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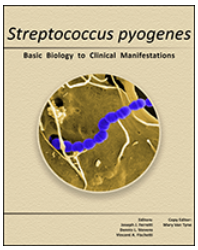

Severe Group A Streptococcal Infections

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Introduction

Life-threatening infections caused by *Streptococcus pyogenes* (group A streptococcus) include scarlet fever, bacteremia, pneumonia, necrotizing fasciitis, myonecrosis and Streptococcal Toxic Shock Syndrome (StrepTSS). This chapter focuses on the clinical and epidemiological features of these infections, as well as treatment options and bacterial pathogenesis. In brief, such invasive infections can simply be defined as any infection in which *S. pyogenes* is isolated from a normally sterile body site. Patients with invasive *S. pyogenes* infections have a relatively low mortality rate, unless they meet the established criteria for StrepTSS.

Patient mortality is also influenced by the site of infection and the patient's presenting history. For example, in patients with *S. pyogenes* necrotizing fasciitis/myonecrosis that lacks a discernable portal of bacterial entry, classical cutaneous signs of a necrotizing process are not initially apparent. In the absence of such clinical clues, the correct diagnosis is often missed or delayed until the patient manifests systemic shock and organ failure. This delay results in high morbidity and mortality rates. Interestingly, patients in this "no portal" category frequently develop soft-tissue infection at a site of relatively minor antecedent soft tissue injury (strain, bruise) that did not break the skin. Pain at the time of presentation is often out of proportion to the injury itself, and is an important clinical clue. A molecular mechanism that links injury to secondary *S. pyogenes* infection has been recently proposed, and is discussed later in this chapter.

Development of severe invasive infections is associated with strains that produce streptococcal pyrogenic exotoxins (Spe)—a family of bacterial superantigens that includes the classical scarlatina toxins SpeA and SpeC, the cysteine proteinase SpeB, and a number of more recently described superantigens (such as mitogenic factor [MF, SpeF] and streptococcal superantigen [SSA]). Superantigens are potent immunostimulators that cause clonal proliferation of T cells and watershed production of pro-inflammatory cytokines that mediate shock and organ failure. This concept, as well as the molecular biology of streptococcal virulence, colonization, and tissue invasion, is discussed in more detail in the section on the pathogenesis of StrepTSS.

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Invasive Streptococcal Infections of Skin and Soft Tissues

In the mid-1980s, outbreaks of invasive streptococcal infections, of a frequency and severity not seen in the preceding decades, began to be reported both in the United States and abroad (Hoge, et al., 1993; Martin & Høiby, 1990; Strömberg, Romanus, & Burman, 1991; Demers, et al., 1993). Although certain *S. pyogenes* M-types (M 1, 3, 11, 12, and 28) account for 50% of the associated isolates (O'Brien, et al., 2002), there has been a definite and consistent tendency for M-types 1 and 3 to be associated with the more life-threatening infections (reviewed in (Wong & Stevens, 2013)). A high proportion of these cases have occurred in adults, and the portal of entry is frequently the skin, mucous membranes, or soft tissues. Invasive infections are often associated with shock and multi-organ failure, features similar to those of severe staphylococcal toxic shock syndrome (StaphTSS) (Silversides, Lappin, & Ferguson, 2010). Thus, the entity attributed to *S. pyogenes* has been termed *StrepTSS.* Clinical features of serious streptococcal skin and soft tissue infections and StrepTSS are described below.

Necrotizing Fasciitis (Streptococcal Gangrene)

Necrotizing fasciitis (NF) is an infection of the deeper subcutaneous tissues and fascia that is characterized by extensive and rapidly spreading necrosis (gangrene) of the skin and underlying structures. While necrotizing soft-tissue infections may be caused by multiple aerobic and anaerobic microorganisms and may vary in their clinical manifestations, the present discussion is limited to necrotizing fasciitis caused by *S. pyogenes* (Bisno & Stevens, 1996), and as described by Meleney in 1924 as hemolytic streptococcal gangrene (Meleney, 1924). Characteristically, streptococcal gangrene begins at a site of trivial or even unapparent trauma or in an operative incision. The initial lesion may appear only as an area of mild erythema, but undergoes a rapid evolution over the next 24–72 hours. The inflammation becomes more pronounced and extensive, the skin becomes dusky and then purplish, and bullae containing yellow or hemorrhagic fluid appear. Bacteremia is frequently present, and metastatic abscesses may occur. By the fourth to fifth day, frank gangrenous changes are evident in the affected skin, followed by extensive sloughing. The process may march inexorably over large body areas unless measures are taken to contain it. The patient with streptococcal gangrene appears perilously ill, with high fever and extreme prostration. Mortality rates are high, even with appropriate treatment (Stevens, 1992).

In modern times, the course of *S. pyogenes* necrotizing fasciitis appears to be much more fulminant than that described by Meleney. Specifically, ecchymoses and bullae may appear within 2-3 days and deep muscle involvement is more common. In addition, the mortality rate in 1924 was only 20%, despite the lack of antibiotics, IV fluids, ventilators, and dialysis. In contrast, mortality rates of as high as 70–80% have been reported in the current era (reviewed in (Wong & Stevens, 2013)). Given the destruction of multiple layers of soft tissue (epidermis, dermis, subcutaneous tissue, fascia, muscle) in today's infections, this author believes that "necrotizing soft-tissue infection" is a more accurate term to describe the modern disease.

Successful management of necrotizing fasciitis is dependent on early recognition, yet patients may initially present with cutaneous findings that appear relatively benign (Bisno, Cockerill, & Bermudez, 2000). Fever, when present (Bisno, Cockerill, & Bermudez, 2000), and severe pain are often the earliest manifestations of disease and are important clinical clues that should not be dismissed. In those patients with a defined portal of entry, such as a surgical incision, burn, insect bite or varicella lesion, there is redness of the skin, pain, and swelling. However, in the 50% of patients who develop necrotizing fasciitis/myonecrosis without a defined portal of entry, the infection begins deep in the tissues, frequently at the site of a hematoma, muscle strain, or traumatic joint injury. In these patients, the classical cutaneous signs of inflammation and infection are absent until late in the course. The most important clinical clue in this setting is crescendo pain.

Routine radiographs, computed tomography (CT) scanning, and magnetic resonance imaging (MRI) may show localized swelling of the deep structures, but characteristically do not show frank abscess formation or gas in the tissue—and *thus are not definitive procedures.* This is particularly problematic in the "no portal" patients who

report antecedent trauma, since this history complicates the interpretation of imaging studies, in that clinicians cannot easily distinguish the cause of the deep swelling. In these cases, such studies often delay, rather than facilitate, a diagnosis. Further, patients with prior injury or surgery may have taken non-steroidal anti-inflammatory drugs (NSAIDs) that mask fever and reduce pain. Unexplained tachycardia, a marked left shift, and an elevated creatine phosphokinase level are also important clues to the diagnosis of necrotizing soft-tissue infections, and their presence should prompt surgical inspection of the deep tissues. Gram stains of aspirated fluid will reveal chains of Gram-positive cocci and few, if any, white blood cells. Similarly, a biopsy with frozen section may aid in the diagnosis of NF (Stamenkovic & Lew, 1984; Majeski & Majeski, 1997).

Myositis and Myonecrosis

Strictly speaking, myositis is a localized purulent infection of muscle. Most cases occur in tropical regions where *S. aureus* is the predominant causative agent; myositis due to *S. pyogenes* is rare. In contrast, non-purulent soft tissue infection due to *S. pyogenes* is common in patients with necrotizing fasciitis, myonecrosis, and StrepTSS. Many of these cases occur at sites of blunt, non-penetrating trauma, or arise spontaneously in the soft tissues. Organisms are likely hematogenously translocated from the throat to the deep soft tissues, though antecedent or concomitant streptococcal pharyngitis is not a prerequisite for this infection. Systemic toxicity is also common, and mortality as high as 80% has been reported (Adams, et al., 1985). The destruction of tissue is poorly understood, but infection within the confined muscle compartment may result in pressures that exceed arterial pressure, which necessitate emergent fasciotomy and debridement. In addition, bacterial toxin-induced formation of intravascular aggregates of platelets and leukocytes could obstruct blood flow, which leads to the ischemic necrosis of tissue (Bryant, et al., 2005).

As previously mentioned, there is a great deal of overlap in the clinical features of necrotizing fasciitis and myonecrosis (Stevens, 1992; Adams, Gudmundsson, Yocum, Haselby, Craig, & Sundstrom, 1985), since later in the disease course, both infections frequently destroy all layers of the soft tissues, including muscle. Differentiation of these entities can be made by surgical inspection or biopsy; however, treatment recommendations are the same for both (Stevens, et al., 2014).

Streptococcal Toxic Shock Syndrome

StrepTSS is more fully defined in Table 1 (The Working Group on Severe Streptococcal Infections, 1993), but, simply stated, is any streptococcal infection that is associated with the sudden onset of shock and organ failure. Definite cases are those in which *S. pyogenes* is isolated from a normally sterile body site. Such cases were first described in the United States and Europe during the mid- to late 1980s (Martin & Høiby, 1990; Stevens, et al., 1989; Francis & Warren, 1988). Since then, reports of StrepTSS in adults and children have emerged worldwide. Most cases have occurred sporadically, though some clusters have been reported. The highest incidence of invasive streptococcal disease occurred in a small Minnesota community, where 26 cases/100,000 population were recorded (Cockerill, et al., 1997). In addition, outbreaks have occurred in closed environments, such as nursing homes (Thigpen, et al., 2007; Hohenboken, Anderson, & Kaplan, 1994; Jordan, Richards, Burton, Thigpen, & Van Beneden, 2007; Harkness, Bentley, Mottley, & Lee, 1992; Ruben, Norden, Heisler, & Korica, 1984) and hospitals (DiPersio, et al., 1996). Secondary cases of StrepTSS are unusual, but transmission to family members (DiPersio, et al., 1996; Gamba, et al., 1997) or health care workers (DiPersio, et al., 1996; Valenzuela, Hooton, Kaplan, & Schlievert, 1991) has been well documented by demonstrating identical pulsed-field gel electrophoresis patterns from cross-infecting strains. Although many of the initial reports described StrepTSS in adults, children are also affected (Cockerill, et al., 1997; Wheeler, Roe, Kaplan, Schlievert, & Todd, 1991; Kiska, et al., 1997; Givner, Abramson, & Wasilauskas, 1991; Brogan, Nizet, Waldhausen, Rubens, & Clarke, 1995; Stockmann, et al., 2012). In 2010, the incidence of invasive infection in children in Utah reached 14 cases/100,000 population (Stockmann, et al., 2012). Thus, persons of all ages can be afflicted and, although some have underlying medical conditions such as diabetes and alcoholism (Francis & Warren, 1988; Wheeler, Roe, Kaplan,

Schlievert, & Todd, 1991; Schwartz, Facklam, & Breiman, 1990; Barnham, 1989; Braunstein, 1991; Holm, Norrby, Bergholm, & Norgren, 1992), many have no predisposing medical condition and are not immunocompromised. This contrasts sharply with reviews of *S. pyogenes* bacteremia from several decades ago (Francis & Warren, 1988; Barnham, 1989; Braunstein, 1991), which found that the disease occurred primarily among the very young, the very old, or patients with predisposing conditions, such as cancer, renal failure, leukemia, severe burns, or iatrogenic immunosuppression.

The common portals of entry for streptococci include the vagina, pharynx, mucosa, and skin (Stevens, et al., 1989). In other cases, surgical procedures such as suction lipectomy, hysterectomy, vaginal delivery, bunionectomy, reduction mammoplasty, hernia repair, bone pinning, and vasectomy have provided portals for entry. StrepTSS rarely occurs secondary to streptococcal pharyngitis (Herold, 1990; Bradley, Schlievert, & Peterson, 1991; Chapnick, et al., 1992), while viral infections, such as varicella and influenza, have provided portals of entry in other cases (Stevens, et al., 1989; Kiska, et al., 1997; Herold, 1990; Lesko, O'Brien, Schwartz, Vezina, & Mitchell, 2001).

Additional factors increase the risk of invasive *S. pyogenes* infections. Three studies have demonstrated that a high or increasing prevalence of M-types 1 or 3 strains among throat isolates may signal an increased incidence of StrepTSS in a community (Kiska, et al., 1997; Holm, Norrby, Bergholm, & Norgren, 1992; Sellers, Woods, Morris, & Saffle, 1996). The use of NSAIDs for pain associated with muscle strain, trauma, chickenpox or childbirth may mask the early signs and symptoms of streptococcal infection or possibly predispose patients to more severe infection, such as necrotizing fasciitis or StrepTSS (Stevens, et al., 1989; Stockmann, et al., 2012; Stevens, 1995a; Barnham, 1997).

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

I	Isolation of group A streptococci (*Streptococcus pyogenes*)
A	From a normally sterile site (e.g., blood, cerebrospinal, pleural, or peritoneal fluid, tissue biopsy, surgical wound)
B	From a nonsterile site (e.g., throat, sputum, vagina, superficial skin lesion)
II	Clinical signs of severity
A	Hypotension: systolic blood pressure ≤ 90 mm Hg in adults or below fifth percentile for age in children
And	
B. Two or more of the following signs:	
1	Renal impairment: creatinine ≥ 177 μmol/L (≥2 mg/dL) for adults or ≥2× the upper limit of normal for age. In patients with preexisting renal disease, a twofold or greater elevation over the baseline level
2	Coagulopathy: platelets ≤ 100×10^9/L (≤ 100,000/mm^3) or disseminated intravascular coagulation defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products
3	Liver involvement: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin levels ≥2× the upper limit of normal for age. In patients with preexisting liver disease, a twofold or greater elevation over the baseline level.
4	Adult respiratory distress syndrome defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in the absence of cardiac failure, or evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia
5	A generalized erythematous macular rash that may desquamate
6	Soft tissue necrosis, including necrotizing fasciitis or myositis, or gangrene

* 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.
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Pathogenesis of StrepTSS

Colonization and Translocation

The entry of *S. pyogenes* into the bloodstream and deeper tissues may occur as a result of a breach of an epithelial barrier, or the organism itself may penetrate intact membranes, such as the pharyngeal mucosa. Although bacteremia rarely follows streptococcal pharyngitis, transient bacteremia likely occurs in ~50% of patients who develop invasive infections without a portal of entry. The organism adeptly avoids destruction by the host's immune system largely because of the anti-phagocytic properties of the M protein (Lancefield, 1933). Adherence of *S. pyogenes* to pharyngeal mucosal cells is a prerequisite to colonization or infection, and has been related to surface structures, such as lipoteichoic acid and fibronectin-binding proteins. Penetration or translocation of the organism through respiratory epithelial cells has been demonstrated for M-type 1 *S. pyogenes*. Some have suggested that M-1 strains possessing an invasin (*inv*+) gene penetrate more efficiently (LaPenta, Rubens, Chi, & Cleary, 1994). If penetration of mucosal barriers occurs readily with these strains, it generally does not result in clinically detectable bacteremia in the vast majority of cases, since the incidence of invasive infection remains generally very low (~3.5 cases/100,000 population) (O'Brien, et al., 2002). Thus, the clearance of *S. pyogenes* by the human immune system must be highly efficient.

Recent studies have suggested that, following the colonization of mucosa or skin, SpeB attenuates the local host response and limits bacterial exotoxin functionality through its proteolytic activity. Later in the course of the disease, production of SpeB is curtailed by in vivo selection of strains that harbor mutations in *covS* (**c**ontrol **o**f **v**irulence), the sensory component of a key 2-component regulatory system, CovRS (Aziz, et al., 2004; Kansal, et al., 2010). This results in a stable phase-shift to a SpeB negative phenotype, which allows these particular strains to bind plasminogen, evade the immune system, and switch to an invasive phenotype (Walker, et al., 2007). In addition, streptolysin O (SLO) likely disrupts the local tissue inflammatory response in much the same way as the related toxin, perfringolysin O from *Clostridium perfringens,* inhibits leukocytosis in gas gangrene (Stevens, Tweten, Awad, Rood, & Bryant, 1997b).

S. pyogenes produces many surface-bound and extracellular virulence factors that contribute to pathogenesis in unique ways (reviewed in (Stevens & Kaplan, 2000)). Temporal and environmental control of virulence factor gene expression depends on multiple complex and interrelated stand-alone or two-component regulatory systems. The most intensively studied of these include Mga (multiple virulence gene regulator of group A streptococcus) (McIver, 2009), Mry (M protein RNA yield) (Perez-Casal & Caparon, 1991), and the two-component regulator CsrRS (capsule synthesis regulator, Response and Sensor components (Levin & Wessels, 1998)) which is alternately known as CovRS (control of virulence (Federle, McIver, & Scott, 1999)). The regulator of proteinase B (RopB) has also been shown to have multiple polymorphisms that control the virulence of *S. pyogenes* (Carroll, et al., 2011).

The Role of Antecedent Soft-Tissue Injury

A critical role for antecedent soft-tissue injury has been well established for some bacterial infections, such as clostridial myonecrosis, where a deep, penetrating injury interrupts the blood supply and directly introduces organisms (or spores) into devitalized tissues. Though the rate at which *S. pyogenes* myonecrosis progresses is comparable to that of clostridial gangrene (inches per hour), the types of predisposing injuries are distinctly different. With *S. pyogenes* infection, a minor muscle strain, sprain, or bruise is often the rule (Adams, et al., 1985; Stevens, et al., 1989). For instance, in our initial report of 20 cases of invasive streptococcal infection, one had a superficial bruise to the hand, and the portal of entry was entirely unknown in the other 7 patients (Stevens, et al., 1989). Thus, 8 of 20 patients (40%) had no known portal of entry, and overall mortality was 30% (Stevens, et al., 1989). Similarly, Adams et al. documented 21 cases of life-threatening *S. pyogenes* infection, 19 of which lacked an obvious portal of entry and 18 (85.7%) died (Adams, et al., 1985). Finally, a recent case-

controlled study found that non-penetrating trauma was significantly associated with *S. pyogenes* necrotizing fasciitis (Nuwayhid, Aronoff, & Mulla, 2007). In these "no portal" cryptic infections, the correct diagnosis is often delayed until after shock and organ failure manifest (Bisno & Stevens, 1996), which often causes mortality to exceed 70% (Adams, et al., 1985). Survivors undergo emergent amputation or extensive surgical debridement and prolonged hospitalization (Bisno & Stevens, 1996; Stevens, et al., 1989; Schurr, Engelhardt, & Helgerson, 1998). Such findings have prompted several authors to conclude that non-penetrating muscle injury may be a prerequisite for *S. pyogenes* necrotizing fasciitis or myonecrosis (Adams, et al., 1985; Nuwayhid, Aronoff, & Mulla, 2007).

Our initial studies of this process demonstrated that injury of cultured human skeletal muscle cells increased the binding of *S. pyogenes* (Bryant, Bayer, Huntington, & Stevens, 2006). While *S. pyogenes* bind host proteins such as fibronectin, collagen, and laminin (reviewed in (Courtney, Hasty, & Dale, 2002)), multiple lines of evidence suggest that these did not contribute to the initial *S. pyogenes*/skeletal muscle interaction within the first 24–48 hrs after injury (reviewed in (Bryant, Bayer, Aldape, & Stevens, 2015)), but could contribute at later times in the disease course. Instead, our findings demonstrated that the ubiquitous intermediate filament protein, vimentin, was the principal *S. pyogenes* adhesin on injured muscle cells (Bryant, Bayer, Huntington, & Stevens, 2006). Though classically an intracellular cytoskeletal protein (reviewed in (Fuchs & Weber, 1994)), our studies clearly demonstrated that injured muscle cells in culture also display vimentin on their surface (Bryant, Bayer, Huntington, & Stevens, 2006)—adding to other reports that describe a cell-surface form of vimentin in platelets, endothelial cells, and lymphocytes (Xu, et al., 2004; Podor, et al., 2002; Boilard, Bourgoin, Bernatchez, & Surette, 2003). Further, *S. pyogenes*, but not *S. aureus*, bound soluble vimentin in vitro (authors' unpublished data) and was associated with vimentin-positive necrotic muscle in a human case of *S. pyogenes* NF (Bryant, Bayer, Huntington, & Stevens, 2006).

In a murine model of injury-associated cryptogenic *S. pyogenes* infection (Hamilton, Bayer, Stevens, Lieber, & Bryant, 2008), vimentin expression was significantly increased by 6 hrs, peaked at 48 hrs, and remained elevated over 72 hrs after injury (Hamilton, Bayer, Stevens, Lieber, & Bryant, 2008). Intravenous infusion of M-type 3 *S. pyogenes* at the peak of vimentin expression resulted in the homing of the organism to the injured site (Hamilton S. M., Bayer, Stevens, Lieber, & Bryant, 2008). Since regenerating muscle cell precursors (satellite cells), but not mature healthy myofibers, express vimentin (Vaittinen, et al., 2001), these results provided the first molecular mechanism to explain the development of severe *S. pyogenes* soft tissue infections precisely at sites of prior minor muscle trauma.

Mechanisms of Shock and Organ Failure: Cytokine Induction

Within the deeper tissues and bloodstream, the induction of cytokine synthesis plays a critically important role in the production of shock and organ failure. Like the staphylococcal enterotoxins and TSST-1, multiple *S. pyogenes* exotoxins (such as streptococcal pyrogenic exotoxins [Spe] A, B and C, MF, and SSA (Norrby-Teglund, et al., 1998)) and potentially M protein fragments (Kotb, et al., 1993) act as superantigens to stimulate T-cell responses, through their ability to bind to both the MHC class II complex of antigen-presenting cells and specific Vβ regions of the T-cell receptor (Mollick & Rich, 1991). The net effect is a watershed induction of both monocyte- and lymphocyte-derived cytokines (tumor necrosis factor [TNF] -α, interleukin [IL]-1β, IL-6 and TNF-β, IL-2, interferon-γ, respectively) (Norrby-Teglund, et al., 1998; Kotb, et al., 1993; Hackett & Stevens, 1993; Fast, Schlievert, & Nelson, 1989; Norrby-Teglund, Newton, Kotb, Holm, & Norgren, 1994a; Norrby-Teglund, Norgren, Holm, Andersson, & Andersson, 1994b). Superantigens drive the clonal proliferation of specific Vβ T-cells, in part through induction of IL-2. Thus, it would be expected to find the expansion of superantigen-specific Vβ T-cell clones in an infected individual. However, studies in patients with StrepTSS demonstrate depletion, rather than expansion, of superantigen-specific T-cell subsets (Watanabe-Ohnishi, et al., 1995). This enigma remains to be reconciled.

Among the 4 alleles of SpeA, alleles 2 and 3 are most common and have the highest affinity for MHC class II on antigen presenting cells (Kline & Collins, 1996). Some clinical studies have suggested that variations in human leukocyte antigen (HLA) haplotype may result in a predisposition to worse outcomes in some patients with StrepTSS (Kotb, et al., 2002). Finally, a lack of anti-SpeA antibodies is a predisposing factor for development of StrepTSS (Mascini, et al., 2000).

Other streptococcal virulence factors can also induce mononuclear cell pro-inflammatory cytokine production. Specifically, SpeB releases active IL-1β from preformed intracellular pools (Kapur, Majesky, Li, Black, & Musser, 1993). SLO also stimulates mononuclear cells to produce TNF-α and IL-1β and, in the presence of SpeA, has synergistic effects on IL-1β production (Hackett & Stevens, 1992). Heat-killed *S. pyogenes*, as well as isolated peptidoglycan and lipoteichoic acid, are also potent inducers of TNF-α and IL-1β (Hackett, Ferretti, & Stevens, 1994; Müller-Alouf, et al., 1994).

Recent evidence suggests that cardiomyocyte-derived cytokines are produced following direct *S. pyogenes* stimulation and after exposure to *S. pyogenes*-activated inflammatory cells (Li, et al., 2011). In addition, viable *S. pyogenes* induced the production of cardiomyocyte-derived stimulator/s that boosts macrophage production of matrix metalloproteinase-9, pro-inflammatory cytokines (IL-1β, IL-6) and cardiodepressant factors (iNOS) (Li, Bryant, Parimon, & Stevens, 2012). These locally produced, cardiomyocyte-derived cytokines (termed "cardiokines") may mediate cardiac contractile dysfunction observed in some patients with StrepTSS who develop a unique and reversible form of cardiomyopathy that is characterized by global hypokinesia and reduced cardiac index (Stevens, Shelly, Stiller, Villasenor-Sierra, & Bryant, 2008).

Other non-cytokine-mediated mechanisms of shock may also play a role in this process. For example, SpeB has been shown to release bradykinin from a high-molecular-weight kininogen (Herwald, Collin, Müller-Esterl, & Björck, 1996). Bradykinin is a potent vasodilator of systemic and pulmonary vasculature and could be at least partially responsible for the early hypotension observed in StrepTSS (Stevens, et al., 1996). Finally, recent studies demonstrated that SLO, through its ability to form membrane pores, is the major *S. pyogenes* exotoxin responsible for direct cardiomyocyte contractile dysfunction (Bolz, et al., 2015). Within minutes of exposure, SLO disrupted the normal contraction response of isolated murine cardiac cells to electrical pacing. Later, SLO induced spontaneous, non-paced contractions that were characterized by hyper-augmented contractile force. These effects were mediated by an influx of calcium through SLO-induced membrane pores. Upon removal of SLO, normal electrical pacing resumed, which suggests that membrane lesions were repaired and normal intracellular calcium levels were restored. These observations are consistent with the clinical observation that cardiomyopathy is a reversible condition in patients who survive StrepTSS (Stevens, Shelly, Stiller, Villasenor-Sierra, & Bryant, 2008).

There are likely many streptococcal and host factors that contribute to the shock and organ failure characteristic of StrepTSS. Experimental evidence suggests that TNF plays a central role in this process. Specifically, high levels of TNFα were observed in a baboon model of *S. pyogenes* bacteremia when profound hypotension was manifest (Stevens, et al., 1996); administration of a neutralizing anti-TNFα antibody restored normal blood pressure and reduced mortality by 50% (Stevens, et al., 1996). Diffuse capillary leaking also contributes to hypotension in StrepTSS and is likely attributable to cytokines and other mediators, though it may also be related to circulating M protein-fibrinogen complexes (Herwald, et al., 2004).

NSAIDs and Severe S. pyogenes Infection

In 1985, a report by Brun-Buisson and colleagues suggested a possible association between NSAID use and development of severe *S. pyogenes* necrotizing fasciitis (Brun-Buisson, et al., 1985). These authors identified 6 previously healthy individuals with no underlying conditions in whom NF either developed spontaneously (2/6) or following minor non-penetrating trauma (4/6). All had received at least one NSAID in the 4–10 days prior to hospitalization. One patient died; survivors underwent multiple surgeries and prolonged hospitalization. The

authors concluded that NSAIDs contributed to the development and/or extension of the disease process. Following this report, other case series and retrospective studies appeared in the literature concerning this possible association (reviewed in (Bryant, Bayer, Aldape, & Stevens, 2015)).

In 1995, Stevens proposed that NSAIDs, through their ability to interrupt the negative feedback loop that limits production of TNFα, may predispose individuals to more severe *S. pyogenes* infections (Stevens, 1995a). Others argued that NSAIDs merely mask the signs and symptoms of developing infections, such that diagnosis and antibiotic treatment are delayed. In an effort to examine a potential cause/effect relationship, Aronoff and Bloch reviewed the available published reports through 2002 (Aronoff & Bloch, 2003) and concluded that because most studies lacked appropriate control groups or had other significant limitations, the data did not support a causal role for NSAIDs in the development of *S. pyogenes* NF or to a worsening of the infection once established. However, their work suggested that further investigations were warranted.

Since then, additional reports have emerged that lend support to an association between NSAIDs and *S. pyogenes*, including one from the United Kingdom that demonstrated that NSAID use was independently associated with a 3-fold increased risk for development of StrepTSS (Lamagni, et al., 2008), a second multicentre prospective study in France (Dubos, Hue, Grandbastien, Catteau, & Martinot, 2008), and a nested case-controlled study in the UK by Mikaeloff et al. (Mikaeloff, Kezouh, & Suissa, 2008) that each found that NSAID use was independently associated with severe secondary complications in children with varicella infections.

Experimental evidence that directly addresses this issue is limited. Guibal et al. challenged rabbits with a combination of viable *S. pyogenes* plus *S. aureus* alpha toxin and treated them immediately thereafter with diclofenac (Guibal, et al., 1998). This relatively COX-2-selective NSAID (Süleyman, Demircan, & Karagöz, 2007) limited the extent of necrotizing fasciitis and lowered the bacterial numbers in the tissues (Guibal, et al., 1998). The authors concluded that any NSAID-induced increase in severity of NF in humans is likely due to the therapeutic delay induced by the misleading clinical effects of the NSAID, and not to any inhibition of antibacterial defenses (Guibal, et al., 1998). Goldmann et al. showed that a highly COX-2-selective NSAID (NS-398), delivered 2 hr before and again 2 hr after intravenous *S. pyogenes* challenge, significantly but transiently delayed the mortality of mice (Goldmann, et al., 2010). Our studies of NSAIDs in experimental *S. pyogenes* myonecrosis demonstrated that a highly COX-2-selective NSAID (SC-236), given 1 hr after IM challenge and continuing every 12 hr for 3 days, showed no benefit in either survival or disease severity (Hamilton, Bayer, Stevens, & Bryant, 2014). Together, these limited data suggest that COX-2-selective NSAIDs provide little to no benefit in *S. pyogenes* infections.

In striking contrast to the results with highly COX-selective NSAIDs, our studies of experimental *S. pyogenes* myonecrosis (Hamilton, Bayer, Stevens, & Bryant, 2014) and those of Weng et al. (Weng, Chen, Toh, & Tang, 2011) clearly demonstrate that different non-selective NSAIDs each accelerated the disease course, worsened outcomes, and reduced antibiotic efficacy. Of note, one non-selective NSAID, ketorolac tromethamine, also significantly augmented *S. pyogenes* infection of experimentally injured muscles in the above-mentioned murine model of cryptogenic *S. pyogenes* infection (Hamilton, Bayer, Stevens, Lieber, & Bryant, 2008).

As a result, a preponderance of clinical evidence and some experimental data suggest that non-selective NSAIDs do more than merely mask the signs and symptoms of developing *S. pyogenes* infection.

Clinical Manifestations and Stages of Infection

The first phase of StrepTSS begins with an influenza-like prodrome that is characterized by fever, chills, myalgias, nausea, vomiting, and diarrhea that precedes hypotension by 24–48 hours (Stevens, et al., 1989). Confusion and/or combativeness is present in 55% of patients. Where there is a defined portal of entry, early cutaneous evidence of streptococcal infection may be present. In contrast, in patients without a portal of entry (~50% of cases) and who subsequently develop necrotizing infection, increasingly severe pain is the most

common symptom. Such pain is so severe as to prompt patients to seek medical care and, interestingly, often precedes cutaneous evidence of localized infection by 12-24 hours (Stevens, et al., 1989). In both children (Kiska, et al., 1997) and adults (Stevens, et al., 1989), the soft tissues are the most common primary site of infection. In the remaining cases, pneumonia, meningitis, endophthalmitis, peritonitis, myocarditis, joint infection, and intrauterine infection have been described.

Phase 2 of StrepTSS is characterized by tachycardia, tachypnea, increasing pain and persistent fever (Stevens, 1995b). In children with varicella infection, toxicity or persistence of fever longer than 4 days should also prompt careful evaluation. Many patients are seen in emergency departments at this stage and frequently sent home on one or two occasions with mistaken diagnoses, such as deep vein thrombophlebitis, muscle strain, viral gastroenteritis, dehydration, or sprained ankle (Bisno, Cockerill, & Bermudez, 2000). High fever and excruciating pain, particularly in individuals with no risk factors for deep vein thrombosis, should arouse suspicion of a deep-seated infection. The laboratory tests described later are helpful, and CT and MRI may be useful to define the level of tissue involvement but are not specific.

In Phase 3 of StrepTSS, the sudden onset of shock and organ failure are manifested. Many patients are in florid shock at the time of admission or within hours thereafter. Clinical evidence of necrotizing fasciitis is frequently a late finding, often occurring after hypotension is present. The appearance of purple bullae and dusky-appearing skin is a bad prognostic sign and should prompt emergent surgical exploration. In modern cases, the progression of necrotizing fasciitis from red skin to purple bullae may occur within a 24-hour period, whereas that described by Meleney in 1924 took 7-10 days (Meleney, 1924). In addition, the rapidity with which shock and multi-organ failure can progress is impressive, and many patients die within 24-48 hours of hospitalization (Stevens, et al., 1989).

Laboratory tests should be performed in patients with aggressive soft tissue infections or patients with severe pain and fever who appear toxic. The serum creatinine measurement is particularly useful because renal impairment (creatinine level more than twice normal) is apparent even during phase 2, before hypotension is apparent. In addition, creatine phosphokinase levels in serum are markedly elevated in those with necrotizing fasciitis and myonecrosis. The white blood count is usually normal or modestly elevated at admission but with a profound left shift that includes myelocytes and metamyelocytes. Finally, serum albumin and calcium levels are usually low on admission and drop precipitously as a diffuse capillary leak syndrome develops. Thrombocytopenia does not develop until later in the course but is the earliest sign of disseminated coagulopathy. Profound metabolic acidosis develops early in phase 3, and serum bicarbonate, lactate, and blood gas pH determinations are crucial tests to follow therapeutic progress. Because the acute respiratory distress syndrome (ARDS) develops in 55% of patients with StrepTSS, pulse oximetry and, later, blood gas levels are necessary to evaluate the need for intubation and ventilation.

Management

Source Control

Prompt and aggressive surgical exploration and debridement of suspected deep-seated streptococcal infection are mandatory. Emergent surgical consultation should be sought in patients with extreme pain and fever or who are toxic. Surgical inspection provides samples for etiologic determination and allows assessment of the extent of necrosis. CT and MRI are helpful to locate the primary site of infection, but because *S. pyogenes* do not elaborate gas in the tissues or form frank abscesses, radiologist interpretations are frequently not definitive. Once necrosis is established, extensive debridement is necessary, since shock and organ failure continue to progress if devitalized tissue remains. While necrosis of the fascia may be present, it is important to recognize that global necrosis of muscle, skin, fascia and sub-cutaneous tissue is commonly present.

Fluid Resuscitation

Because of intractable hypotension and diffuse capillary leak, massive amounts of IV fluids (10 to 20 L/day) in an adult may be required. If several liters of crystalloid intravenous fluid challenge do not rapidly improve blood pressure (mean arterial pressure to more than 60 mm Hg) or tissue perfusion, then invasive monitoring or echocardiography is indicated. If despite adequate crystalloid administration, hypotension persists, the serum albumin concentration and hematocrit should be checked because capillary leak contributes to profoundly low albumin levels (< 2 g/dL) and because hemolysins produced by *S. pyogenes* can cause dramatic drops in circulating red cell mass. Thus, transfusion with packed red blood cells, with or without albumin, may be useful to improve blood pressure and preserve tissue perfusion.

Antimicrobial Treatment

Prompt antimicrobial therapy is mandatory, and empirical broad-spectrum coverage for septic shock should be initially instituted. Once the etiology of *S. pyogenes* is confirmed, high-dose penicillin and clindamycin should be given (Stevens, et al., 2014). This recommendation is based on the following: (1) all strains of *S. pyogenes* remain sensitive to penicillin; (2) resistance to clindamycin has only rarely been reported and erythromycin resistance among *S. pyogenes* is currently <5% in the United States, though some locales have reported higher rates; (3) clindamycin is more efficacious in experimental models of necrotizing fasciitis and myonecrosis; (4) penicillin-binding proteins are not expressed during stationary-phase growth of *S. pyogenes*, and thus penicillin is ineffective in severe deep infections in which large numbers of bacteria are present; (5) clindamycin suppresses *S. pyogenes* exotoxin and M protein production; (6) clindamycin has a much longer half-life and post-antibiotic effect; (7) no antagonistic effects between penicillin and clindamycin were found when used together in vitro at clinically relevant concentrations (Stevens, Madaras-Kelly, & Richards, 1998); and (8) clindamycin suppresses pro-inflammatory cytokine production by human mononuclear cells (Stevens, Bryant, & Hackett, 1995; Stevens, Hackett, & Bryant, 1997a). When combined, these facts have resulted in the current (2014) recommendation by the Infectious Disease Society of America to use clindamycin as the main antibiotic to treat invasive *S. pyogenes* infections (Stevens, et al., 2014); penicillin is included in this recommendation, largely due to the potential for clindamycin resistance.

Management in the Intensive Care Unit

In patients with persistent hypotension, monitoring of cardiac outputs, pulmonary artery occlusion pressure, and mean arterial pressure is important. Intubation and ventilator support are usually required because of the high incidence of ARDS (55%) in patients with StrepTSS. Vasopressors such as dopamine are used frequently, although no controlled trials have been performed in StrepTSS. In patients with intractable hypotension, high doses of dopamine, epinephrine, or phenylephrine have been used, but caution should be exercised in those with evidence of disseminated intravascular coagulation (DIC) and in particular in those with cold, cyanotic digits. Symmetrical gangrene involving all fingers and toes, the tip of the nose, and the breast areola has been described. In addition, amputation of 1–4 extremities has been observed (Stevens & Bryant, 2015). In these cases, both excessive vasopressors and DIC are likely to contribute to symmetrical gangrene.

Dialysis and Hemoperfusion

Dialysis and/or hemoperfusion may be necessary because more than 50% of patients develop acute renal failure. Both techniques may also non-specifically reduce the concentrations of circulating toxins. A Swedish study of severe *S. pyogenes* infection suggested that plasma exchange might be a beneficial adjunct to treatment of patients who fail conventional treatment (Stegmayr, et al., 1992). Finally, a polystyrene superantigen absorbing device (SAAD) was developed in Japan and was shown to be highly efficacious in absorbing both streptococcal pyrogenic exotoxin A and staphylococcal toxic shock syndrome toxin 1 (TSST-1) from plasma and, when used

extra-corporeally in animals infused with TSST-1 and lipopolysaccharide (LPS), mortality was reduced from 100% to 50% (Miwa, Fukuyama, Ida, Igarashi, & Uchiyama, 2003).

Intravenous Immune Globulin

The rationale for the use of intravenous immune globulin (IVIG) in the treatment of StrepTSS is based on the data implicating extracellular toxins as mediators of shock and organ failure. This concept was demonstrated as early as 1924, when George and Gladys Dick showed that convalescent sera from scarlet fever patients neutralized scarlatina toxins in vitro and, when passively administered, attenuated the course of severe scarlet fever in humans (Dick & Dick, 1925). Anti-scarlatina toxin horse serum became commercially available in the United States shortly thereafter, but because of the new widespread availability of penicillin and the decline in the severity of scarlet fever, it was never used.

Several reports have described the successful use of IVIG in patients with StrepTSS (Lamothe, D'Amico, Ghosn, Tremblay, Braidy, & Patenaude, 1995; Barry, Hudgins, Donta, & Pesanti, 1992; Stevens, 1998). The largest treatment study (15 patients) showed a significant reduction in mortality with IVIG, as compared with matched historical controls (Kaul, et al., 1999). However, the mortality rate of 70% in the control group was among the highest ever reported, whereas mortality in the IVIG group (30%) was similar to that of some series that did not use IVIG (Stevens, et al., 1989). A double-blind clinical trial was undertaken in northern Europe that compared IVIG with albumin in patients with StrepTSS. All patients received clindamycin. The mortality rate in the IVIG group was 16%, whereas that in the albumin group was 32% (Darenberg, et al., 2003). Unfortunately, the study was stopped because of low enrollment, and only seven or eight patients with proven *S. pyogenes* infections were in each group. Thus, the differences were not significant. A retrospective study in patients with StrepTSS has also shown no benefit of IVIG on mortality (Beaulieu, McGeer, & Muller, 2008). It is hoped that further double-blind studies with sufficient numbers of cases will resolve the continuing dilemma regarding the potential efficacy of IVIG (Stevens, 2003). It is clear that if IVIG were to be used, it should be given early and probably more than one dose should be given, because batches of IVIG have variable neutralizing activity against streptococcal exotoxins (Norrby-Teglund, et al., 1998; Norrby-Teglund, et al., 1996).

Hyperbaric Oxygen

There have been no comparative trials describing the efficacy of hyperbaric oxygen treatment in StrepTSS, although some state that such treatment reduces mortality and the need for further debridements (Riseman, et al., 1990). Certainly, use of this modality should not delay (or be used in preference to) surgical debridement, when the latter is indicated.

Bacteremia

Group A streptococcal bacteremia has been relatively uncommon in the antibiotic era (Weinstein, Reller, Murphy, & Lichtenstein, 1983). Before the mid-1980s, bacteremia predominantly occurred at the extremes of life and was usually community-acquired. Occasional cases were seen in young and middle-aged adults, and were associated with surgical wound infections and endometritis.

During the past decade, however, there has been an increase in the number of reported cases of *S. pyogenes* bacteremia, which reflects the changing epidemiology and clinical patterns of invasive streptococcal infection, as noted earlier. Many of the patients were previously healthy adults between the ages of 20 and 50 years. There has also been an apparent increase in cases associated with parenteral injection of illicit drugs (Stevens, et al., 1989; Braunstein, 1991), as well as nosocomial outbreaks in nursing homes (Thigpen, et al., 2007; Hohenboken, Anderson, & Kaplan, 1994; Jordan, Richards, Burton, Thigpen, & Van Beneden, 2007; Harkness, Bentley, Mottley, & Lee, 1992; Ruben, Norden, Heisler, & Korica, 1984).

Bacteremia in children may emanate from an upper respiratory infection, but it is more commonly associated with cutaneous foci, including burns and varicella (Valenzuela, Hooton, Kaplan, & Schlievert, 1991). Older patients with streptococcal bacteremia present with a variety of chronic illnesses; their relation to the bacteremia is often unclear. Diabetes mellitus and peripheral vascular disease do appear to be predisposing factors in older adults, and, as in children, the portal of entry is usually the skin. Malignancy and immunosuppression are risk factors in both age groups (Stevens, 1992; Duma, Weinberg, Medrek, & Kunz, 1969). Although *S. pyogenes* bacteremia may be transient and relatively benign at times (Dan, Maximova, Siegman-Igra, Gutman, & Rotmensch, 1990), it is more often fulminant. The onset is abrupt, with chills, high fever, and prostration. Rarely, patients may present with acute abdominal pain (Dan, Maximova, Siegman-Igra, Gutman, & Rotmensch, 1990; Ispahani, Donald, & Aveline, 1988). Mortality in five modern series (Francis & Warren, 1988; Dan, Maximova, Siegman-Igra, Gutman, & Rotmensch, 1990; Ispahani, Donald, & Aveline, 1988; Bucher, et al., 1992; Burkert & Watanakunakorn, 1992) has ranged from 27% to 38%.

Other Streptococcal Infections

Infection Associated with Pregnancy

S. pyogenes infection associated with pregnancy (also referred to as puerperal sepsis, childbed fever, or postpartum infection) was first described by Semmelweis in the 1850s and remains an important cause of maternal and infant mortality worldwide (reviewed in (Hamilton, Stevens, & Bryant, 2013)). Unlike in Semmelweis' era, only 14% of modern-day *S. pyogenes* postpartum infections in developed countries are nosocomially acquired. Rather, the majority occur after hospital discharge. Nearly 20 percent of cases of *S. pyogenes* infection occur during the third trimester, prior to the onset of labor or rupture of membranes (Hamilton, Stevens, & Bryant, 2013).

Patients with *S. pyogenes* puerperal sepsis typically present with fever, abdominal pain, and hypotension without tachycardia or leukocytosis. About 220 cases occur annually in the United States, for an overall rate of 6 cases per 100,000 live births (Chuang, Van Beneden, Beall, & Schuchat, 2002). In 2002, the case fatality rate was about 3.5 percent. Maternal mortality is highest when infection develops within four days of delivery or during the late third trimester (Hamilton, Stevens, & Bryant, 2013).

Meningitis and Endocarditis

Although endocarditis caused by *S. pyogenes* was relatively common in the pre-antibiotic era, it is now rarely seen (Ramirez, Naragi, & McCulley, 1984; Baddour, 1998). Meningitis caused by *S. pyogenes* usually follows upper respiratory infection, including sinusitis or otitis (van de Beek, et al., 2002), or neurosurgical conditions (Sommer, et al., 1999). It is clinically indistinguishable from other forms of acute pyogenic meningeal infection (Murphy, 1983).

Pneumonia

Pneumonia caused by *S. pyogenes* is frequently associated with antecedent viral infections such as influenza, measles, or varicella, or with chronic pulmonary disease. Numerous epidemics have been described in military recruit populations (Basiliere, Bistrong, & Spence, 1968; Crum, et al., 2005). An increased number of cases has been reported over the past few years in association with the resurgence of invasive streptococcal infections. In one-third or fewer of the cases, there was a history of preceding streptococcal upper respiratory infection. The onset is typically abrupt and the disease is characterized by chills, fever, dyspnea, cough productive of blood-streaked sputum, pleuritic chest pain, and, in more severe cases, cyanosis. The pulmonary picture is that of bronchopneumonia, with consolidation being uncommon. Empyema develops in 30–40% of cases, tends to appear early in the disease, and typically consists of copious amounts of thin serosanguinus fluid. Bacteremia occurs in 10-15% of cases. Complications include mediastinitis, pericarditis, pneumothorax, and bronchiectasis,

and the clinical course of the disease is often prolonged. Mortality has generally been low with penicillin therapy and adequate drainage of empyema, which perhaps reflects its occurrence in healthy military recruits. However, in a recent Canadian report of 222 cases of community-acquired pneumonia among adults (with a median age of 56 years), the case-fatality rate was 38% (Muller, et al., 2003). Interestingly, a recent review of the 1918 pandemic of influenza has demonstrated that the major cause of death was secondary bacterial pneumonia (Morens, Taubenberger, & Fauci, 2008). While *S. pneumoniae* was the most common etiologic agent, *S. pyogenes* was second, followed by *S. aureus*. Among patients with pneumonia with empyema, *S. pyogenes* was first. Investigators have demonstrated in a mouse model that a non-lethal influenza infection greatly enhanced the severity and mortality of secondary respiratory infection with *S. pyogenes* (Okamoto, et al., 2003).

Prophylaxis for, and Risk of, Secondary StrepTSS

StrepTSS is most commonly community-acquired and sporadic in nature, yet clusters of invasive cases have been described in nursing homes (Thigpen, et al., 2007; Hohenboken, Anderson, & Kaplan, 1994; Jordan, Richards, Burton, Thigpen, & Van Beneden, 2007; Harkness, Bentley, Mottley, & Lee, 1992; Ruben, Norden, Heisler, & Korica, 1984), families (DiPersio, et al., 1996; Gamba, et al., 1997), and hospital workers (Valenzuela, Hooton, Kaplan, & Schlievert, 1991; Kakis, et al., 2002). In San Francisco, 23 hospital workers became colonized or infected with *S. pyogenes* as a result of contact from a single case of StrepTSS (Kakis, et al., 2002). This example, as well as many historical studies in schools, military posts, and nursing homes, has taught us that *S. pyogenes* is highly contagious. Fortunately, mere contact or colonization is usually not sufficient to cause a secondary case of invasive *S. pyogenes* infection. Epidemiologic studies by the Centers for Disease Control and Prevention found one secondary case of invasive infection among more than 1500 contacts (Prevention of Invasive Group A Streptococcal Infections Workshop Participants, 2002). This would extrapolate to 66/100,000 population/year for secondary cases (Robinson, et al., 2003). As noted, the current incidence of primary cases of invasive *S. pyogenes* infections in the United States is 3.5/100,000 population/year. Thus, the risk to contacts is roughly 20 times greater than that for the general population, but still remains very low. Given the relative infrequency of these infections and the lack of a clearly effective chemoprophylactic regimen, routine screening for and prophylaxis against streptococcal infection are not recommended for household contacts of index patients (Prevention of Invasive Group A Streptococcal Infections Workshop Participants, 2002). In deciding who should receive prophylaxis, the clinician needs to consider the duration and intimacy of contact and underlying host factors of individual contacts. Specifically, contacts with open wounds, who have had recent surgery or childbirth, who have concurrent viral infections such as varicella or influenza, or those with immunodeficiency diseases should receive prophylaxis. In a multicenter study of adults aged 18–45 years, human immunodeficiency virus infection and injecting drug use were independently associated with an increased risk of invasive *S. pyogenes* disease. In those aged 45 years of age or older, diabetes, cardiac disease, cancer, and corticosteroid use were significant risk factors (Factor, et al., 2003). Moreover, persons aged 65 years or older are at an increased risk of mortality, should they contract invasive disease. Thus, it may be prudent to initiate prophylaxis in households with older adults or those with the above-mentioned risk factors.

As there is a present lack of firm data on which to base antimicrobial prophylaxis, it seems reasonable to choose those agents that have achieved highest rates of pharyngeal eradication in asymptomatic individuals; among these are penicillin, clindamycin, and azithromycin. Specific regimens have been published elsewhere (Prevention of Invasive Group A Streptococcal Infections Workshop Participants, 2002).

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