ failure. Among the extracellular virulence factors that have been isolated are pyrogenic exotoxins such as streptococcal pyrogenic exotoxins A, B, C (SPEA, SPEB, SPEC), mitogenic factor (MF or SPEF), streptococcal mitogenic exotoxin (SME) and streptococcal superantigen (SSa).^{30,31}

One of the proposed mechanisms whereby these virulence factor cause shock is that the streptococcal toxins and streptolysins O, are potent inducers of the cytokines tumor necrosis factor (TNF)- α and interleukin (IL)-1 and -6.^{32,33} TNF- α secreted primarily by monocytes and macrophages has been implicated as a pivotal mediator in the shock associated with staphylococcal and streptococcal TSS.^{34,35,79} It is thought to cause fever, increase host susceptibility to exogenous endotoxin and suppress IgM synthesis.^{36,37} In addition, similar to the staphylococcal toxic shock toxin and enterotoxins, streptococcal exotoxins as well as M proteins are also thought to act as superantigens, in that they bind to the V β region

of T-cell receptor outside of antigen recognition site and join it to MHC class II molecules of antigen-presenting cells without the usual requirement of antigen processing by phagocytic cells.^{38,39,40,41} Superantigens induce proliferation in 5 to 20% of T cells, compared to activation of 0.001% T-cells via the conventional antigen presentation pathway. As a result, this nonspecific interaction between the STSS superantigens and host immunity induces activation of large numbers of T cells, leading to release of large quantities of cytokines, such as IL-2, TNF- α and β , IFN- γ , IL-1, and IL-6. In addition, non-cytokine mechanisms of shock may also play a role. SPEB is a cysteine protease and releases bradykinin from kininogen, resulting in vasodilation of the systemic and pulmonary vasculature.⁴²

Seminal studies published early on during the resurgence of invasive GAS infections characterized the serotypes and pyrogenic exotoxins of available isolates from patients with STSS. The authors found that M-types 1 and 3 were most common and that 80% of these isolates produced pyrogenic exotoxin A and/or exotoxin B which were associated with shock, rash, and organ system involvement.^{7,43,44} The predominant prevalence of M types 1 and 3 as well as types 12 and 28 in GAS strains associated with STSS has since been documented in subsequent studies.^{45,46} However, whether the M1 strains have higher invasive potential than other serotypes is still being debated, since most of available data is based on referred strains that can be subject to bias. It is possible that the prevalence of a particular GAS serotype in invasive infections may largely represent the general spread of that serotype in a population.⁴⁷ Moreover, considerable genetic variability has been demonstrated among strains causing STSS.⁴⁸

Antimicrobial therapy for invasive GAS infection

S. pyogenes remains uniformly susceptible to beta-lactam antibiotics. Penicillin has been shown to be efficacious in treating soft tissue infections such as erysipelas, impetigo, cellulitis, and in preventing the development of rheumatic fever following streptococcal pharyngitis.⁴⁹ However, in aggressive GAS infections such as STSS, necrotizing fasciitis, myositis, and empyema, the mortality rate ranges from 30-85% despite penicillin therapy.⁵⁰ In a mouse model of myositis caused by *S. pyogenes*, penicillin was ineffective when treatment was delayed >2 hours after initiation of infection. Survival of erythromycin-treated mice was greater than penicillin-treated mice, but only if treatment was begun within 2 hours. However, mice receiving clindamycin had survival rates of 70-100%, even if treatment was delayed. In fact, several studies in experimental models suggest that penicillin becomes less effective when large numbers of organisms are present or when they are making the transition from the logarithmic to the stationary phase of growth, the so-called Eagle effect.^{51,52} This is attributed to the decrease in the production of penicillin-binding proteins through which penicillin mediates its antibacterial action against GAS in stationary cells relative to cells in the logarithmic phase of growth.⁵³

The use of clindamycin, a protein synthesis inhibitor via 50S ribosome, in the treatment of STSS was initially based on efficacy studies in animal models and *in vitro* suppression of bacterial toxins. It has several advantages over penicillin in that its efficacy is not affected by inoculum size or stage of growth and has a longer effect than beta-lactams. In addition, clindamycin suppresses the synthesis of bacterial exotoxins, antiphagocytic M-protein, and tumor necrosis factor.^{54,55} These findings were recently validated clinically by a retrospective analysis demonstrating clindamycin use was associated with better outcomes than beta-lactam antibiotics in pediatric patients with STSS.⁵⁶ Based on these data, it is reasonable to treat STSS with clindamycin alone given that fewer than 0.1% of isolates of GAS in the US are resistant to clindamycin. However, the current standard of practice is to use clindamycin in conjunction with penicillin in treating STSS.

Historically, in penicillin-allergic patients, erythromycin is the therapy of choice for treatment of GAS infections. However, rates of erythromycin resistance in excess of 5% have been reported in certain areas, such as U.S., Canada, Japan, Finland, Australia and Great Britain.^{57,58,59} In these instances, erythromycin resistance has been correlated with increased erythromycin usage. In areas where resistance to erythromycin is known to be prevalent, antimicrobial-susceptibility testing should be performed if this agent or the newer macrolides are used to treat group A streptococcal infections.

Intravenous immunoglobulin in streptococcal toxic shock syndrome

Given the high mortality and morbidity rate of 30-70% associated with STSS despite appropriate antimicrobial therapy, the search for novel therapies has focused on modulating the inflammatory response elicited by GAS virulence factors. It has been hypothesized that only those individuals who lack neutralizing antibodies to the major streptococcal virulence factors, such as the SPEs and M-protein, develop invasive GAS infection and STSS.⁶⁰ Supporting this concept are studies that demonstrated that patients with bacteremia and STSS did indeed lack antibodies against SPEB.⁶¹ Furthermore, a European group found that sera from patients with group A streptococcal bacteremia had lower titers of neutralizing antibodies against various SPE than did patients with tonsillitis.⁶² Therefore, passive immunization given to patients lacking neutralizing antibody to virulence factors should modify the course of toxin-mediated disease. This was demonstrated in 1925 when the course of scarlet fever was attenuated by convalescent serum from patients with scarlet fever, suggesting the presence of neutralizing antibodies to scarlet fever toxin.⁶³ Other possible therapeutic effects of immunoglobulins include nonspecific inhibition of immune system by interactions with complement, superantigens, monocytes, reticuloendothelial system, T-cell receptors, MHC II molecules, as well as promotion of phagocytosis of organisms by granulocytes.^{64, 65}

Commercially available pooled preparations of intravenous human gamma globulin (IVIG) have been shown in some studies to contain neutralizing antibodies against a variety of streptococcal superantigens as well as the ability to block the induction of inflammatory cytokines.^{66, 67, 68} However, it is of note that a study in 1998 found significant differences in the neutralizing activities against SPE between 5 different IVIG preparations.⁶⁹

In terms of clinical data supporting the use of IVIG in STSS, there are various case reports describing improvements in clinical outcomes in STSS from 1992 to 1999.^{70, 71, 72, 73, 74, 75, 76} More notably, there are three larger clinical series that support use of IVIG. The first was published by a group in Sweden reporting use of IVIG on 4 out of 11 patients with serious GAS infection. Three of 4 patients survived compared to none of the untreated patients.⁷⁷ However, it was difficult to assess the utility of specific interventions in these cases since other interventions were given to some patients, including steroids, plasma exchange, fresh frozen plasma. A subsequent study was an observational cohort consisting of 21 patients with STSS between 1994-1995 who were treated with a median dose of 2 grams/kg of IVIG compared with 32 patients between 1992-1995 who did not receive IVIG therapy. The outcome measure was 30-day survival. Sixty-seven percent of treatment cases survived, compared with 34% of controls (P=0.02).⁷⁸ In addition, IVIG was shown to enhance plasma ability to neutralize bacterial mitogenicity and reduce production of IL-6 and TNF- α *in vitro*. One of the potential confounders in this study was that the treatment group was enrolled prospectively and received more clindamycin therapy and aggressive surgery than the historical control patients.

Most recently, the first randomized, double-blinded, placebo-controlled trial was published by the Swedish Streptlg Study Group in August, 2003. The trial was prematurely terminated because of slow patient recruitment and results were obtained from 21 enrolled patients, of whom 10 patients received IVIG and 11 patients received placebo. In this study, the patients received 3 infusions of IVIG with the highest dosage (1g/kg) at day 1, followed by 0.5g/kg on days 2 and 3. The primary end point was mortality at 28 days, and a 3.6-fold higher mortality rate was found in the placebo group than in the IVIG group, but statistical significance was not reached (P=0.3), presumably because of the small sample size.⁷⁹ However, there was a significant decrease in the sepsis-related organ failure assessment score at days 2 and 3 in the IVIG group. In addition, there was a significant increase in plasma neutralizing activity against superantigens expressed by autologous isolates after treatment in the IVIG group. In terms of serotypes, M1, M3, M4, as well as nontypeable strains with SPEA, SPEH, and SSA were represented in both groups. Although this most recent study was not powered to show conclusive evidence supporting the use of IVIG as adjunctive therapy for STSS, it may be the closest we will realistically achieve given larger trials are logistically difficult for a condition that is of low incidence.

The toxicities of IVIG therapy include anaphylactic hypersensitivity in IgA-deficient patients, renal failure, thrombosis, headache, and volume overload. The MGH blood bank stocks Polygam® S/D and Venoglobulin®-S at a cost of \$45-100 per gram to the blood bank, but charged at a rate of \$842 per gram

to the patients. In a study comparing levels of neutralizing activities against group A streptococcal superantigens in different IVIG preparations, Venoglobulin®-S had significantly higher neutralizing titers than other preparations.⁶⁸ Polygam® S/D was not tested. Based on these numbers, the average cost of IVIG therapy using standard doses used in the clinical studies is approximately \$14,000 to \$100,000 per course.

Potential adjunctive therapies include activated protein C and potentially anti-TNF α monoclonal antibody as demonstrated in antibody treatment in a baboon model of group A streptococcal bacteremia.⁸⁰ In this study, profound hypotension, leukopenia, metabolic acidosis, renal impairment and disseminated coagulopathy developed within 3 hours after intravenous infusion of M type 3, SPEA- producing group A streptococci with mortality rate of 100%. Anti-TNF α treatment markedly improved mean arterial blood pressure, tissue perfusion, and survival by 50%.

The diverse clinical manifestations and the changing spectrum of group A streptococcal infection present a challenge to clinicians. In the recent decade, the pathogenic potential of this old organism has gained new appreciation among the medical community. Prevention of severe streptococcal disease should begin with better characterization of the epidemiology of streptococcal virulence factors, while novel treatment therapies require better understanding of its virulence factors and mechanisms of pathogenesis.

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