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*Group A beta-hemolytic streptococcus (GABHS) is a common cause of infections involving the upper respiratory tract and skin in children. Most clinicians are familiar with GABHS as a cause of pharyngitis. However, GABHS also can cause a number of skin and soft-tissue infections. While most infections caused by GABHS do not result in significant morbidity or mortality, some can be severe or life-threatening. Such infections include necrotizing fasciitis and streptococcal toxic shock syndrome. Acute rheumatic fever, acute glomerulonephritis, and suppurative complications such as peritonsillar abscess can complicate GABHS pharyngitis. Clinicians should be aware of the varied presentations of GABHS disease. In this issue, the author presents a review of the microorganism as well as its most common clinical manifestations. Current recommendations for the diagnosis and treatment of each illness are included.*

*— The Editor*

# Spectrum of Group A Beta-Hemolytic Infections in Children

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## Introduction

Children commonly present to their pediatrician or to the emergency room with a complaint of a sore throat. GABHS is the most common bacterial cause of pharyngitis in children. Because of its frequency and its potential for inciting acute rheumatic fever, many clinicians consider GABHS only in the context of pharyngitis. However, recent reports of a possible resurgence in invasive group A streptococcal infections serve as a reminder that the pathogen can cause a variety of skin and soft-tissue infections, some of which can be severe or life-threatening.

Historically, infections in children caused by GABHS often resulted in serious morbidity and mortality. However, toward the end of the 1960s, a marked decline in the incidence and severity of such infections occurred in the United States. This decline was thought to be due to the advent of effective antimicrobial therapies as well as to a general improvement in socioeconomic conditions throughout the country.

Since the early 1980s, reports of individual cases and outbreaks of acute rheumatic fever have been described in widely separated geographic locales. Such outbreaks have been restricted to distinct geographic locales.[1] Cases of rheumatic fever have occurred primarily in children of middle-class families, suggesting that socioeconomic factors have assumed less importance in the pathogenesis of acute rheumatic fever (ARF) and that increased virulence of the organism may be primarily responsible for current outbreaks.[1,2] Interestingly, the apparent resurgence of ARF has not occurred in other industrialized countries as it has in North America.

However, rheumatic fever and its clinically significant sequelae, rheumatic heart disease, remain a major health problem in nonindustrialized countries.[3] In contrast, an increase in severe, invasive group A streptococcal infections involving the skin and soft tissues has been documented worldwide.

## Biology and Immunology

GABHS, or *Streptococcus pyogenes*, are gram-positive, nonmotile, non-spore-forming, catalase-negative, and facultatively anaerobic organisms.[4] Colonies are typically spherical or ovoid, and will appear in pairs or as short to moderate-sized chains in clinical specimens.[4] When cultured on blood agar plates, *S. pyogenes* appears as white to gray colonies 1-2 mm in diameter surrounded by zones of complete (beta) hemolysis.

The organism is enveloped in a hyaluronic capsule that serves as an accessory virulence factor by retarding phagocytosis by polymorphonuclear leukocytes and macrophages.[4] Strains that produce large amounts of hyaluronate capsular material appear mucoid. The organism's cell wall contains many different antigenic substances, most importantly an M protein.

The M protein is the major virulence antigen of group A streptococci.[4] Strains that do not express M protein are considered avirulent. Group A streptococci are divided into serotypes based on antigenic differences in the M protein molecule. More than 80 serotypes are recognized. Strains of group A streptococcus that cause pharyngitis normally differ from those that cause skin and soft-tissue infections in regard to their M serotypes. The most common M serotypes that cause pharyngitis are 1, 3, 5, 6, 12, 18, 19, and 24. "Skin strains" are known to colonize the pharynx but are rarely associated with acute episodes of pharyngitis. Acquired human immunity to streptococcal infection is dependent on the development of opsonic antibodies directed against the M protein.[4] Such immunity is type specific and can last for many years. Cross-protection between different serotypes has been known to occur.

GABHS produce a number of extracellular products when grown either in vitro or in vivo, though not all have been identified.[4] Streptococcal pyrogenic exotoxin (SPE) is responsible for the rash associated with scarlet fever. The toxin has been shown to exhibit a variety of toxic properties, including pyrogenicity, cytotoxicity, and enhancement of susceptibility to the lethal effects of endotoxin. Three serologically distinct pyrogenic exotoxins have been identified (A-C).

Two distinct hemolysins are known to be produced by GABHS: streptolysin O and streptolysin S.[4] Streptolysin O is produced by nearly all strains of GABHS and is considered antigenic. Measurement of antistreptolysin-O (ASO) antibodies can be used to document recent GABHS infection. Streptolysin S is considered nonantigenic and is produced by most strains of GABHS. Both hemolysins are known to cause damage to the membranes of polymorphonuclear leukocytes, platelets, and subcellular organelles.

Several other extracellular products elaborated by GABHS help facilitate the liquefaction of pus and the spreading of streptococci through tissue planes.[4] These include: 1) four antigenically distinct enzymes that degrade deoxyribonucleic acid (DNAases A, B, C, and D); 2) hyaluronidase; and 3) streptokinase.

## Streptococcal Pharyngitis

**Epidemiology.** GABHS infection of the pharynx is the most common bacterial infection of childhood. The disease primarily occurs among school-aged children (ages 5-15 years) during late fall, winter, and early spring. While most episodes occur in children between 5 and 8 years, all age groups are susceptible.

Recent investigators have looked at the incidence of GABHS pharyngitis in children younger than 5 years of age. One group obtained throat cultures in children younger than 3 years of age with evidence of pharyngitis. Fifteen percent of children were found to have a throat culture positive for GABHS, compared to 3% of controls.[5] One researcher found 8% of children between 3 months and 5 years with evidence of pharyngitis to have a throat culture positive for GABHS.[6] Both investigators used the presence of a rise in ASO titers to document true infection.

There has been no documented sex predilection for GABHS pharyngitis. Crowding, such as occurs in schools, favors inter-

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personal spread of the organism and accounts for the majority of cases, which occur during the school year.

**Pathophysiology.** GABHS is ordinarily spread by direct person-to-person contact, most likely via droplets of saliva or nasal secretions. Food and waterborne outbreaks have been documented. Once infected, the typical incubation period is 2-4 days.

The first step in the pathophysiology of GABHS pharyngitis is the penetration of GABHS through a mucus film that covers the oropharyngeal mucosa and subsequent attachment to surface epithelial cells.[7] Adherence of *Streptococcus pyogenes* to tonsillar epithelial cells is a precondition for bacterial colonization.[7] Adherence to epithelial cells triggers cell activation; internalization of bacteria into epithelial cells; and cytokine release from epithelial cells, with subsequent induction of an inflammatory reaction in underlying tissues.

**Clinical Features.** The onset of GABHS pharyngitis is heralded by abrupt onset of sore throat, which is accompanied by malaise, fever, and headache. Children often will complain of nausea, vomiting, and abdominal pain. Typical physical examination findings include an erythematous pharynx; hyperemic tonsils; grayish white tonsillar exudates; enlarged, tender anterior cervical lymph nodes; and fever.

Some children with GABHS pharyngitis may develop a rash. Scarlet fever is defined by the presence of a scarlatina rash in the presence of pharyngitis. Scarlet fever results from infection with a streptococcal strain that elaborates a streptococcal pyrogenic exotoxin. Normally associated with pharyngeal infections, scarlet fever may follow streptococcal infections at other sites, such as the skin or soft tissues. The rash typically appears on the second day of clinical illness as a diffuse red blush. The rash will often begin on the upper part of the chest and then spread to the rest of the body. The palms, soles, and face often are spared. Deeper lines of red can appear in the skin folds of the neck, axillae, groin, elbows, and knees (Pastia's lines). Children also may present with scattered petechiae. Occlusion of sweat glands imparts a sandpaper texture to the skin.

In the absence of suppurative complications, the disease is often self-limited. Most patients will become afebrile within 3-5 days. The remainder of signs and symptoms normally subside within seven days.

**Diagnostic Studies.** Throat culture remains the diagnostic test of choice in managing children with pharyngitis. Rarely are other diagnostic studies required for the management of children with pharyngitis. The standard throat culture is simple to perform and fairly sensitive. Its accuracy, however, is dependent upon the quality of the specimen obtained and how the specimen is subsequently processed. Both tonsillar regions and the posterior pharyngeal wall should be swabbed. Blood agar plates are subsequently inoculated from the throat culture. A single throat culture has a documented sensitivity between 90% and 97%.[8] Incubating blood agar plates under anaerobic conditions or using selective media will increase the sensitivity of culture. Bacitracin discs often are used with blood agar plates to distinguish group A streptococci from non-group A streptococci.

Clinical scoring systems have been used to diagnose streptococcal pharyngitis. A recently described clinical scoring system utilized six factors: age (5-15 years), presentation during the months of November to May, fever, clinical evidence of pharyngitis, tender adenopathy, and the absence of viral symptoms.[9] In children with all six factors, the scoring system had a positive predictive value of 75%. However, only 15% of children presented with all six factors. Clinical scoring systems are generally considered not sensitive enough to clinically diagnose GABHS pharyngitis without benefit of throat culture, but they may aid in deciding which child should have a throat culture performed.

Rapid antigen detection kits have been developed to diagnose GABHS infection. While kits are generally easy to use and offer readily available results, low-test sensitivity potentially limits their use. Reported sensitivities have ranged from 77% to 98.9%.[10-15] In addition, rapid antigen detection kits are more expensive than standard throat cultures. In the acute care setting, a positive rapid antigen detection kit for GABHS can be used to diagnose GABHS pharyngitis; a negative test should have a confirmatory throat culture performed.

**Management.** Treatment of children with GABHS pharyngitis is primarily aimed at preventing the nonsuppurative and suppurative complications. Standard treatment remains penicillin VK, administered orally for 10 days. Shorter courses of therapy with penicillin have resulted in a substantial number of treatment failures. Penicillin has been shown to be effective when given as infrequently as twice a day.[16] A single intramuscular injection of penicillin G benzathine still remains an effective therapy for children with GABHS pharyngitis and for a long time was considered the gold standard.[4]

Penicillin's efficacy in preventing rheumatic fever has been well established. Prevention of ARF is thought to occur through the eradication of the organism from the pharynx, and is more dependent upon prolonged, rather than high dose, therapy. Penicillin has been shown to prevent ARF when therapy is started within nine days of onset of symptoms.[4] Treating children with GABHS pharyngitis will not prevent the onset of acute glomerulonephritis.

Erythromycin remains the drug of choice in patients who are known to be allergic to penicillin. However, resistance to erythromycin can develop quickly when it is used to treat GABHS infections in a large population. The newer macrolides, such as azithromycin and clarithromycin, appear to be efficacious in the treatment of GABHS pharyngitis. Antimicrobial resistance to azithromycin and clarithromycin is rare.[17]

Amoxicillin has been shown to be effective in treating GABHS pharyngitis. In contrast to penicillin, amoxicillin is more palatable and provides easier dosing. Once-daily therapy for streptococcal pharyngitis with amoxicillin has been shown to be as effective as penicillin given three times a day.[18]

Oral cephalosporins and clindamycin also are effective therapies for the treatment of GABHS pharyngitis. However, resistance to clindamycin can develop quickly in populations. GABHS is considered resistant to treatment with tetracyclines and sulfonamides.

**Disposition.** A favorable clinical response is generally obtained within 24 hours of beginning therapy, and most children will have a negative throat culture by 48 hours and can return to school at that time.[19] The persistence of symptoms beyond this time period may signify the development of a complication, lack of compliance with antimicrobial therapy, or the presence of another underlying disease. In most cases, tests of

cure generally are not recommended.

Complications of GABHS pharyngitis are generally grouped into suppurative and nonsuppurative categories. Nonsuppurative complications of GABHS pharyngitis include ARF and acute glomerulonephritis (AGN). Table 1 lists criteria for the diagnosis of ARF. Suppurative complications of GABHS pharyngitis include peritonsillar abscess, peritonsillar cellulitis, retropharyngeal abscess, otitis media, sinusitis, uvulitis, endocarditis, osteomyelitis, meningitis, and brain abscesses. Poststreptococcal reactive arthritis (PSRA) often is considered a nonsuppurative complication of GABHS pharyngitis that some investigators postulate may be a variant of, or precursor to, ARF. Some clinicians suggest that patients who present with PSRA require antimicrobial prophylaxis to prevent the occurrence of rheumatic heart disease.[1]

Interestingly, episodes of GABHS pharyngitis may herald a first attack of guttate psoriasis or reactivate chronic plaque psoriasis.[20] GABHS is thought to act as an initiator of the disease in a significant number of genetically susceptible individuals. Eradication of GABHS has been shown to result in clinical improvement in some patients, though controlled clinical trials have not been performed. Several neuropsychiatric disorders, such as obsessive-compulsive disorder and Tourette's syndrome, also have been associated with episodes of GABHS pharyngitis.[21,22] Many investigators believe that there are subsets of patients with obsessive-compulsive disorder and Tourette's syndrome for whom GABHS infections act as a trigger of, or to exacerbate, symptoms. GABHS pharyngitis also has been linked to cases of Henoch-Schonlein purpura.[23]

## Streptococcal Pyoderma (Impetigo)

**Epidemiology.** Streptococcal pyoderma is defined as a localized purulent infection of the skin and often is used synonymously with streptococcal impetigo and impetigo contagiosa. Streptococcal pyoderma is most commonly seen in children between ages 2 and 5 years and often occurs among economically disadvantaged children in tropical or subtropical climates.[4] There is no known sex predilection to infection, and all races appear susceptible.[4]

**Pathophysiology.** Pyoderma most often results following direct inoculation of the skin with GABHS following minor trauma, an abrasion, or an insect bite (hippelates fly). In most cases, coinfection occurs with *Staphylococcus aureus*. Strains of GABHS that typically cause pyoderma differ from those associated with episodes of pharyngitis in respect to their M serotypes.

**Clinical Features.** Streptococcal pyoderma often begins as a papule that rapidly evolves into a vesicular lesion surrounded by erythema. The vesicular lesion often will give rise to pustules that gradually enlarge and then break down over a period of 4-6 days to form thick, honey-colored crusts. Lesions heal slowly and can leave depigmented areas. Lesions that extend more deeply into the epidermis and produce shallow ulcers are known as ecthyma.

Pyoderma often occurs on exposed areas of the body, in particular the lower extremities. While lesions may remain well localized, there are frequently many of them. Rarely do children present with systemic symptoms, although regional lymph nodes may become enlarged.

**Diagnostic Studies.** The diagnosis of pyoderma or impetigo is made clinically. Diagnostic studies are generally not required. Interestingly, the ASO response after a cutaneous streptococcal infection often is weak. This may be due to local inactivation of streptolysin O by skin lipids. Therefore, ASO titers are not helpful in diagnosing GABHS as the causative organism in children with pyoderma.

**Management.** Historically, pyoderma was treated with penicillin. However, penicillin therapy now more commonly is associated with treatment failures. Recent reports have documented *Staphylococcus aureus*, either alone or in combination with GABHS, as the predominant etiologic agent in nonbullous impetigo.[24] Because most such staphylococci produce penicillinase, treatment of nonbullous impetigo with penicillin alone frequently fails. Cloxacillin, cephalexin, and cefadroxil are recommended first-line therapies. Erythromycin can be used for penicillin-allergic patients. The efficacy of erythromycin may be compromised in areas where erythromycin-resistant staphylococci or streptococci are prevalent. Patients should be treated for 10 days. Mupirocin ointment, applied directly to skin lesions, has been shown to be as effective as enteral therapy but is considerably more expensive.[4] Mupirocin has excellent in vitro activity against both streptococci and staphylococci.

**Disposition.** While ARF is not a known complication of GABHS pyoderma, skin infections caused by nephritogenic strains (e.g., 45 and 55) of group A streptococcus are the major antecedent of poststreptococcal glomerulonephritis.[25] Treatment of streptococcal pyoderma has not been shown to prevent acute glomerulonephritis.[26] Septicemia rarely occurs following GABHS pyoderma.

### Table 1. Revised Jones Criteria for the Diagnosis of Acute Rheumatic Fever

**Supporting evidence of preceding streptococcal infection must be present.**

MAJOR MANIFESTATIONS

- Carditis
- Polyarthritis
- Chorea
- Erythema marginatum
- Subcutaneous nodules

MINOR MANIFESTATIONS

- Clinical
  - Fever
  - Arthralgia
  - Previous rheumatic fever or rheumatic heart disease
- Laboratory
  - Increase of acute phase reactants:
    - Erythrocyte sedimentation rate, leukocytosis
    - C-reactive protein
  - Prolonged P-R interval

A probable case occurs when two major criteria or one major and two minor criteria are present.

## Erysipelas

**Epidemiology.** Erysipelas is characterized by an acute inflammation of the skin with involvement of cutaneous lymphatic vessels. Erysipelas most commonly occurs in infants, very young children, or adults older than 30 years.

**Pathophysiology.** Erysipelas classically involves the more superficial layers of the skin and cutaneous lymphatics. This is in contrast to cellulitis, which typically extends more deeply into subcutaneous tissues. The anatomic distinction is the basis for clinically differentiating between the two diseases.

The great majority of cases of erysipelas are due to group A streptococcus. Groups G, C, and B streptococci and, rarely, staphylococci species, also may cause erysipelas.[25] In a typical case, infection begins following direct inoculation of the skin with GABHS. Typical portals of entry include local trauma or abrasions and psoriatic, eczematous, or tineal lesions.[25] Occasionally, hematogenous infection may occur. Following an incubation period of 2-5 days, a small area of redness will develop that gradually enlarges to form a characteristic tense, hot, painful, shiny bright red, brawny infiltrated plaque with a distinct and well-marginated border.

**Clinical Features.** Erysipelas historically has involved the face. Infections of the face often were preceded by a sore throat. Recent reports, however, have documented up to 85% of cases involving the legs and feet.[25] When involving the trunk or extremities, erysipelas most commonly occurs at the site of a wound or of a surgical incision.

Erysipelas is typically accompanied by fever and characterized by a rash that spreads centrifugally. The rash is normally scarlet-red or salmon color with a well-defined border. The advancing red margins of the lesion are raised and well demarcated from adjacent normal tissue. This is in contrast to cellulitis, with which there often is no clear distinction between infected and uninfected tissues. Marked edema, associated with bleb formation, can occur, and in facial erysipelas the eyes often are swollen shut. The rash of erysipelas may demonstrate central clearing while continuing to expand. Approximately 5% of patients will become bacteremic.[25] Lymphangitis and lymphadenitis also may occur.

**Diagnostic Studies.** The diagnosis of erysipelas is made clinically. There are no diagnostic studies that are required in the majority of cases. A complete blood count will reveal leukocytosis with a neutrophil predominance. Blood cultures are positive for GABHS in 5% of cases.[25]

**Management.** Children with erysipelas should be treated with penicillin. Superficial infections may be treated orally for 10 days, while more aggressive infections require parenteral therapy. Patients allergic to penicillin can be treated with erythromycin.

**Disposition.** Facial erysipelas often spontaneously resolves in 4-10 days.[4] However, untreated lesions on the trunk or extremities typically will involve large areas of the body surface and can lead to increased morbidity and mortality. Penicillin-resistant staphylococci often coexist in chronic or persistent cases. In such patients, a semisynthetic penicillinase-resistant penicillin, such as nafcillin or cefazolin, is recommended.

## Necrotizing Fasciitis

**Epidemiology.** Necrotizing fasciitis (NF) is a rapidly progressing, deep-seated infection of the deep subcutaneous tissues and fascia. NF is characterized by extensive and rapidly spreading necrosis of the fascia and fat. Although necrotizing fasciitis caused by GABHS has been recognized for years, a recent increase in the reporting of such infections has occurred.[27] In addition, NF now is associated more commonly with the early onset of shock and organ failure, characteristics of streptococcal toxic shock syndrome.[27,28] There is no recognized age or sex predilection for NF.[29]

**Pathophysiology.** As in other invasive streptococcal and staphylococcal skin infections, the primary site of inoculation is usually an area of minor trauma or the skin lesions of varicella.[30] It has been reported to occur following burns, splinters, surgical procedures, childbirth, blunt trauma, and muscle stain.[28] In neonates, omphalitis and circumcision are common predisposing factors.[31,32]

NF of the head and neck is rare. When NF does involve the head or neck regions, it tends to be polymicrobial and is associated with higher rates of mortality.[29]

Coinfection with both GABHS and *S. aureus* often characterizes NF that develops in patients following trauma to the skin and soft tissues, or in patients with varicella. Necrotizing fasciitis involving the abdominal wall and NF that follows abdominal surgery often are mixed infections involving both anaerobic and aerobic gram-negative bacteria. Hematogenous spread from a distant site of infection probably occurs and likely accounts for reports of necrotizing fasciitis following a sore throat (presumably GABHS pharyngitis).[29]

In NF, the infection typically spreads along fascial planes, causing widespread necrosis, suppuration, and thrombosis of vessels. Tissue damage and systemic toxicity is believed to be due to the release of bacterial toxins and endogenous cytokines, including exotoxins A and B.[28]

**Clinical Features.** The first cutaneous clue to necrotizing fasciitis may be diffuse swelling of an arm or leg followed by the appearance of bullae filled with clear fluid.[25] The fluid may rapidly take on a maroon or violaceous color. Some patients may present with an erythematous, tender, swollen, hot area of cellulitis accompanied by pain and fever. Induration or distinct margins are typically absent. Unless appropriate intervention is undertaken, lesions will progress to frank cutaneous gangrene after 4-5 days that, in 50% of patients, is associated with myonecrosis.

Necrosis of the superficial fascia and fat produces a watery, thin, and foul-smelling fluid termed "dishwater pus."[29] The extent of fascial necrosis is generally more widespread than changes in the overlying skin might indicate. Thrombosis of the skin's nutrient arteries can cause focal areas of necrosis. The subcutaneous nerves often are destroyed during the infectious process, leading to hypesthesias or anesthesias. Lymphangitis and lymphadenitis are rare.[29] As organisms and toxins are liberated into the bloodstream, patients will develop marked systemic symptoms, including evidence of shock and multiorgan failure. Septic emboli can be seen, as well as metastatic abscesses.[29] During the second week of infection, the skin may slough spontaneously.

**Diagnostic Studies.** Differentiating between cellulitis and necrotizing fasciitis may be difficult during the early stages of the disease. However, differentiation is critical, as appropriate treatment is markedly different among the two diseases. Computed tomographic or magnetic resonance imaging (MRI) is helpful in locating the site and depth of infection.[33] MRI is able

to demonstrate tissue contrasts, detect soft-tissue fluid, and visualize the pathologic process of NF.[29] Frozen-section biopsy also may aid in the clinical diagnosis.[34] Rapid antigen detection kits for GABHS have been used to identify the presumptive causative organism in patients with necrotizing fasciitis.[35]

Measurement of compartment pressures may be helpful in patients who present with severe pain and symmetric swelling of an extremity, but have no cutaneous evidence of infection.[25] Elevated compartment pressures contribute to myonecrosis, whether of infectious or noninfectious origin, and generally require immediate fasciotomy.[25]

Aspirated material from an area of fascial necrosis can aid in identifying the causative organism. Gram's stain and culture should be performed on aspirated material. The necrotic center of the lesion is preferred, in contrast to cellulitis where the leading edge often is sampled.[29]

If the diagnosis remains in doubt, surgical exploration is indicated.[25] Surgery can establish a definitive diagnosis by providing material for culture, as well as histopathological examination. Direct observation of the extent of the infection also may aid in deciding on the necessity for simple drainage, radical debridement, or amputation.

**Management.** Necrotizing fasciitis should be managed with early and aggressive surgical debridement of the site of infection as well as appropriate antimicrobial therapy. Even with appropriate and early antibiotic use, infection often progresses because thrombosis of superficial vessels precludes effective antibiotic penetration to the site of infection. In addition, tissue hypoxia impairs the oxidative killing mechanisms of leukocytes. As a result, early surgical intervention is critical.

Due to an inoculum effect, penicillin may be less effective in the treatment of necrotizing fasciitis than other antimicrobial agents.[36] Penicillin is known to be relatively ineffective in the treatment of soft-tissue infections with a high concentration of organisms. This is thought to occur due to the slow rate of replication of group A streptococcus, decreased expression of penicillin-binding proteins, and because penicillin primarily acts by interfering with cell wall synthesis.

Many investigators recommend that patients with GABHS toxic shock syndrome (TSS) be treated with a combination of a beta-lactam and a protein synthesis inhibitor: penicillin in combination with clindamycin.[37] Clindamycin acts by inhibiting protein synthesis, decreasing the production of M proteins and toxins, and is unaffected by slow-growing toxin-producing streptococci. In addition, clindamycin may prevent group A streptococcus from expressing a capsule, an important virulence factor.[38] A combination of nafcillin and clindamycin also may be used.[39]

Intravenous immune globulin (IVIG) has been used to treat patients with NF. However, the benefits of IVIG have not been well established.[40,41] Patients with necrotizing fasciitis in whom the etiologic agent or agents cannot be definitively identified should be treated with broad-spectrum antimicrobial regimens effective against both aerobic and anaerobic organisms.

Hyperbaric oxygen therapy has been used to treat necrotizing fasciitis.[39,42,43] Hyperbaric oxygen therapy is thought to promote leukocyte response through oxygenation of devitalized tissue. In addition, it may aid in collagen deposition, angiogenesis, and reepithelialization. However, there are currently no prospective, randomized, controlled trials demonstrating its efficacy.

Several recent case reports have raised concern regarding a potential association between necrotizing fasciitis and nonsteroidal anti-inflammatory drugs (NSAIDs).[44,45] A recent case control study reported similar findings.[46] While the published reports suggest an association between necrotizing fasciitis and NSAIDS, causation has not been proven. Randomized, placebo-controlled, prospective studies are needed to better define the relationship. Currently, some clinicians recommend caution when using NSAIDs to treat patients with skin or soft-tissue infections or with varicella.

**Disposition.** Necrotizing fasciitis often is associated with severe systemic involvement and an associated high mortality rate.[47] Untreated, the disease is almost invariably fatal.[29] Even treated, mortality rates as high as 76% have been reported.[48] Investigators have shown that delays in diagnosis and treatment, particularly that of surgical debridement and fasciotomy, correlate with poor outcome.[48] The usual cause of death is overwhelming sepsis or multiple organ system failure.

Clinicians should be aware of the association of invasive GABHS disease in children with varicella. A recent, prospective, population-based surveillance of pediatric invasive GABHS disease in Ontario, Canada, found that 15% of children identified had preceding chickenpox infection.[49] Children with invasive GABHS disease and recent chickenpox were more likely to develop NF.

## GABHS Bacteremia

**Epidemiology.** Recently, an increase in the number of cases of children with group A streptococcal bacteremia has been recognized. Most cases have occurred in children diagnosed with varicella. Like NF, a clear association between varicella and GABHS bacteremia has been documented. Close to 10% of patients found to have GABHS bacteremia also have varicella.[50] GABHS bacteremia often occurs during invasive GABHS skin and soft-tissue infections and in GABHS TSS.

**Pathophysiology.** GABHS bacteremia in varicella is thought to develop secondarily to a superinfected lesion. Malignancy and immunosuppresion are known contributing risk factors to the development of GABHS bacteremia. Serotypes M-1 and M-3 most commonly have been isolated in patients with GABHS bacteremia. Serotypes M-1 and M-3 are considered highly invasive and are associated with higher rates of morbidity and mortality. M type 1 strains are known to produce pyrogenic exotoxins A and B, which may play a role in the development of bacteremia.

**Clinical Features.** The onset of GABHS bacteremia often is abrupt and is characterized by high fever and chills. Rarely, children may present with abdominal pain. High fever and signs of toxicity and severe systemic involvement may indicate the presence of bacteremia.

**Diagnostic Studies.** Blood cultures should be obtained in all children suspected of being bacteremic. Further diagnostic studies often are obtained to diagnose a precipitating event or underlying disease.

**Management.** Children with GABHS bacteremia can be treated with parenterally administered penicillin. Patients aller-

## Table 2. Case Definition of Streptococcal Toxic Shock

I. ISOLATION OF GROUP A STREPTOCOCCI

a. Isolation of group A streptococci from a normally sterile site
b. Isolation of group A streptococci from a nonsterile site

II. CLINICAL SIGNS OF SEVERITY

a. Hypotension
b. More than two of the following signs:
- Renal impairment
- Coagulopathy
- Liver involvement
- Adult respiratory distress syndrome
- Generalized, erythematous macular rash that may desquamate
- Soft-tissue necrosis or gangrene

Definite case: Fulfill criteria 1a, 2a, and 2b.
Probable case: Fulfill criteria 1b, 2a, and 2b and no other etiology identified.

gic to penicillin can be treated with clindamycin, vancomycin, or a first-generation cephalosporin. However, combination antimicrobial therapy may be warranted in bacteremic children with signs and symptoms of severe, invasive, GABHS infections of the skin and soft-tissues.

**Disposition.** Documented mortality rates in children with GABHS bacteremia have ranged from 27% to 38%.[50] Children with bacteremia should be hospitalized and receive intravenous antibiotics. Treatment generally lasts 10 days.

## GABHS Toxic Shock

**Epidemiology.** Cases of GABHS TSS have been reported in North America, Europe, and Australia. Patients often have no predisposing conditions and, in most cases, the initial site of infection is the skin or soft tissue.[37] Fifty percent of patients with GABHS TSS will have necrotizing fasciitis.[25] In children, many cases develop following bacterial superinfection of varicella lesions. However, in contrast to adults, children are more likely to develop GABHS toxic shock in the absence of invasive local disease.[37] GABHS TSS has been reported following GABHS pharyngitis.

**Pathophysiology.** GABHS toxic shock most commonly occurs following infection with the M1 serotype of GABHS but has been associated with types 3, 12, and 28.[51-53] Recent investigations into the pathophysiology of this disorder have focused on the role of streptococcal pyrogenic exotoxins, extracellular products of group A streptococci that mediate not only scarlatiniform-like rashes but also multiorgan damage and shock. These toxins increasingly have been noted in cases of GABHS TSS.[27,53]

SPE-A is the most common exotoxin found in the United States and has been shown to be both a superantigen and a potent inducer of tumor necrosis factor.[4,54] SPE-A has been linked with the recent resurgence of severe, invasive group A streptococcal infections.[27,55] A second exotoxin, SPE-B, also has been implicated but is more commonly found in cases of TSS that occur in European countries.[52,53]

**Clinical Features.** GABHS toxic shock may develop with no clinically obvious preceding infection. However, it more commonly occurs following a soft-tissue infection, particularly as a superinfection of varicella lesions or as a complication of necrotizing fasciitis or myositis. Streptococcal toxic shock can occur following an episode of pharyngitis.

In a typical case, infection will begin at a site of minor trauma, with 20% of children developing an influenza-like prodrome. Early signs and symptoms are similar to that of necrotizing fasciitis. Within 1-3 days, patients will develop intense, local pain at the initial site of infection (seemingly out of proportion to physical findings), high fever, localized swelling, and erythema. Patients also can develop vesicles or bullae with a violaceous or bluish hue; such findings are considered ominous. Untreated patients will subsequently develop hypotension and a constellation of signs and symptoms indicative of multiorgan failure. Evidence of renal impairment often precedes signs of hypotension.[25] Many patients will develop a generalized macular erythematous rash that subsequently desquamates.

**Diagnostic Studies.** A consensus definition has been developed to identify patients with GABHS TSS.[56] Table 2 lists the clinical criteria used in the definition. Diagnostic studies often are obtained to determine if the patient meets the case definition for GABHS TSS and to determine the clinical severity of the disease. A complete blood count, with platelets and differential, prothrombin, partial thromboplastin time, electrolytes, calcium, magnesium, phosphorous, liver function tests, blood urea nitrogen, creatinine, albumin, and total protein should be obtained.

The white blood cell count will be elevated in patients with GABHS toxic shock, with a predominance of immature granulocytes, including myelocytes and metamyelocytes. Hemoglobin concentrations and platelet counts tend to decline during the course of the illness. Azotemia, elevated creatine kinase, hypoalbuminemia, and hypocalcemia often are present.[25,37] Blood cultures are positive in approximately 60% of cases of streptococcal TSS. This is in marked contrast to that of staphylococcal TSS.

Imaging studies are generally not helpful in the management of GABHS TSS. However, they may be helpful in diagnosing NF as previously described.

**Management.** Children with GABHS TSS require intensive management of hemodynamic abnormalities and vital functions. Patients with a soft-tissue focus of infection may require surgical intervention (see description of management of NF). Broad-spectrum antibiotic coverage should be instituted until the presence of group A streptococcus has been confirmed. High dose, parenterally administered penicillin then can be used. Patients allergic to penicillin can be treated with a first-generation cephalosporin or vancomycin.

Patients who develop GABHS toxic shock following a skin or soft-tissue infection should be treated with combination therapy, a combination of a beta-lactam and a protein synthesis inhibitor such as penicillin and clindamycin. As in cases of necrotizing fasciitis, evidence suggests that in GABHS TSS secondary to a skin or soft-tissue infection, tissue destruction continues despite high concentrations of penicillin.

Intravenous immunoglobulin has been used to treat patients with GABHS toxic shock and may provide some benefit.[37] IVIG is thought to work through toxin neutralization.

**Disposition.** Patients with suspected GABHS TSS should be

hospitalized for appropriate management. Antimicrobial therapy is generally provided for 10 days. As in patients with necrotizing fasciitis, delays in diagnosis and treatment, particularly the use of surgical debridement and fasciotomy in cases associated with skin and soft-tissue infections, lead to poor outcomes. The usual cause of death in patients with GABHS toxic shock is overwhelming sepsis or multiple organ system failure.

## Summary

Group A beta-hemolytic streptococcus is an important and common cause of infections involving the upper respiratory tract and skin in children. Most clinicians are familiar with GABHS pharyngitis, as well as its suppurative and nonsuppurative complications. However, clinicians also should be aware that the pathogen can cause a variety of skin and soft-tissue infections, some of which are severe and even life threatening.

GABHS continues to be susceptible to beta-lactam antibiotics. Numerous studies continue to document its clinical efficacy in the treatment of most GAHBS infections, including pharyngitis, erysipelas, impetigo, and cellulitis. However, in more aggressive infections such as necrotizing fasciitis, bacteremia, and TSS, penicillin has been associated with high mortality and extensive morbidity. In these cases, combination antimicrobial therapy should be used (e.g., penicillin and clindamycin). In addition, early surgical debridement and fasciotomy in patients with skin and soft-tissue infection improves clinical outcomes.

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## Physician CME Questions

9. Which of the following toxins is thought to be responsible for the rash in children with scarlet fever?
   A. M protein
   B. DNAase B

C. Streptococcal pyrogenic exotoxin
D. Streptolysin O

10. GABHS is serotyped based on which protein or toxin?
    A. M protein
    B. Streptolysin O
    C. SPE-A
    D. Hyaluronidase

11. Antimicrobial therapy for children with GABHS pharyngitis is thought to prevent all of the following *except*:
    A. ARF.
    B. AGN.
    C. peritonsillar abscess.
    D. otitis media.

12. Rapid antigen detection kits for GABHS are limited by:
    A. poor specificity.
    B. poor sensitivity.
    C. difficulty of use.
    D. low cost.

13. Coinfection with what bacteria often occurs in children with GABHS pyoderma?
    A. *Neisseria menigitidis*
    B. *Staphylococcus aureus*
    C. *Streptococcus pneumoniae*
    D. *Eschericia coli*

14. The lesions of erysipelas, unlike those of cellulitis:
    A. are warm.
    B. are tender.
    C. are red.
    D. have a well-defined border.

15. Morbidity and mortality in children with necrotizing fasciitis is most dependent on:
    A. treatment with hyperbaric oxygen.
    B. combination antimicrobial therapy.
    C. use of IVIG.
    D. early and aggressive surgical debridement of the site of infection.

16. Penicillin is thought to be relatively ineffective in the treatment of soft-tissue infections caused by GABHS because:
    A. GABHS has become highly resistant to penicillin.
    B. of the slow rate of replication of group A streptococcus and decreased expression of penicillin-binding proteins.
    C. of its inability to be given parenterally.
    D. of its high rate of allergic reactions.

17. What is considered the drug of choice in penicillin-allergic children with GABHS pharyngitis?
    A. Erythromycin
    B. Tetracycline
    C. Bactrim
    D. Doxycycline

18. GABHS infections have been linked with, or are considered a precursor to, which infection?
    A. HSP
    B. SLE
    C. Wegener's granulomatosis
    D. Eczema

## In Future Issues:

Lower Airway Disease