

AMERICAN ACADEMY OF PEDIATRICS

Committee on Infectious Diseases

Severe Invasive Group A Streptococcal Infections: A Subject Review

ABSTRACT. The course of severe invasive group A β -hemolytic streptococcal (GABHS) infections is often precipitous, requiring prompt diagnosis and rapid initiation of appropriate therapy. Therefore, physicians must have a high index of suspicion of this disease, particularly in patients at increased risk (eg, those with varicella or diabetes mellitus). Although a relationship between the use of nonsteroidal antiinflammatory drugs and severe invasive GABHS infections has been suggested, at present data on which to base a clinical decision about the use or restriction of nonsteroidal antiinflammatory drugs in children with varicella are insufficient. When necrotizing fasciitis is suspected, prompt surgical drainage, debridement, fasciotomy, or amputation often is necessary. Many experts recommend intravenously administered penicillin G and clindamycin for the treatment of invasive GABHS infections on the basis of animal studies. Some evidence exists that intravenous immunoglobulin given in addition to appropriate antimicrobial and surgical therapy may be beneficial. Although chemoprophylaxis for household contacts of persons with invasive GABHS infections has been considered by some experts, the limited available data indicate that the risk of secondary cases is low (2.9 per 1000) and data about the effectiveness of any drug are insufficient to make recommendations. Because of the low risk of secondary cases of invasive GABHS infections in schools or child care facilities, chemoprophylaxis is not indicated in these settings. Routine immunization of all healthy children against varicella is recommended and is an effective means to decrease the risk of invasive GABHS infections.

ABBREVIATIONS. GABHS, group A β -hemolytic streptococcal; TSS, toxic shock syndrome; SPE, streptococcal pyrogenic exotoxin; NSAID, nonsteroidal antiinflammatory drug.

In recent years, an increased incidence of severe invasive group A β -hemolytic streptococcal (GABHS) infections, including the group A streptococcal toxic shock syndrome (TSS) and necrotizing fasciitis, has been observed.¹⁻⁴ Because invasive GABHS infections are associated with significant morbidity and mortality, it is important for pediatricians to be familiar with the diagnosis, management, and prevention of these infections.¹⁻⁴ In addition, sensationalized reports in the lay literature have contained considerable misinformation about these infections, including the incidence, the relationship to acute pharyngitis, and the presence of antibiotic resistance among strains of GABHS. Pediatricians need

accurate information to put these infections into proper perspective for patients and their families.

Invasive GABHS disease is defined as an infection associated with the isolation of GABHS from a normally sterile body site and includes three overlapping clinical syndromes.^{4,5} The first is group A streptococcal TSS that is differentiated from other types of invasive GABHS infections by the occurrence of shock and multiorgan system failure early in the course of the infection. In 1993, the Centers for Disease Control and Prevention Working Group on Severe Streptococcal Infections developed a case definition for the streptococcal TSS (Table).⁵ The second group is GABHS necrotizing fasciitis characterized by extensive local necrosis of subcutaneous soft tissues and skin and the isolation of GABHS from a normally sterile body site. The third is a group of infections characterized by the isolation of GABHS from a normally sterile site in patients not meeting the criteria for streptococcal TSS or necrotizing fasciitis. Included in this group are bacteremia with no identified focus and focal infections (eg, meningitis, pneumonia, peritonitis, puerperal sepsis, osteomyelitis, septic arthritis, myositis, and surgical wound infections) with or without bacteremia. These severe invasive GABHS infections rarely occur after an episode of acute GABHS pharyngitis.⁴

HISTORICAL PERSPECTIVE

Severe, invasive GABHS infections had become uncommon in the United States and western Europe during the second half of the 20th century.⁶ However, during the mid-1980s, reports began to appear of an increasing incidence of invasive disease, septicemia, and deaths attributable to GABHS infections in Great Britain and the United States.⁶ The reasons for this increase have not been identified clearly; however, history is replete with periodic epidemics of GABHS infections. During most of the 18th century, scarlet fever was considered by parents and physicians to be a benign disease of early childhood. However, during the early 19th century, this situation changed dramatically. In 1831, a lethal epidemic of scarlet fever was reported in Dublin, and the following year, an equally lethal epidemic was reported in Augusta, GA.⁶ At the same time, in several large cities in the United States and Europe, localized clusters of severe cases of scarlet fever with case fatality rates of $\geq 30\%$ were reported. Scarlet fever continued to be an extremely severe disease for the next half century, and then suddenly in approximately 1885, the character of this disease in Europe and the United States changed again quite dramatically.⁶ Severe

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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TABLE. Case Definition for Streptococcal TSS*5

I. Isolation of group A β -hemolytic streptococci
A. From a normally sterile site (eg, blood, cerebrospinal fluid, peritoneal fluid, tissue biopsy specimen)
B. From a nonsterile site (eg, throat, sputum, vagina)
II. Clinical Signs of Severity
A. Hypotension: systolic blood pressure \leq 90 mm Hg in adults or $<$ 5th percentile for age in children and
B. \geq 2 of the following signs:
1. Renal impairment, creatinine \geq 2 mg/dL for adults or \geq twice the upper limit of normal for age
2. Coagulopathy: platelets \leq 100 000 μ L or disseminated intravascular coagulation
3. Hepatic involvement: alanine aminotransferase (SGPT), aspartate aminotransferase (SGOT), or total bilirubin levels \geq twice the upper limit of normal for age
4. Adult respiratory distress syndrome
5. A generalized erythematous macular rash that may desquamate
6. Soft-tissue necrosis, including necrotizing fasciitis or myositis, or gangrene

* An illness fulfilling criteria IA and II (A and B) can be defined as a *definite* case. An illness fulfilling criteria IB and II (A and B) can be defined as a *probable* case if no other cause for the illness is identified.

cases became much less common, and the case fatality rates dropped to \leq 1%.

PATHOGENESIS

The pathogenic mechanisms responsible for severe, invasive GABHS infections, including streptococcal TSS and necrotizing fasciitis, have yet to be defined completely, but an association with streptococcal pyrogenic exotoxins (SPE) has been suggested.^{4,7,8} Three SPEs (SPE A, SPE B, SPE C) have traditionally been called erythrogenic toxins and are responsible for the rash of scarlet fever. Two newly discovered SPEs have been isolated from GABHS and have been named mitogenic factor (or SPE F) and streptococcal superantigen. The pyrogenic exotoxins and potentially other as-yet unidentified toxins produced by GABHS may belong to a family of bacterial proteins known as superantigens. Superantigens stimulate an intense activation and proliferation of T lymphocytes and macrophages resulting in the production of large quantities of cytokines. These cytokines (eg, tumor necrosis factor- α , interleukin-1 β , and interleukin-6) are capable of producing shock and tissue injury.⁸ Host factors, such as the presence or absence of type-specific antistreptococcal or antitoxin antibodies, the type of cytokine(s) response, and the presence of underlying disease, could influence the susceptibility to specific virulent strains and the severity of the clinical manifestations.

The portal of entry for GABHS is unknown in almost 25% of the cases of severe invasive disease. The infection usually begins in the skin or soft tissues, frequently at the site of minimal or inapparent local trauma. Severe invasive GABHS infections rarely occur after an episode of acute GABHS pharyngitis.^{4,7}

RECENT EPIDEMIOLOGY

Severe invasive infections caused by GABHS are not reportable diseases in all states in this country, and until recently there was no accepted case defini-

tion of the streptococcal TSS.⁵ Therefore, our understanding of the epidemiology of severe invasive GABHS infections is limited and comes primarily from active surveillance in several geographic areas and extrapolation from several isolated outbreaks. Published incidence rates of severe invasive GABHS infections in North America have ranged from 1.5 to 7.0 cases per 100 000 persons annually.^{2,9,10} The Centers for Disease Control and Prevention has estimated that the annual incidence in this country is 4 to 5 cases per 100 000 persons, with \sim 10 000 cases occurring nationwide each year.^{2,11} Although most of the reports of severe invasive GABHS disease in adults have noted a mortality rate of 30% to 80%, the overall mortality rate in most of the published pediatric series has been 5% to 10%.¹²

Results of population-based surveillance suggest that \sim 85% of invasive infections occur sporadically in the community, 10% are hospital acquired, 4% occur in residents of long-term care facilities, and 1% occur after close contact with a case.^{9,13} Although cases of severe invasive GABHS disease have occurred among children attending school or out-of-home child care, there have been no reported subsequent cases of invasive GABHS infection in schools and only a single subsequent case of invasive GABHS infection associated with varicella in a child care facility.¹⁴ However, outbreaks of severe invasive GABHS infections have occurred in some closed environments, such as military bases, nursing homes, and hospitals.^{15,16}

Although several clusters of invasive GABHS disease in families have been reported, only one study has assessed the risk of secondary household infection on a population basis.⁹ Results of population-based active surveillance in Ontario, Canada, suggest that the rate of secondary invasive GABHS infection is \sim 2.9 cases per 1000 household contacts. This rate was about 200 times the baseline risk in the community; however, the 95% confidence interval around this estimated rate are wide (0.8 to 7.5 per 1000).

Secondary invasive diseases in households and hospital personnel have occurred several hours to 3 weeks after the index case.^{9,11,15,16} Secondary cases of streptococcal TSS or necrotizing fasciitis occurred after similar clinical manifestations in the index cases; of the five patients with secondary invasive disease who died, all had streptococcal TSS or meningitis, and all cases occurred after an index case with streptococcal TSS. In many of the clusters, additional family members (usually children) were identified with pharyngitis or with carriage of the same strain of GABHS that caused the invasive disease.^{9,15,16}

RISK FACTORS

The incidence of severe invasive GABHS infections appears to be highest among young children and the elderly.² There is a smaller peak among young adults that may be the result of increased exposure to children, high-risk behaviors (eg, intravenous drug use), or infections associated with childbirth. Other groups identified as being at increased risk for severe invasive infections include persons with diabetes mellitus, chronic cardiac or pulmonary disease, hu-

man immunodeficiency virus infection or acquired immunodeficiency syndrome, intravenous drug use, and alcoholism, and children with varicella.^{2,9}

Varicella is a particularly important risk factor for severe invasive GABHS infections in previously healthy children, and in recent years an increasing proportion of cases in the United States have been associated with varicella.¹⁷⁻¹⁹ A GABHS infection should be considered in any child with varicella who also has localized skin findings of erythema, warmth, swelling, or induration, and in any child with varicella who becomes febrile after having been afebrile, who has a temperature of $\geq 39^{\circ}\text{C}$ beyond the third day of illness, or who has any fever beyond the fourth day of illness. When present, GABHS infections are usually painful, and initially the amount of pain is frequently out of proportion to the clinical findings.

Several reports have suggested a relationship between the use of nonsteroidal antiinflammatory drugs (NSAIDs) and necrotizing fasciitis attributable to GABHS.^{18,20} There is evidence that NSAIDs can impair granulocyte function and enhance production of cytokines.²¹ In addition, NSAIDs may mask the signs of disease progression by relieving pain, reducing swelling, and suppressing fever, all of which contribute to a delay in diagnosis, resulting in more severe infection at the time of diagnosis. Although some physicians have suggested that NSAIDs should not be used to treat children with varicella, a causal relationship between NSAID use and severe invasive GABHS infections has not been established. Data are insufficient on which to base a clinical decision about the use or restriction of NSAIDs in children with varicella.

DIAGNOSIS

The course of severe invasive GABHS infections is often precipitous, requiring rapid diagnosis and initiation of appropriate therapy. Many persons with streptococcal TSS have been treated as outpatients on one or more occasions before admission. Although initial signs and symptoms of streptococcal TSS are nonspecific, physicians should have a high index of suspicion for this evolving syndrome, especially in patients at increased risk (eg, persons with varicella or diabetes mellitus). Although patients who present with muscle aches and fever often are sent home with a diagnosis of flu, clues suggesting streptococcal TSS can include more localized or severe pain than is typical of influenza, the absence of either respiratory signs or a contact history, and the presence of a skin lesion or history of blunt trauma at the site of pain. Culture of focal lesions is helpful in patients with skin or soft tissue involvement. Results of blood cultures from patients with sepsis without an apparent focus of infection may also show GABHS. Blood pressure should be monitored frequently and carefully. If necrotizing fasciitis is a possibility, magnetic resonance imaging has been demonstrated to be helpful in confirming the diagnosis.²²

MANAGEMENT

Management of a child with a severe invasive GABHS infection includes hemodynamic stabilization and specific antimicrobial therapy to eradicate the bacteria. When necrotizing fasciitis is suspected, prompt surgical drainage, debridement, fasciotomy, or amputation often is essential. For hypotensive patients, fluid resuscitation should be started as soon as possible. Patients frequently require multiple boluses of fluid because of severe volume depletion and ongoing capillary leakage. Inotropic agents (eg, dobutamine, dopamine, norepinephrine) should be considered when fluid resuscitation alone is insufficient to maintain adequate tissue perfusion.

Parenteral antibiotic therapy should be instituted promptly, providing coverage for both GABHS and *Staphylococcus aureus* until the results of bacteriologic studies are available. Once GABHS has been identified, intravenously administered penicillin G (200 000 to 400 000 U/kg per day) in four to six divided doses is the drug of choice based on in vitro sensitivities. No GABHS isolates resistant to penicillin G have been reported.²³ However, in a mouse model of streptococcal myositis, when treatment was started 2 hours after initiation of infection, penicillin was ineffective (ie, performed no better than untreated controls), but clindamycin resulted in a 100% survival rate.²⁴ The failure of penicillin to eradicate the GABHS in this model may be explained by the slow replication rate of GABHS when a large inoculum is present, a situation commonly seen with severe invasive GABHS infections. This reduced replication rate of GABHS results in diminished expression of the target sites for penicillin activity (ie, penicillin-binding proteins). Because clindamycin inhibits protein synthesis, its efficacy is not dependent on penicillin-binding proteins. In addition, clindamycin inhibits the synthesis of both M protein (an important antiphagocytic virulence factor) and SPEs. Furthermore, the action of clindamycin on bacteria persists longer than that of penicillin. Therefore, many experts recommend intravenously administered clindamycin (25 to 40 mg/kg per day in three or four divided doses) in addition to penicillin. However, there are no controlled clinical studies demonstrating that the addition of clindamycin improves the outcome of patients with severe invasive GABHS infections compared with therapy with penicillin G alone. Clindamycin should not be used alone for treating a severe invasive GABHS infection until the isolate is determined to be sensitive to this agent, because a small portion of strains of GABHS are clindamycin-resistant.²⁵

Data from a few case reports and one controlled trial suggest that treatment with intravenous immunoglobulin (1 to 2 g/kg given once) may be beneficial when given in addition to appropriate antimicrobial therapy for streptococcal TSS.²⁶⁻²⁸ Intravenous immunoglobulin is postulated to work by blocking or inactivating the SPEs that stimulate proliferation of T lymphocytes resulting in a decrease in the production of inflammatory cytokines. Because cytokines appear to have a major role in the pathogenesis of

this disease, other agents (eg, corticosteroids, monoclonal antibodies) that decrease production or block the activity of cytokines may be beneficial in the treatment of severe invasive GABHS infections. However, no controlled clinical studies have demonstrated the effectiveness of these agents. Although hyperbaric oxygen has been used in the treatment of necrotizing fasciitis and myositis attributable to GABHS, no controlled clinical studies have been performed, and its usefulness is not clear.²⁹

PREVENTION

Opportunities for the prevention of severe invasive GABHS infections are limited and differ depending on the setting in which these infections occur. Primary prevention of some sporadic community-acquired infections may be possible by reducing the risk in specific settings. Among healthy children, routine immunization against varicella is recommended and should decrease the risk of invasive GABHS infections. Similarly, some nosocomial GABHS infections should be prevented by improving infection control practices for surgical and obstetric procedures, and for placement and care of intravenous catheters.

Some experts have encouraged consideration of chemoprophylaxis for persons who have been in close contact with patients who have severe invasive GABHS infections.⁹ Several antimicrobial regimens, including rifampin plus intramuscular benzathine penicillin or a 10-day course of a second-generation cephalosporin or clindamycin, have been shown to be more effective than penicillin in eradicating GABHS from the pharynx of chronic carriers.^{30,31} However, no data are available about the effectiveness of any regimen for chemoprophylaxis of severe invasive GABHS infections. Furthermore, although rifampin alone is effective for chemoprophylaxis of close contacts of persons with invasive *Haemophilus influenzae* type b or meningococcal infections, this regimen is not effective in eradicating GABHS from the pharynx.³² In addition, no data are available about the usefulness of throat cultures or antigen detection tests in identifying contacts at increased risk of severe invasive GABHS disease.

The data currently available about the risk of secondary invasive GABHS infections are limited, and the effectiveness of chemoprophylaxis is uncertain. Therefore, no recommendations for the routine use of chemoprophylaxis can be made. Physicians contemplating chemoprophylaxis for household contacts should consider factors including the severity of disease in the index case, the extent of contact with the index case, underlying conditions in contacts that may increase the risk of disease or mortality (eg, advanced age, immunosuppression, diabetes mellitus, varicella infection), and the costs and potential adverse effects of chemoprophylaxis. Because of the rarity of subsequent cases and the low risk of invasive GABHS infections in children in general, chemoprophylaxis is not recommended in schools or child care facilities.

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