Group A *Streptococcus*

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Education Gaps

1. Clinical prediction rules for group A *Streptococcus* pharyngitis are unreliable in children, and unless viral etiology is strongly suspected, throat swab with a rapid antigen detection test should be performed.
2. Avoid "proof of cure" cultures when treating pharyngitis.
3. Clindamycin is important in invasive group A *Streptococcus* infection for toxin mediation but should not be used alone secondary to possible resistance.

Objectives

After completing this article, readers should be able to:

1. Understand the epidemiology, transmission, and major virulence factors of group A *Streptococcus* (GAS) infections.
2. Plan the appropriate diagnostic evaluation of suspected GAS infection.
3. Recognize the clinical features of, and major complications associated with, invasive and noninvasive GAS infections.
4. Plan appropriate management for a patient with a GAS infection.

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ABBREVIATIONS

ANF	acute necrotizing fasciitis
ARF	acute rheumatic fever
GAS	group A *Streptococcus*
IVIG	intravenous immunoglobulin
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *S aureus*
PANDAS	pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
PSGN	poststreptococcal glomerulonephritis
STSS	streptococcal toxic shock syndrome

INTRODUCTION

In 1933, Rebecca Lancefield changed our understanding of β-hemolytic streptococci by developing a system of serologic classification based on the carbohydrate composition of cell wall antigens. Of these organisms, the most significant in human pathogenicity is group A *Streptococcus* (GAS), otherwise known as *Streptococcus pyogenes*. (1) GAS is responsible for an impressively wide variety of clinical manifestations, from noninvasive infections, such as pharyngitis, scarlet fever, erysipelas, and cellulitis, to invasive disease, including sepsis, streptococcal toxic shock syndrome (STSS), and necrotizing fasciitis (Table 1). It has also been linked to multiple nonsuppurative complications including acute rheumatic fever (ARF), poststreptococcal glomerulonephritis (PSGN), and the controversial pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Globally, an estimated 18 million people are suffering from a serious GAS-related illness, with about 1.78 million new cases annually. Hundreds of millions of people develop less serious GAS infection every

year, placing a massive burden on healthcare systems. The complications of GAS infections disproportionately affect those in low- and middle-income countries. Transmission of GAS is via droplets from those with pharyngeal infection or colonization, direct contact, contaminated fomites, or food-borne contamination. (2)(3)

The virulence and range of infection and complications of GAS can be attributed to certain characteristics that this gram-positive bacterium possesses, including cellular constituents, extracellular products, and unique autoimmune responses it can produce. Important virulence factors include a hyaluronic acid capsule, which protects GAS from phagocytosis, and the M protein, a surface protein that is used to define serotypes of GAS. The M protein also contributes to virulence in many ways, including inhibition of opsonization and phagocytosis, as well as facilitating tissue invasion. Extracellular products are numerous and play many different roles, and include the streptococcal pyrogenic exotoxins. Toxins play a particularly important role in invasive GAS infections like STSS, in which mediation of toxin production with the protein synthesis inhibiting clindamycin is especially important. A particular group of streptococcal toxins, called *superantigens*, stimulate massive cytokine release, which is responsible for the overwhelming and rapid progression of disease that can be seen in invasive streptococcal infections. A protease toxin, SpeB, is also known to play an important role in virulence, implicated as contributing to both superficial and invasive disease. (1)(3)(4)

This review covers the major noninvasive and invasive GAS infections and complications in children, and will touch on recent research, including vaccine development and burgeoning resistance.

TABLE 1. **Various Infection Types with Group A *Streptococcus***

TYPES OF INFECTION	
Noninvasive	Pharyngitis Otitis media Sinusitis Impetigo Erysipelas Cellulitis Vulvovaginitis Dactylitis Pneumonia without bacteremia
Invasive	Sepsis Focal infections with bacteremia Streptococcal toxic shock syndrome Necrotizing fasciitis Meningitis Peritoneal infection Septic arthritis Osteomyelitis Cardiac—endocarditis, pericarditis
Non-suppurative complications	Acute rheumatic fever Poststreptococcal glomerulonephritis Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections

NONINVASIVE GAS INFECTIONS

Streptococcal Pharyngitis

Pharyngitis accounts for about 6% of all primary care physician visits, and about 40% of children older than 3 years presenting with a complaint of sore throat will test positive for GAS. (5)(6) It occurs most commonly in children 5 to 15 years of age during winter months. (1) Clinical signs and symptoms in school-age and older children include sore throat, fever, tender anterior cervical adenopathy, pharyngeal and tonsillar exudate (Fig 1), vomiting, and headache. Younger children and infants, on the other hand, may present with generalized lymphadenopathy, fever, and serous nasal discharge. (7)

If GAS pharyngitis is suspected, the diagnostic approach should begin with a rapid antigen detection test in children older than 3 years followed by throat culture in those who test negative. Children younger than 3 years of age are unlikely to manifest ARF, and thus diagnosis and treatment are less important. However, physicians may choose to test children younger than 3 years if risk factors are significant, for example, when symptoms are present and the child has a relative with GAS. (8) Culture is not necessary in those who test positive with the antigen test. (9) Multiple clinical prediction rules are available to aid in the diagnosis of GAS. The Centor criteria, for example, assign a point each to temperatures greater than 101.3°F (38.5°C), swollen and tender anterior cervical lymph nodes, tonsillar exudate, and absence of cough. These criteria were tested in studies that showed them to be effective in ruling out GAS pharyngitis in adult patients with 2 or fewer criteria. These criteria must be used with caution in children, however, because multiple studies have demonstrated the unreliability of clinically observable signs and symptoms. (5)(10)(11) Unless clinical findings strongly suggest a viral etiology (conjunctivitis, rhinitis, coryza, rash, cough), throat swab with the rapid test should be used to rule out GAS, and these clinical prediction rules should not be used in isolation.

The need to treat all cases of GAS pharyngitis in high-resource settings with low incidence of rheumatic fever is controversial. However, current recommendations in the

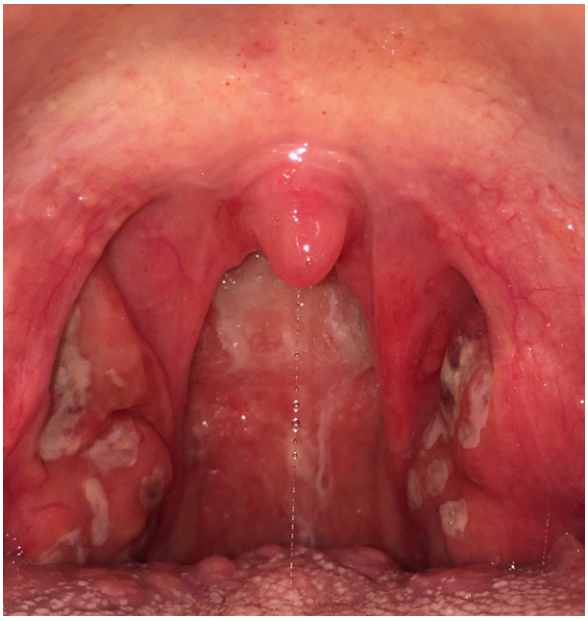

Figure 1. Tonsillar exudate and palatal petechiae in a patient with group A *Streptococcus* pharyngitis.

United States are to do so. To prevent rheumatic fever, treatment must be started within 9 days of symptom onset. Preferred oral antibiotic regimen is penicillin V or amoxicillin for 10 days. Physicians should note the benefit of once-daily dosing of amoxicillin, which may be preferred. Another option, particularly in patients who may have difficulty reliably taking oral medications, is intramuscular benzathine penicillin G. Procaine penicillin has decreased pain associated with the injection. In penicillin-allergic patients who have not had a systemic anaphylactic reaction, a first-generation cephalosporin is recommended for 10 days. Otherwise, physicians may give clarithromycin or clindamycin for 10 days, or azithromycin for 5 days. (8) Posttreatment throat cultures as proof of cure are unnecessary unless symptoms persist 2 to 7 days after completion of therapy. (12)

Scarlet Fever

Scarlet fever, or scarlatina, results from the systemic elaboration of erythrogenic GAS exotoxins, most commonly in association with GAS pharyngitis but occasionally from skin and skin structure infection. More severe manifestations are less common in areas where antibiotic treatment is readily available. The most characteristic symptom is a rash that typically begins on the upper chest or neck 1 to 2 days after the onset of GAS infection and will spread to the extremities and face. There is diffuse erythema which blanches, with a finely papular "sandpaper" texture of the skin (Fig 2), with pinpoint areas of deeper red scattered petechiae that do not blanch, and "Pastia's lines" (Fig 3), which are areas of deeper red in the skin creases. Other findings include circumoral pallor (Fig 4), strawberry tongue, and later desquamation (Fig 5). (1)(13) Treatment is focused on the underlying bacterial infection that is the nidus of toxin production and the subsequent symptoms of scarlet fever.

Acute Rheumatic Fever

ARF is an illness that involves multiple organ systems, and is the leading cardiovascular cause of death in children in low-income countries. (12) It has an onset typically 2 to 4 weeks after GAS pharyngitis; other types of GAS infection have not reliably shown an association with ARF, though there is some evidence of its occurrence. (14)(15)(16)(17) ARF is thought to be an autoimmune response via molecular mimicry. (18) The link between prior GAS infection and onset of ARF is clear, with the advent of antibiotic treatment for GAS pharyngitis leading to a sharp decline in the incidence of ARF. (19) Diagnosis is made using the Jones criteria, in which 2 major, or 1 major and 2 minor, criteria must be fulfilled along with evidence of preceding GAS infection (Table 2). Major criteria are carditis, arthritis, chorea, erythema marginatum (Fig 6), and subcutaneous nodules, while minor criteria include arthralgia, fever, elevated erythrocyte sedimentation rate, and prolonged PR interval. In 2015, the American Heart Association updated the Jones criteria, distinguishing between low- and moderate- to high-risk populations, and emphasizing the use of echocardiography in diagnosing carditis, and the inclusion of monoarthritis and polyarthralgia as major criteria in moderate- or high- risk populations. A low-risk population is one that has an ARF incidence of less than or equal to 2 per 100,000 school-aged children or all-age rheumatic heart disease prevalence of less than or equal to 1 per 1,000 population per year. (20) The incidence of primary ARF is greatest in children from 5 to 14 years of age with equal

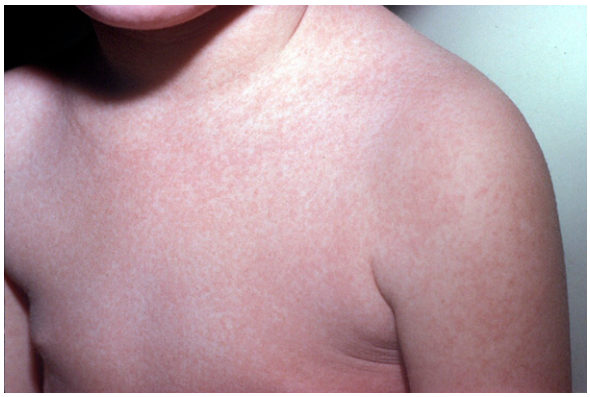

Figure 2. Diffuse erythematous sandpaper rash of scarlet fever. (74)

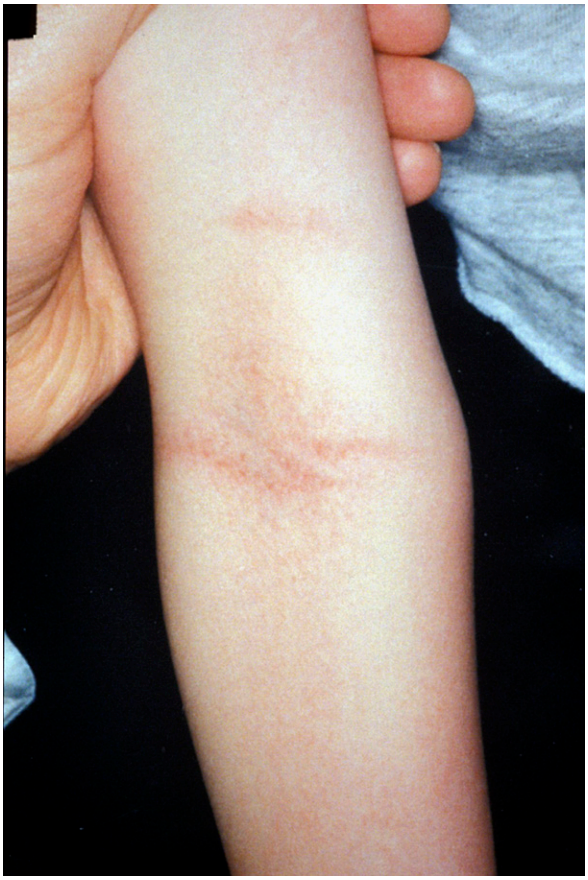

Figure 3. Pastia's lines in a patient with scarlet fever. (74)

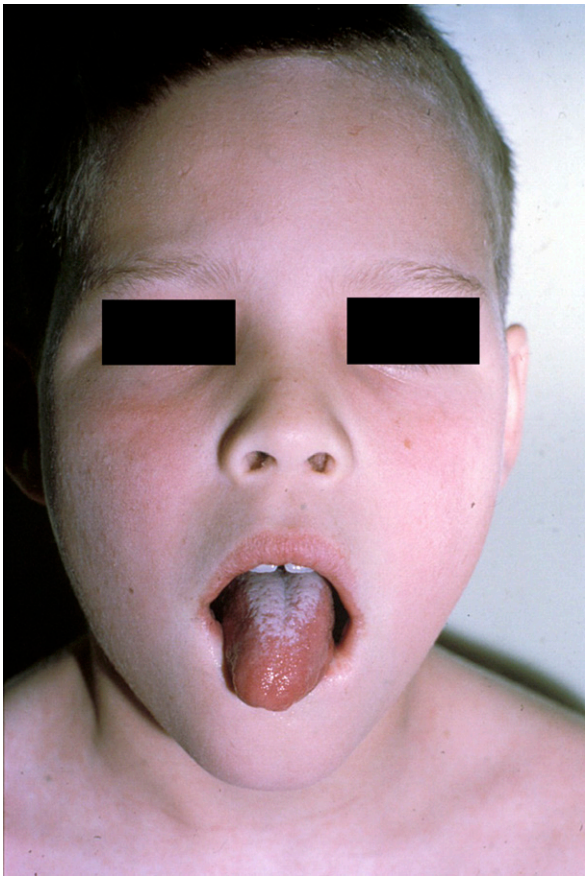

Figure 4. Circumoral pallor and strawberry tongue in a patient with scarlet fever. (74)

distribution between boys and girls, though girls have a greater incidence of associated heart disease. (18)

Management of ARF focuses on eradication of GAS along with targeted therapy toward individual manifestations. Echocardiography with Doppler should be performed on initial presentation even in the absence of auscultatory findings, and serial echocardiography should be strongly considered even if carditis is not present on initial diagnosis. (20) Carditis is treated with bed rest, fluid restriction, cardiac medications and corticosteroids, (18) though it is unclear whether corticosteroids have a true impact on long-term outcomes. (21) There has been no evidence to demonstrate the efficacy of immune-modulating medications such as intravenous immunoglubulin (IVIG). (22) Arthritis is treated with aspirin at 50 to 70 mg/kg per day tapered over several weeks, (14)(15)(16)(17)(18)(19)(20)(21)(22)(23) though there is some evidence that the naproxen is an effective alternative to control inflammation and pain, and circumvents the rare risk of Reye syndrome. (24)(25)(26) Anti-inflammatory medications should be used with caution, however, before a definitive diagnosis of ARF is made, because they can mask developing symptoms that may contribute to the diagnosis. Sydenham chorea is typically benign and self-limiting, though it can be severe and onset can be up to months after initial infection. Pharmacologic treatment may be considered in patients with severe symptoms, and may include valproic acid, carbamazepine, and short courses of steroids. (18)(27)(28)

Children with a history of ARF are at greater risk of ARF recurrence with subsequent GAS infections and should

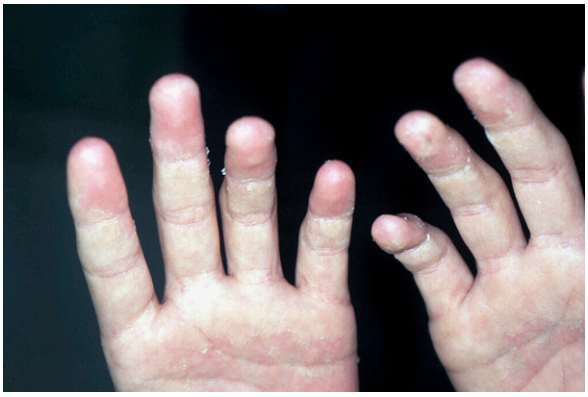

Figure 5. Desquamation of the fingertips in a patient with scarlet fever; desquamation typically occurs about 7 to 10 days after onset of illness. (74)

TABLE 2. **Revised Jones Criteria for ARF from 2015 American Heart Association Statement (20)**

Diagnosis of initial ARF requires 2 major criteria, or 1 major plus 2 minor criteria.
Diagnosis of recurrent ARF requires 2 major criteria, or 1 major plus 2 minor criteria, or 3 minor criteria.

	MAJOR CRITERIA	MINOR CRITERIA
Low-risk populations: ARF incidence ≤2 per 100,000 school-aged children or all-age rheumatic heart disease prevalence of ≤1 per 1,000 population per year	Carditis[a] (clinical and/or subclinical) Arthritis (polyarthritis only) Chorea Erythema marginatum Subcutaneous nodules	Polyarthralgia Fever (≥38.5°C) ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dL[b] Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)
Moderate- and high-risk populations	Carditis[a] (clinical and/or subclinical) Arthritis (monoarthritis or polyarthritis) OR Polyarthralgia[c] Chorea Erythema marginatum Subcutaneous nodules	Monoarthralgia Fever (≥38°C) ESR ≥30 mm/h and/or CRP ≥3.0 mg/dL[b] Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

ARF=acute rheumatic fever; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate.
[a]*Subclinical carditis indicates echocardiographic valvulitis as defined by Gewitz et al. (20)*
[b]*CRP value must be greater than upper limit of normal for laboratory. Also, because ESR may evolve during the course of ARF, peak ESR values should be used.*
[c]*Applicable as a major criterion only after careful consideration and exclusion of other causes of arthralgia.*

begin prophylaxis as soon as ARF is diagnosed. Prophylaxis may be intramuscular benzathine penicillin G once monthly or daily oral penicillin, and for penicillin-allergic patients a macrolide is typically used. Duration of prophylaxis is 5 years since the last episode of ARF or until 21 years of age in patients who did not have carditis, whichever is later. In patients with carditis who do not have residual heart disease (no valvular disease) duration is 10 years since the last ARF episode, or until 21 years of age, whichever is later. Finally, when there are persistent manifestations of rheumatic heart disease, penicillin prophylaxis is continued until 40 years of age at a minimum, and depending on severity of disease, many clinicians choose to provide prophylaxis for life. (12)(29)

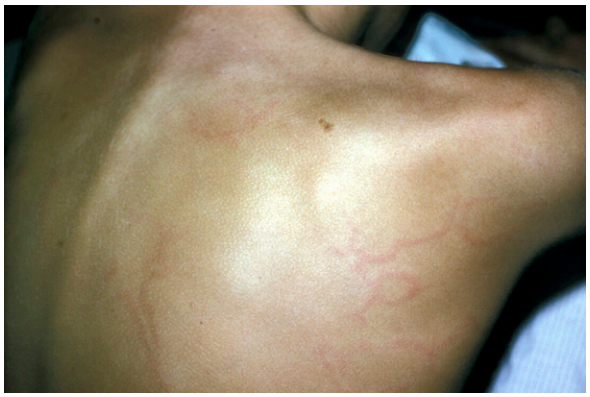

Figure 6. Erythema marginatum in a patient with acute rheumatic fever. This rash is characterized by nonpruritic, mildly raised ringlike erythema with central clearing. Although present in only a minority of cases of rheumatic fever, this finding is considered a major Jones criterion. (74)

Impetigo

Impetigo is an extremely common superficial infection of the skin described either as bullous or nonbullous. Bullous lesions are much more likely to be caused by *Staphylococcus aureus* with strains that commonly elaborate an erythrogenic toxin, whereas nonbullous impetigo may result from either GAS or *S aureus*. (30) From the 1950s through the 1970s, GAS was a more common cause of impetigo than *S aureus*, but since that time *S aureus* has become more common, accounting for more than 80% of these skin infections today. This change in etiology accounts for the decreased incidence of acute glomerulonephritis in children. Appearance of the lesion is not sufficient to identify the responsible organism; thus, if bacterial identification is desired, culture is necessary. The infection is most common in children 2 to 5 years of age, though it can occur in any age. (30) Nonbullous impetigo typically manifests in exposed areas, such as the face and limbs. It is characterized by erythematous papules, which evolve to vesicles that rapidly rupture to form characteristic "honey-colored" exudate and thick crusts (Fig 7). (31)

For more localized lesions, treatment consists of topical mupirocin or retapumulin. For more extensive or multiple

lesions, oral therapy may be considered. Cephalexin, a first-generation cephalosporin, will effectively treat GAS and methicillin-susceptible *S aureus* (MSSA). Physicians should be aware of the prevalence of methicillin-resistant *S aureus* (MRSA) in their communities, and if it is suspected, consider clindamycin or trimethoprim/sulfamethoxazole for oral therapy in more severe cases. (32)(33)(34) Although impetigo is a self-limited disease, treatment can shorten the time to resolution, and thus decrease spread of the infection. Culture of the lesion to identify the offending organism can be helpful, but it is also appropriate to empirically treat most cases without performing a culture. Children with impetigo should be withheld from school or daycare for 24 hours after the initiation of treatment.

Erysipelas and Cellulitis

Impetigo is an infection of the epidermis, erysipelas is an infection of the deeper dermis, and cellulitis involves the dermis and subcutaneous tissue. These latter infections are caused primarily by GAS, though they can also result from infections with group C or G streptococci, group B streptococci, or less commonly *S aureus*. (31)(34)(35)(36) Skin lesions such as eczema, chickenpox, or lacerations can become secondarily infected with GAS (impetiginized) leading to an abscess with surrounding cellulitis termed *pyoderma*.

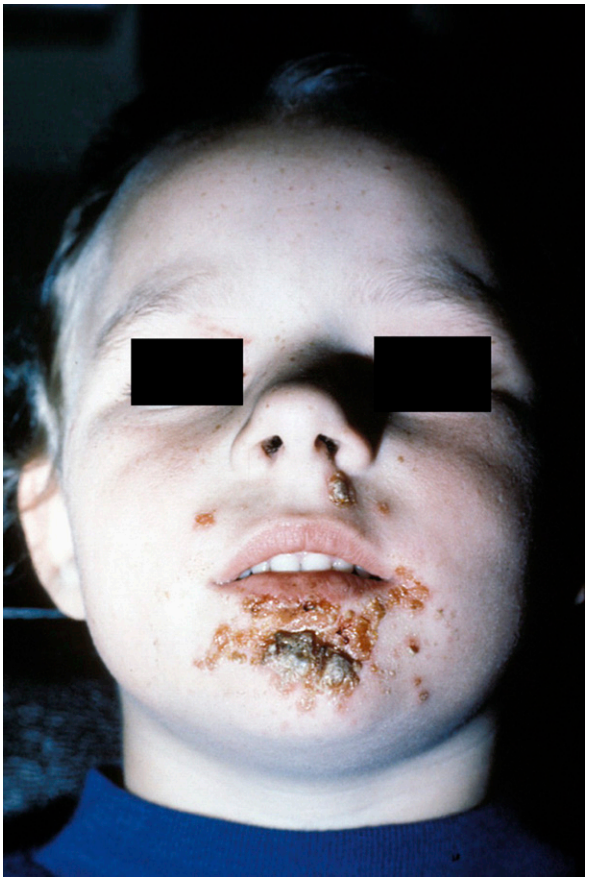

Figure 7. Impetigo with characteristic honey-colored exudate and thick crusts. (74)

Erysipelas presents as a raised, painful skin erythema with distinct borders, most often on the face or extremities (Fig 8). Frequently lymphatic involvement is seen with erythematous streaking termed *ascending lymphangitis*. Cellulitis presents as edema and erythema that is not sharply demarcated, but also with tenderness, pain, and warmth. (31) Presence of a purulent lesion is less common with GAS and should raise suspicion for *S aureus*. Treatment for erysipelas and cellulitis without purulent lesions and without systemic signs of infection should target streptococci, and many clinicians choose to include coverage against MSSA as well. For erysipelas, which is almost always caused by β-hemolytic streptococci, clinicians may treat with penicillin or amoxicillin. In cases in which it may be more difficult to distinguish between erysipelas and cellulitis and when MSSA is a consideration, for outpatient therapy a first-generation cephalosporin, such as cephalexin, or clindamycin is appropriate. Treatment for uncomplicated erysipelas and cellulitis is typically for 5 days. For more severe infections with systemic symptoms, evidence of MRSA infection elsewhere, history of penetrating trauma, or known MRSA nasal colonization, coverage against both MRSA and streptococci is recommended. Parenteral treatment should be considered for very young children; rapidly progressing erysipelas or cellulitis; large areas of involvement; involvement of the face, neck, or genitals; and children who have systemic symptoms, including fever and tachycardia. (1)(31)(34)

Vulvovaginitis and Perianal Cellulitis

Vulvovaginitis is the most common gynecologic complaint in the prepubescent girl treated by the primary care physician. Typically, a child with GAS vulvovaginitis will present with vulvar pain or itching, spotting of serous to purulent discharge on the underwear, and vulvar erythema. Perianal cellulitis with GAS presents as a sharply demarcated perianal erythema that is often painful and pruritic. Although most cultures of vulvovaginitis in prepubertal girls are polymicrobial, the most consistent agent identified is GAS. (37)(38)(39)(40) Unlike other organisms found on cultures from patients with vulvovaginitis, GAS is not considered normal vaginal bacterial flora. (41) Several reports have linked GAS vulvovaginitis to a previous pharyngeal infection or colonization with the organism, though this is not required for diagnosis. (42) Although some clinicians

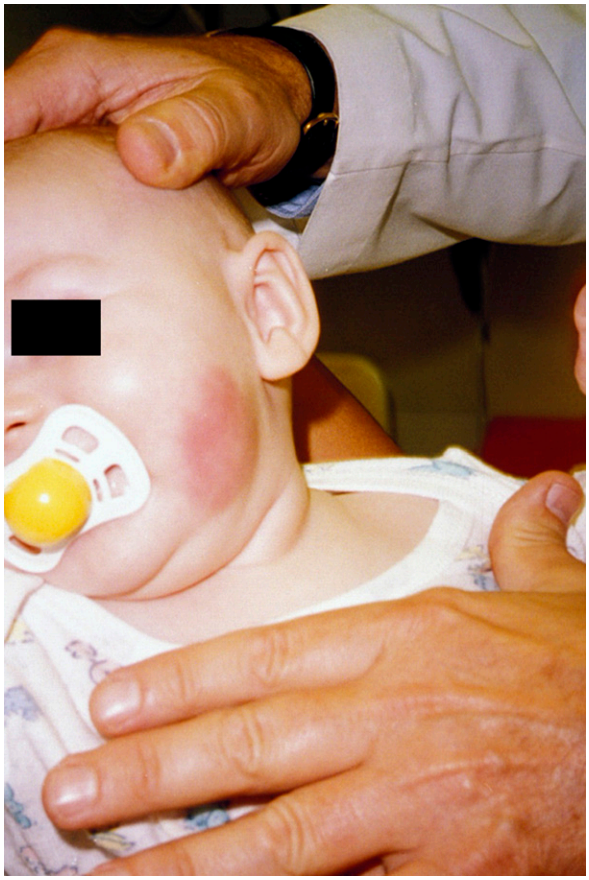

Figure 8. Erysipelas on the face of a young child. Note the distinct, raised borders of the lesion. (74)

do use rapid antigen diagnostic tests for diagnosing vulvovaginitis or perianal cellulitis, these assays have not been validated for genital infections. Etiologic diagnosis is best achieved via culture from a vaginal or perianal swab. The recommended treatment of GAS vulvovaginitis and perianal cellulitis is a 10-day course of amoxicillin; for the penicillin-allergic child, clarithromycin has been described. (41)(43)(44) If vulvovaginitis is recurrent, one should consider testing the child for pharyngeal carrier status and decolonizing. Evidence to dictate a preferred regimen is not sufficient; thus, decolonizing protocols for pharyngeal carriage may be considered (see section on "Carrier State"). Although 1 study demonstrated promising results for recurrent vulvovaginitis using topical localized treatment, this approach has not been adequately studied. (45)

Poststreptococcal Glomerulonephritis

Poststreptococcal glomerulonephritis (PSGN) is a nonsuppurative complication during and after streptococcal infection, most commonly GAS impetigo. It can range from asymptomatic to severe with subsequent renal failure, though most cases in children have few long-term complications. PSGN has an onset 2 to 4 weeks after infection in the skin and 7 to 10 days after streptococcal pharyngitis. PSGN will usually manifest as an acute nephritic syndrome, though it can also cause nephrotic syndrome, and more rarely, rapidly progressive glomerulonephritis. Presenting symptoms include hematuria, which may be microscopic or macroscopic, proteinuria, hypertension, and edema. Laboratory studies will typically be significant for evidence of a past streptococcal infection with positive ASO or anti-DNAse B antibody titers, as well as low levels of complement C3. At diagnosis of PSGN, if the GAS infection is still present, it should be treated with appropriate antibiotics. Treatment of PSGN is typically supportive in nature and depends on clinical presentation, but may include antihypertensive medications, sodium and fluid restrictions, steroid administration and, if necessary, dialysis. It is important to note that treating streptococcal infections may not prevent PSGN, but importantly, will prevent nephritogenic strains of PSGN from spreading to family members and other contacts. (46)(47)

Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections

Under the umbrella of obsessive compulsive and tic disorders is the subtype pediatric acute-onset neuropsychiatric syndrome, which falls within PANDAS. (48) The defining symptoms, pathophysiology, and treatment of this condition have been controversial since the diagnosis was first suggested. In general, an abrupt onset of obsessive-compulsive behaviors, tics, choreiform movements, and various behavioral manifestations characterize the disorder. (49) PANDAS must be preceded by a proven streptococcal infection with positive ASO or anti-DNAseB antibody titers and occurs typically within a few days to weeks after infection. A leading hypothesis of etiology is autoimmune, with possible basal ganglia antigens as targets. (50)

Evidence for the management of suspected PANDAS is not robust. Typically, management includes psychiatric treatments focusing on symptoms of obsessive-compulsive behaviors, tics, and behavioral manifestations. Children with active GAS pharyngitis should be treated appropriately, and prophylactic penicillin for children with frequent PANDAS exacerbations should be considered; studies for the latter have shown mixed results. (50) A recent 2015 study demonstrated a non–statistically significant improvement in tic symptoms with a 30-day course of cefdinir after a recent onset of obsessive-compulsive disorder or tics. (51) Case reports have documented improvement of PANDAS after tonsillectomy/adenoidectomy, but a large study by Murphy et al did not demonstrate a difference in children who did and did not undergo the procedure. (52) Some studies have indicated a possible benefit of plasma exchange

TABLE 3. **Suggested Antibiotic Dosing for Select Group A *Streptococcus* Infections**[a]

INFECTION/CONDITION	ANTIBIOTIC	DOSING	DURATION
Pharyngitis (8)(12)	Penicillin V (oral)	Children <27 kg: 250 mg 2 or 3 times daily; children ≥27 kg, adolescents, and adults: 250 mg 4 times daily or 500 mg 2 times daily	10 days
	Amoxicillin (oral)	50 mg/kg once daily	10 days
	Benzathine penicillin G (intramuscular)	<27 kg: 600,000 U; ≥27kg: 1,200,000 U	1 dose
	Cephalexin (oral)	40 mg/kg per day divided 2 times daily (max = 500 mg/dose)	10 days
	Azithromycin (oral)	12 mg/kg once daily (max = 500 mg)	5 days
	Clarithromycin (oral)	15 mg/kg per day divided 2 times daily (max = 250 mg/dose)	10 days
	Clindamycin (oral)	20 mg/kg per day divided 3 times daily (max = 300 mg/dose)	10 days
Decolonization (8)	Clindamycin (oral)	20–30 mg/kg per day divided 3 times daily (max = 300 mg/dose)	10 days
	Penicillin and rifampin (oral)	Penicillin V: 50 mg/kg per day divided 4 times daily for 10 days (max = 2,000 mg/day) and rifampin: 20 mg/kg once daily for the last 4 days of treatment (max = 600 mg/day)	10 days
	Amoxicillin-clavulanic acid (oral)	40 mg amoxicillin/kg per day divided 3 times daily (max = 2,000 mg amoxicillin/day)	10 days
	Benzathine penicillin G (intramuscular) and rifampin (oral)	Benzathine penicillin G: <27 kg: 600,000 U; ≥27 kg: 1,200,000 U and rifampin: 20 mg/kg per day divided 2 times daily (max = 600 mg/day)	1 dose of Benzathine penicillin G, and 4 days of rifampin
ARF prophylaxis (12)	Benzathine penicillin G (intramuscular)	<27 kg: 600,000 U; ≥27 kg: 1,200,000 U	1 dose every 4 weeks
	Penicillin V (oral)	250 mg 2 times daily	
	Azithromycin (oral) (erythromycin and clarithromycin can also be used)	5 mg/kg once daily	
Impetigo (34)	Mupirocin (topical)	Apply 2 times daily	5 days
	Retapumulin (topical)	Apply 2 times daily	5 days
	Cephalexin (oral)	25–50 mg/kg/day divided 3–4 times daily (max = 250 mg/dose)	7 days
	Clindamycin (oral) *(if MRSA also suspected)*	20–30 mg/kg per day divided 3 times daily (max = 300 mg/dose)	7 days
Erysipelas: Mild, nonpurulent, no systemic signs of infection, outpatient treatment[b](30)(34)(75)	Amoxicillin (oral)	40–90 mg/kg per day divided 2 or 3 times daily	5 days

Continued

TABLE 3. (Continued)

INFECTION/CONDITION	ANTIBIOTIC	DOSING	DURATION
Cellulitis, mild, nonpurulent, no systemic signs of infection, outpatient treatment[b](34)(75)	Cephalexin (oral)	50 mg/kg per day divided 4 times daily (max = 500 mg/dose)	5 days
	Clindamycin (oral)	25–30 mg/kg per day divided 3 times daily (max = 1,800 mg daily)	5 days
Vulvovaginitis and perianal cellulitis (42)(43)	Amoxicillin (oral)	50 mg/kg per day divided 3 times daily (max = 500 mg/dose)	10 days
	Clarithromycin (oral)	15 mg/kg divided 2 times daily (max = 1,000 mg daily)	7–10 days
Empiric therapy for STSS and streptococcal ANF (34)(29)(75)	Clindamycin (IV)	40 mg/kg per day divided 3 to 4 times daily (max = 2,700 mg daily)	
	AND		
	Meropenem (IV) (other carbapenems may also be used) OR	30–60 mg/kg per day divided 3 times daily (max = 1,000 mg/dose)	
	Piperacillin-tazobactam (IV) (other β-lactam/β-lactamase inhibitor combinations may also be used)	For children ≥9 months of age, 300 mg/kg per day piperacillin component divided 3–4 times daily (max = 16 g)	
	AND		
	Vancomycin (if Staphylococcus cannot be ruled out)	45–60 mg/kg per day divided 3–4 times daily (max = 4 g)	
Chemoprophylaxis for high-risk contacts of patients with invasive GAS (76)	Benzathine penicillin G (intramuscular) and rifampin (oral)	Benzathine penicillin G: <27 kg: 600,000 U ≥27 kg: 1,200,000 U and rifampin: 20 mg/kg per day divided 2 times daily (max = 600 mg/day)	1 dose of benzathine penicillin G and 4 days of rifampin
	Clindamycin (oral)	20 mg/kg per day divided 3 times daily (max = 300 mg/dose)	10 days
	Azithromycin (oral)	12 mg/kg per day once daily (max = 500 mg/day)	5 days

ANF=acute necrotizing fasciitis; ARF=acute rheumatic fever; GAS=group A Streptococcus; IV=intravenous; MRSA=methicillin-resistant Streptococcus aureus*; STSS=streptococcal toxic shock syndrome.*

[a]*Doses listed are not necessarily appropriate for neonates.*

[b]*For parenteral treatment or if concern for MRSA, see Stevens et al. (34)*

and IVIG in severe cases of PANDAS. (53)(54)(55) One randomized controlled trial of IVIG demonstrated no statistically significant difference between IVIG and placebo during the blinded portion of the trial, though improvement was seen during the open-label portion. (56)

INVASIVE GAS INFECTIONS

In invasive GAS infections, the organism is found in typically sterile sites such as blood, joint fluid, or cerebrospinal fluid. Based on surveillance data from the Centers for Disease Control and Prevention, between 2005 and 2012, between 1,136 and 1,607 deaths occurred per year in both adults and children in the United States secondary to invasive GAS. Among children, peak incidence occurs before 2 years of age. Invasive GAS occurs more frequently in winter and early spring. (57) Although the spectrum of invasive GAS is wide, for the purposes of this review, we will focus on 2 presentations that are important for the general pediatrician to quickly recognize: STSS and acute necrotizing fasciitis.

Streptococcal Toxic Shock Syndrome

STSS consists of infection with GAS accompanied by hypotension and evidence of multiorgan failure. STSS is usually preceded by skin or soft tissue infections with GAS, but can be seen with GAS infection at any site. In STSS, superantigen toxins trigger massive T-cell proliferation and a subsequent "cytokine storm." (58) The patient may present initially with fevers and a generalized erythroderma and then progress to develop hypotension and multiorgan failure. The pillars of treatment for STSS are aggressive management of shock and organ failure, antibiotic therapy, and consideration of IVIG administration. If soft tissue involvement is noted, including necrotizing fasciitis, emergent surgical evaluation is warranted. (29) Antibiotic treatment is dual, with a β-lactamase–resistant β-lactam, such as a penicillin/penicillinase-inhibitor combination or carbapenem, as well as clindamycin, which serves to reduce the production of superantigens by GAS. (58)(59) In addition, if staphylococcal infection cannot be ruled out, vancomycin should be added to the empiric therapy regimen. Multiple studies, including several observational studies (59)(60)(61) and 1 small, randomized control trial, (62) indicate that IVIG as an adjunctive therapy may decrease mortality in STSS. Use of IVIG is still in debate, however, and individual clinical judgment is appropriate. If IVIG is given, an acceptable dosing regimen is 1 g/kg on day 1, followed by 0.5 g/kg on days 2 and 3. (29) In the United States, there is currently no recommendation to provide chemoprophylaxis to close contacts.

Acute Necrotizing Fasciitis

Type II acute necrotizing fasciitis (ANF) is an aggressive, rapidly progressing deep tissue infection caused by GAS, usually alone, but to a lesser extent in combination with *S aureus* or anaerobes. ANF accounted for 7% of all cases of invasive GAS infections in the United States between 2005 and 2012, with just less than 1% presenting with combined ANF and STSS. Mortality for all cases of ANF was 20%, though this was much lower in the pediatric population. (57) Mortality of combined ANF and STSS is much higher, with some estimates as high as 60%. (63) ANF will typically begin as an apparently innocuous lesion that may be accompanied by pain that is out of proportion with the examination findings. Infants may have profound irritability. Children may also present with fever, tachycardia, leukocytosis, elevated creatine phosphokinase, hypoalbuminemia, hypocalcemia, and evidence of coagulopathy. Within 24 to 72 hours, there is a rapid progression to more pronounced inflammation, followed by purplish discoloration of the skin, evolving into hemorrhagic or serous bullae. Over the next few days, the involved tissue, which may go as deep as muscle, will become frankly necrotic. The most important step in halting the progression of the necrosis is surgical debridement, which should not be delayed for further diagnostics if the suspicion for ANF is high. Magnetic resonance imaging may be helpful in the diagnosis but cannot rule out ANF; although gas visualized in the tissues is a classic finding in ANF, often all that is seen is localized tissue swelling. Antibiotic therapy is the same as in STSS: dual therapy with a β-lactamase–resistant β-lactam antimicrobial combined with clindamycin to mediate GAS toxin, with the addition of vancomycin until MRSA can be ruled out. (29)(63)(64) A recent large study in adults demonstrated no benefit of IVIG in mortality or length of hospital stay in patients with ANF who had undergone surgical debridement and received antibiotic therapy. (65)

CONCLUSIONS

Vaccination

Currently there is no commercially available GAS vaccine, though it has been widely pursued and was included as one of the priorities in the 2014 Global Vaccine Action Plan. There have been many roadblocks in finding a successful vaccine, including the large diversity of strains of GAS. Chiefly, vaccine developers have been targeting the M surface protein, but a recent approach has also used streptococcal pyrogenic exotoxins A and B (66) as well as another antigen, M-related protein, in the already existing multivalent M protein vaccines. (67) A phase 1 trial is being conducted of a 30-valent M protein vaccine in adults. (68) The governments of Australia and New Zealand, countries which harbor particularly high incidence of GAS-related disease, especially in indigenous populations, came together in 2014 to develop a Coalition to Advance New Vaccinations against group A *Streptococcus* (CANVAS). (69)

Evolving Resistance of GAS

Practitioners should be cognizant of the evolving resistance patterns of GAS to antibiotics other than penicillin. Several recent publications note fairly significant resistance to macrolides and clindamycin. One such study in Wisconsin demonstrated resistance to azithromycin in 15% of isolates from primary care clinics. (70)(71)(72) This emphasizes the importance of penicillins as the preferred antimicrobial and should be avoided only in definite penicillin allergy. In streptococcal pharyngitis, azithromycin may be used, but culture sensitivities should be obtained to ensure susceptibility. In addition, in invasive GAS, clindamycin should not be used

alone but in combination with a β-lactam because 4% to 8% of GAS strains are resistant to clindamycin.

Carrier State

Children harboring GAS in the pharynx without clinical symptoms of disease are said to be carriers. A meta-analysis in 2010 estimated the prevalence of GAS carriage at about 12%. (6) GAS carriers are typically not infectious and the colonizing bacteria are less virulent. Colonized GAS is unlikely to become pathologic in the host or result in nonsuppurative complications. In general, antibiotic therapy is not recommended to eradicate the carrier state. Thus, if a throat swab is positive for GAS, but the patient lacks symptoms of streptococcal pharyngitis, treatment is not recommended. In the same vein, "proof of cure" after treatment of streptococcal pharyngitis is not recommended unless symptoms persist. Eradication may be considered in select situations, such as a community outbreak of PSGN or ARF, or a family history of ARF. Antibiotic options for eradication include 10 days of clindamycin, penicillin and rifampin, and amoxicillin/clavulanic acid. (12)(29)(73)

Prophylaxis

The only indication for GAS prophylaxis with robust evidence is for ARF and may consist of monthly intramuscular benzathine penicillin G or daily oral penicillin, or for penicillin-allergic patients, sulfisoxazole or a macrolide (see section on ARF for more details). (12)(29) Some clinicians may choose to provide prophylaxis to certain high-risk close contacts of patients with invasive GAS disease. These include people who are 65 years of age or older, those who are immunocompromised (eg, human immunodeficiency virus–positive individuals), or those with diabetes mellitus. Prophylaxis is not recommended in schools or child-care facilities. (29) Prophylaxis may consist of benzathine penicillin G, clindamycin, or azithromycin. (76) Finally, some physicians may choose to provide penicillin prophylaxis to patients with frequent PANDAS exacerbations; this decision should be made on a case-by-case basis because the evidence is not robust. Table 3 lists antibiotic indications and dosages.

Summary

- Group A *Streptococcus* (GAS) infections are highly prevalent, and account for major morbidity and mortality worldwide, from both primary infections and subsequent complications.
- On the basis of strong research evidence, all children older than 3 years who present with pharyngitis without features that strongly suggest a viral etiology should undergo testing for GAS pharyngitis, with negative rapid antigen detection tests followed by a throat swab culture. Posttreatment diagnostics are not recommended. (8)
- Diagnosis of acute rheumatic fever (ARF) should be made using the updated 2015 Jones criteria, which now include separate criteria for low- and moderate- to high-risk populations. Based on research evidence and consensus, echocardiography should be performed in all cases of suspected or confirmed ARF, even in the absence of auscultatory findings. (20) On the basis of strong research evidence, prophylaxis is recommended for patients with well-documented histories of rheumatic fever. (12)
- Based on strong research evidence, topical therapy with mupirocin or retapamulin is appropriate for localized impetigo, whereas numerous lesions or an outbreak situation should be treated with oral therapy. On the basis of research and observational studies, treatment of cellulitis without systemic involvement should target streptococci. On the basis of consensus, physicians may choose to treat cellulitis with systemic symptoms with an agent that covers methicillin-resistant *Staphylococcus aureus.* (34)
- On the basis of expert consensus and observational studies, antimicrobial choice for acute necrotizing fasciitis should include a β-lactam antibiotic with clindamycin to mediate toxin GAS toxin. Vancomycin should also be added initially to cover methicillin-resistant *S aureus* until cultures are complete. (29)

References for this article are at http://pedsinreview.aappublications.org/content/39/8/379.

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1. A previously healthy 10-year-old boy is brought to the office in March with a sore throat that he has had for the past day. He has had fever at home up to 101.8°F (38.7°C). He has not had a cough or congestion. He had taken amoxicillin 4 months ago for acute bacterial sinusitis. He has no known allergies to medication. On examination he is awake and alert. Vital signs are normal except for an oral temperature of 101.5°F (38.6°C). There is an exudative pharyngitis with mildly tender anterior cervical adenopathy. The remainder of his examination findings are normal. Which of the following is the most appropriate next step in management?
    A. Intramuscular ceftriaxone.
    B. Oral azithromycin.
    C. Oral penicillin.
    D. Nasopharyngeal swab for viral multiplex polymerase chain reaction assay.
    E. Throat swab for group A *Streptococcus* antigen.
2. A previously healthy 8-year-old girl is brought to the office with a 2-day history of fever and sore throat. She has not had a cough, vomiting, or diarrhea. When she was 1 year of age, she had had a rash after taking amoxicillin for 5 days, which had been prescribed for acute otitis media. She did not have respiratory distress when she had the rash. On physical examination her temperature is 101.2°F (38.4°C). There is an exudative pharyngitis with bilateral anterior cervical adenopathy. A rapid antigen detection test from a throat swab is positive for group A *Streptococcus.* Which of the following is the most appropriate treatment?
    A. Azithromycin.
    B. Ceftriaxone.
    C. Cephalexin.
    D. Clindamycin.
    E. Trimethoprim-sulfamethoxazole.
3. A 7-year-old girl is admitted to the hospital with a 3-day history of joint pain and swelling of her knees, ankles, and wrists. It started with her left knee and then moved to her right ankle, right knee, and both wrists. The pain is significantly improved with ibuprofen. She has also had fever, with temperatures ranging from 101°F to 102°F (38.3°C–38.8°). She had a sore throat when she was with her family on a spring break vacation 2 to 3 weeks ago, which resolved after 3 days without any antimicrobial therapy. Currently on physical examination she has swelling and pain of her right knee, right ankle, and both wrists. There is no murmur on cardiac examination. Her physical examination findings are otherwise normal. Her C-reactive protein is 50 mg/L (476 nmol/L) and erythrocyte sedimentation rate 85 mm/hr. ASO and anti-DNASE B antibody levels are significantly elevated. Electrocardiography shows prolonged PR interval. In addition to starting naproxen and oral penicillin, which of the following is the most appropriate next step in management?
    A. Brain magnetic resonance imaging.
    B. Cardiac magnetic resonance imaging.
    C. Echocardiography.
    D. Intravenous immunoglobulin.
    E. Pulse methylprednisolone.
4. A previously healthy 3-year-old boy is brought to the emergency department because of perianal itching and pain with defecation. He has not had fever. His review of systems is otherwise negative. On examination there is sharply demarcated 3 to 4 cm circumferential erythema around his anus. He has no known drug allergies. Which of the following is the most appropriate next step in management?

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A. Oral clindamycin.
B. Swab of the perianal area for culture.
C. Throat swab for culture.
D. Throat swab for group A *Streptococcus* antigen.
E. Topical neomycin.

5. A 14-year-old boy is brought to the emergency department with fever and a very painful right thigh. Three days ago, he developed what appeared to be a bug bite on his right thigh and then the area of redness increased. Over the past day he has had fever with worsening pain in his thigh. Now the area has started to become purple and there are blisters. He also seems confused. On examination his temperature is 102°F (38.8°C). He has tachycardia and his blood pressure is 118/76 mm Hg. Palpation of the right thigh has a hard, wooden feel that extends beyond the area of erythema. There is purplish discoloration centrally with 2 bullae. He is going to the operating room for debridement. He has no known allergies. In addition to starting intravenous fluids, piperacillin/tazobactam, and vancomycin, which of the following is the most appropriate management?

A. Computed tomography with contrast of the thigh.
B. Fresh frozen plasma transfusion.
C. Intravenous clindamycin.
D. Intravenous immunoglobulin.
E. Intravenous metronidazole.