Severe, Invasive Group A Streptococcal Disease and Toxic Shock

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Group A streptococci are usually recognized for their association with purulent infections and the non-purulent complications of these infections in humans. The most common purulent infections are pharyngitis-tonsillitis and impetigo. Less common infections include peritonsillar abscess, mastoiditis, pneumonia, arthritis, osteomyelitis, erysipelas, puerperal sepsis, septicemia, and meningitis. Acute rheumatic fever and acute glomerulonephritis are the two non-purulent sequelae. Of these two complications, acute rheumatic fever carries the higher risk for morbidity. The incidence of rheumatic fever was high in this country and western Europe during the first half of this century but declined drastically after 1950 until about 1985 when a resurgence of this disease was noted in several areas of the United States.\textsuperscript{1,2} Simultaneously, reports of severe invasive group A streptococcal infections presenting as necrotizing fasciitis, myositis, or bacteremia associated with toxic shock began appearing.\textsuperscript{3} These infections were particularly alarming because they were associated with severe morbidity and a relatively high mortality. This review summarizes current information regarding the clinical characteristics of necrotizing fasciitis and streptococcal toxic shock syndrome, the epidemiology and pathogenesis of these diseases, and recommendations regarding their treatment.

EDUCATIONAL OBJECTIVES
1. Discuss the biology of group A streptococcus and the change in epidemiology of streptococcal infections.
2. Recognize the clinical manifestations and the criteria for the diagnosis of invasive streptococcal infections, streptococcal toxic shock syndrome, and necrotizing fasciitis.
3. Review recent recommendations for the management of invasive streptococcal infections.
The occurrence of severe, invasive GABHS infections associated with high mortality was reported as early as 1931.

BIOLOGY OF THE GROUP A STREPTOCOCCUS

Group A streptococci, commonly referred to as Streptococcus pyogenes, comprise one of the serogroups of the β-hemolytic streptococci. According to the Lancefield classification, β-hemolytic streptococci comprise 20 serologically defined groups: A through H and K through V. Separation of β-hemolytic streptococci into these groups is based on differences in the chemical structure and immunogenic specificity of the cell wall polysaccharide. The cell wall of group A β-hemolytic streptococci (GABHS) also contains the M protein, an important virulence factor for this organism. It is estimated that 120 different M proteins exist among GABHS of which 80, types M1 through M80, have been identified by serologic methods. M proteins are responsible for type specificity among GABHS. Infection by GABHS elicits type-specific antibody to the M protein, which provides immunity against subsequent infection by the corresponding serotype. Streptococcal strains belonging to serotypes M1, M3, M12, and M28 have been recovered in a higher frequency from patients with acute rheumatic fever and invasive streptococcal infections than from patients who had acute streptococcal infection without these complications. Some of the streptococcal isolates recovered from patients with rheumatic fever were characterized by the formation of large mucoid colonies when cultured on blood agar.

The extracellular products of GABHS include the streptococcal pyrogenic exotoxins (Spe). The Spes comprise three previously recognized pyrogenic exotoxins, SpeA, SpeB, and SpeC, and two recently identified ones, mitogenic factor (MF), also designated as SpeF, and the streptococcal superantigen (SSA). These pyrogenic exotoxins have been the subject of much attention because of their biologic activity. They act as superantigens and induce the proliferation of T lymphocytes in vitro and the synthesis and release of several cytokines in vivo, including tumor necrosis factor-α, interleukin-1β, and interleukin-6. The production of these exotoxins in vivo is associated with a marked febrile response, alteration of membrane permeability, and enhancement of host susceptibility to the lethal shock of endotoxin. This biologic activity is ascribed to the ability of the superantigens to bind simultaneously to the Vβ region of the T-cell receptor and to class II major histocompatibility antigens of the antigen-presenting monocytes. This interaction results in widespread, non-specific T-cell proliferation and increased production of interleukin-2.

INVASIVE GROUP A STREPTOCOCCAL INFECTIONS

The occurrence of severe, invasive GABHS infections associated with high mortality was reported as early as 1931 by Weech. Little mention of such infections was encountered thereafter until 1987 when Cone and colleagues described two adults with severe GABHS infection complicated by toxic shock similar to the staphylococcal toxic shock syndrome of which one patient died. The GABHS isolated from these patients were examined for the production of Spe. The strain from the patient who died produced large amounts of SpeA and the other strain produced SpeB. A review of the production of these toxins in 80 group A streptococcal isolates collected before this event revealed that none of these strains produced SpeA, the exotoxin that had structural and immunologic similarity with the staphylococcal toxic shock toxin (TSST-1). Neither of the patients reported on by Cone et al had antibodies to the streptococcal pyrogenic toxins at the time of admission.

A compelling report by Stevens and colleagues described 20 adults with severe, invasive soft tissue infection, most commonly necrotizing fasciitis, with or without myositis. This report was instrumental in attracting the attention of the medical community to the resurgence of severe invasive GABHS disease. Two of these patients used intravenous drugs, and one patient had adult onset diabetes mellitus, but most had no underlying illness. At presentation, 16 patients had evidence of renal impairment, and 11 had respiratory distress syndrome; 19 had shock during the course of their illness, and 6 died. Nineteen of the patients had tissue cultures positive for GABHS, and 12 had positive blood cultures. Studies performed on 10 of these isolates revealed that three strains were serotype M1, three were M3, two were M28, and two were non-typable. One of the strains produced mucoid colonies when cultured on blood agar. Analysis of the Spe production by the 10 strains showed that 8 of the 10 isolates produced SpeA, 5 produced SpeB, and one produced SpeC. Although this finding provided support for the potential association between the production of SpeA by some strains of group A streptococci recovered from patients with streptococcal toxic shock syndrome, data from subsequent studies did not confirm this association.

Reports of severe, invasive infection by the GABHS in children began emerging in 1987. The initial reports originated from outside the United States. Begovic and colleagues were the first to report the association of severe invasive streptococcal infection and toxic shock with varicella in children. A subsequent report by Brogan and colleagues described 14 patients with severe streptococcal invasive disease after varicella infection, 5 of whom had toxic shock. An additional 24 patients with varicella complicated by severe GABHS invasive disease were
reported by Vugia and coworkers. This group included two patients with toxic shock. Risk factors for severe invasive GABHS disease in children with varicella were reported by Peterson et al (Table 1). The most notable of these factors is the association of this disease with administration of nonsteroidal anti-inflammatory drugs (NSAIDs). However, the significance of this association is not established and is still under investigation.

The National Center for Disease Control estimates the annual incidence of severe invasive streptococcal disease in the United States at 4 to 5 cases per 100,000, with about 10,000 cases occurring nationwide each year.

Clinical manifestations

Necrotizing fasciitis is an acute, rapidly progressive, severe deep-seated infection of the subcutaneous tissue associated with extensive destruction of the superficial and, sometimes, deep fascia (Figure). In necrotizing fasciitis there is microbial and leukocytic infiltration of the superficial fascial and deep dermal layers of the skin with resultant thrombosis, vasculitis, and necrosis. The high morbidity and significant mortality seen in this disease and other invasive GABHS infections are to a large extent toxin-mediated. Although necrotizing fasciitis can affect any part of the body, the extremities are most commonly involved. Predisposing factors for the development of necrotizing fasciitis include varicella, penetrating injuries, minor cuts, burns, splinters, surgical procedures, childbirth, blunt trauma, and muscle strain. Necrotizing fasciitis of the abdominal wall can complicate omphalitis in the newborn.

The onset and course of necrotizing fasciitis is summarized in Table 2. The onset is marked by a diffuse, erythematous swelling with exquisite tenderness at the affected site. Pain is very prominent. The inflammation progresses rapidly, with changes in color from a red-purple color to a bluish discoloration in 2 to 3 days. The latter is an ominous sign. If untreated, there is rapid progression on days 4 and 5 to the formation of bullae filled with dark fluid, and the appearance of frank cutaneous gangrene sometimes with myonecrosis and extension of the inflammatory process along the fascial planes. Marked systemic toxicity with high fever (103°F to 105°F) accompany this stage of the disease.

A study of patients with necrotizing fasciitis following varicella in children reported that the most common presenting symptoms were local erythema (71%), focal pain (79%), fever greater than 38.5°C (85%), and localized tissue swelling (71%). Pain was often described as being out of proportion to the other clinical findings. In the majority of the patients, no obviously infected lesions were found overlying the anatomic site of the fasciitis. Five of the 14 patients developed hypotension, tachycardia, and oliguria. The interval between the appearance of varicella lesions and the onset of necrotizing fasciitis or invasive GABHS infections ranged from 3 to 4 days.

Streptococcal toxic shock syndrome is characterized by hypotension and multiple organ failure. The early symptoms of streptococcal toxic shock syndrome include myalgia, malaise, chills, fever, nausea, vomiting, and diarrhea. As many as 50% of patients may have necrotizing fasciitis with or without myonecrosis. In these patients focal pain or erythema of the affected site may be the initial symptom. Persistent fevers, tachycardia, and tachypnea indicate progression of disease that subsequently leads to development of shock and organ failure. Hypotension, the hallmark of toxic shock syndrome, may be present initially in about half of the patients but develops subsequently in all. Renal impairment occurs in about 80% of patients. In the majority of these patients renal impairment is reversible and usually precedes the development of hypotension. Almost half of patients develop respiratory distress syndrome. Hepatic dysfunction has been observed in as many as 65% of patients. Other manifestations may be secondary to abnormal coagulation, which also occurs frequently.

A review of the literature reveals some notable dif-
ferences in severe invasive group A streptococcal disease and toxic shock between children and adults (Table 3). The most significant of these are the occurrence of varicella as a predisposing factor and the high frequency of pharyngitis as the only antecedent event in children. In addition, arthritis and osteomyelitis occur more commonly as complications in children compared to adults. In contrast, necrotizing fasciitis is seen frequently in adults, and toxic shock has been reported more frequently in adults in association with invasive group A streptococcal infection than in children.

Diagnosis

Necrotizing fasciitis remains difficult to diagnose in its early stages because of the absence of specific clinical findings.15 A delay in initial diagnosis occurs when necrotizing fasciitis is confused with cellulitis. Surgical exploration can provide a rapid diagnosis. Unlike the finding in cellulitis, probing of the affected tissue with a hemostat through a small cutaneous incision reveals little resistance in the superficial planes. Frozen section biopsy is also useful and provides timely and specific information.21 In circumstances in which there is severe pain and symmetric swelling in the absence of cutaneous evidence of infection, measurement of compartment pressure may be helpful. If the pressure is elevated, immediate fasciotomy is indicated.20 Although bacteremia can be present in more than half of the patients,16 physicians should not wait for the culture results to establish the diagnosis because doing this may delay treatment. Early treatment is crucial to outcome.

Non-specific laboratory results that may be helpful include an elevated white cell count, elevated erythrocyte sedimentation rate, and C-reactive protein. An elevated creatinine kinase value is present in the majority of patients.22 Gram stain of tissue aspirate can aid in rapid diagnosis because presence of gram positive cocci in chains distinguishes necrotizing fasciitis from erysipelas (in which bacteria are very rarely isolated from the lesion).22 Magnetic resonance imaging for the early diagnosis of necrotizing fasciitis has been recommended because other radiographic studies frequently do not elucidate the severity of the infection.22

Criteria proposed by the Working Group on Severe Streptococcal Infections for the diagnosis of necrotizing fasciitis and streptococcal toxic shock are outlined in Table 4. A definite diagnosis of streptococcal toxic shock syndrome is predicated on the isolation of GABHS from a normally sterile site in the presence of hypotension, plus two or more of the six additional clinical criteria listed in the table. Isolation of GABHS from a non sterile site allows for a probable diagnosis.

Laboratory studies should include performance of blood cultures as well as culture of tissue at the affected site. Positive blood culture has been reported in 60% to 72% of patients with toxic shock syndrome.5,24 In addition, patients with suspected toxic shock syndrome should be evaluated for renal and hepatic dysfunction. Renal involvement is indicated by marked elevation of serum creatinine levels and hemoglobinuria. Hypocalcemia, hypernatremia, and hypoalbuminemia may exist in varying degrees.
Involvement of the liver is reflected by elevation of transaminases and bilirubin levels. An elevated creatinine phosphokinase concentration suggests myositis. Thrombocytopenia, prolonged clotting times, low fibrinogen levels, and increased concentration of fibrin split products indicate the presence of coagulopathy. Abnormalities on a chest roentgenogram and blood gas studies should suggest the possibility of acute respiratory distress syndrome.

**Treatment**

Because of the rapidly progressive and potentially fatal nature of GABHS invasive disease, early and intensive medical care should be instituted, together with thorough surgical debridement when indicated. The mainstay of medical treatment is the use of antibiotics and supportive care in the form of inotropic or pressor agents for the treatment of shock. Because the pathologic process of invasive GABHS infection is primarily toxin mediated, antimicrobial agents such as clindamycin that inhibit bacterial protein synthesis and reduce toxin production are theoretically more advantageous. Studies in a mouse model of GABHS myositis have shown that clindamycin is superior to penicillin in reducing mortality even after a delay in starting therapy. Another factor that contributes to the superiority of clindamycin in this infection, is the "inoculum effect." Large concentrations of bacteria resulting from rapid growth are often encountered in overwhelming infections like necrotizing fasciitis, myositis, and sepsis. These large concentrations lead to rapid attainment of the stationary growth phase, which is associated with decreased expression of cell wall penicillin-binding proteins. This renders penicillin less effective. Clindamycin, unlike penicillin, does not require cell wall binding proteins to exert its antibacterial effect and, therefore, is not subject to the inoculum effect.

Anecdotal reports suggest that intravenous immunoglobulin administration may improve outcome in some patients with invasive GABHS disease. Studies regarding the efficacy of this treatment are lacking. Based on this and in view of the current national shortage of intravenous immunoglobulin, its use in this condition is not currently recommended.

In addition to its therapeutic contribution, surgical intervention assists in providing a rapid diagnosis. Direct observation of the nature and extent of the pathologic process is important in guiding a decision regarding the necessity for simple drainage or radical surgery. Hyperbaric oxygen has been used as an adjunct to the treatment of necrotizing
fasciitis. Although its effectiveness has not been well established, it has been reported to reduce mortality and the need for additional debridement (Figure). However, a decision regarding the use of hyperbaric oxygen should not delay surgical intervention.

Both necrotizing fasciitis and streptococcal toxic shock syndrome have been associated with very high mortality. Case fatality rates of about 43% and 30% to 58% have been reported for necrotizing fasciitis and streptococcal toxic shock syndrome in adults respectively. Mortality in children with this disease is 5% to 10%. Early diagnosis and aggressive medical and surgical treatment, however, have been shown to improve the outcome significantly.

REFERENCES