Streptococcal Toxic-Shock Syndrome: Spectrum of Disease, Pathogenesis, and New Concepts in Treatment

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Since the 1980s there has been a marked increase in the recognition and reporting of highly invasive group A streptococcal infections with or without necrotizing fasciitis associated with shock and organ failure. Such dramatic cases have been defined as streptococcal toxic-shock syndrome. Strains of group A streptococci isolated from patients with invasive disease have been predominantly M types 1 and 3 that produce pyrogenic exotoxin A or B or both. In this paper, the clinical and demographic features of streptococcal bacteremia, myositis, and necrotizing fasciitis are presented and compared to those of streptococcal toxic-shock syndrome. Current concepts in the pathogenesis of invasive streptococcal infection are also presented, with emphasis on the interaction between group A Streptococcus virulence factors and host defense mechanisms. Finally, new concepts in the treatment of streptococcal toxic-shock syndrome are discussed.

An emerging pathogen can be one that is totally new (e.g., human immunodeficiency virus), one that was known but has only recently been identified (e.g., Helicobacter pylori), or one that is old but has learned new tricks. The last type is, as Dr. Stanley Falkow contends, merely trying to “make a living” in a changing environment. Regardless of environmental pressures, many old pathogens have become major clinical problems because of increased virulence or antibiotic resistance (e.g., penicillin-resistant pneumococcus, multidrug-resistant Mycobacterium tuberculosis, methicillin-resistant Staphylococcus aureus, and vancomycin-resistant Enterococcus faecium).

Arguably, group A Streptococcus (GAS) is the quintessence of an old organism that has become more virulent. In this manuscript, the epidemiology, clinical spectrum, and pathogenesis of GAS infection are discussed in relation to the streptococcal toxic-shock syndrome (TSS).

Current and Historical Perspectives on the Prevalence and Severity of Streptococcal Infections

The British tabloids have recently coined the term “flesh-eating bacteria” to describe invasive necrotizing infections caused by GAS and have suggested that epidemics of streptococcal infection are imminent. Such aggrandizement is unfounded, yet it has served to heighten public awareness of this sporadic, but serious, infectious disease. Strictly speaking, an epidemic is defined as an increase in the prevalence of disease over a baseline endemic rate. In this context, we are, in fact, experiencing an epidemic of severe invasive GAS infections; however, few concrete prospective population-based data support this notion. Estimates suggest that the incidence of these infections is 10 to 20 cases/100,000 population. Thus, the stimulus for such public interest has not been the incidence of the syndrome, but more likely, the dramatic nature of these infections.

Whether these types of group A streptococcal infections will decline, stay the same, or increase is not known. History is replete with descriptions of epidemics of GAS infections and their nonsuppurative sequelae. In the 1600s, epidemics of scarlet fever spread from Italy and Spain to Northern Europe (1), and in 1736, an outbreak occurred in the American colonies, killing 4,000 people (2). Major epidemics of rheumatic fever occurred in World War II in the U.S. military (3). Soon afterward post-streptococcal glomerulonephritis struck several regions of the United States (4,5).

Many of these epidemics waxed and waned before the advent of antibiotics, suggesting that either changes in socioeconomic conditions or variations in the expression of virulence factors by the pathogen were responsible. This concept is best exemplified by the extraordinary mortality rate of scarlet fever documented in the latter part of the 1880s in New York, Chicago, and Norway; 25% to 30% of children with scarlet fever died during that period (5,6). By 1900, the mortality rate had dropped to under 2% in all three locations. Since socioeconomic conditions...
likely did not change markedly during that time and antibiotics were not yet available, the decrease in mortality rates must have been caused by reduced expression of a streptococcal virulence factor or by the slow acquisition of herd immunity to that factor.

The epidemiology of GAS infection is complex. More than 80 different M types of S. pyogenes exist, and five separate and distinct scarlatina toxins, streptococcal pyrogenic exotoxins (SPEs) (5) have also been described; some of these can be transmitted to different M types by bacteriophage. Minor drifts in the antigenic or virulence properties of GAS could account for the 5- to 6-year cycles of scarlet fever documented by Kohler (9). In the same way as antigenic shifts in influenza virus cause pandemics, major alterations in GAS virulence properties could cause major changes in clinical disease. The recent increases in severe GAS infections, following a 50- to 60-year span of relatively benign clinical disease, support this notion.

Acute Life-Threatening Group A Streptococcal Infections

Streptococcal TSS

Recently, severe invasive GAS infections associated with shock and organ failure have been reported with increasing frequency, predominantly from North America and Europe (8-18). These infections have been termed streptococcal toxic-shock syndrome (TSS; Table 1) (19). Persons of all ages are affected; most do not have predisposing underlying diseases (11,20-25). This is in sharp contrast to previous reports of GAS bacteremia, in which patients were either under 10 or over 60 years of age, and most had underlying conditions such as cancer, renal failure, leukemia, or severe burns or were receiving corticosteroids or other immunosuppressing drugs (20-22). The complications of current GAS infections are severe; bacteremia associated with aggressive soft tissue infection, shock, adult respiratory distress syndrome and renal failure are common; 30% to 70% of patients die in spite of aggressive modern treatments (Table 2) (1,8,24-26).

Acquisition of Group A Streptococcus

The portal of entry of streptococci cannot be proven in at least half the cases (8) and can only be presumed in many others. Patients with symptomatic pharyngitis rarely develop streptococcal TSS, though such cases have been reported, especially in the last year. Procedures such as suction lipectomy, hysterectomy, vaginal delivery, bunionectomy and bone pinning have provided a portal of entry in many cases (author’s unpublished observations). Most commonly, infection begins at a site of minor local trauma, which frequently does not result in a break in the skin (8). Numerous cases have developed within 24 to 72 hours of minor nonpenetrating trauma, resulting in hematoma, deep bruise to the calf, or even muscle strain. Virus infections, such as varicella and influenza, have provided a portal in other cases. In some cases the use of nonsteroidal antiinflammatory agents may have either masked the early symptoms or predisposed the patient to more severe streptococcal infection and shock (1). For the most part, these infections have occurred sporadically and have not been associated with clusters of cases or minor epidemics, though outbreaks of severe GAS infections have occurred in closed environments such as nursing homes (27,28).

Clinical Symptoms

Pain—the most common initial symptom of streptococcal TSS—is abrupt in onset and severe, and usually precedes tenderness or physical findings. The pain usually involves an extremity but may also mimic peritonitis, pelvic inflammatory disease, pneumonia, acute myocardial infarction, or pericarditis. Twenty percent of patients have an influenza-like syndrome characterized by fever, chills, myalgia, nausea, vomiting, and diarrhea (8).

Fever is the most common early sign, although hypothermia may be present in patients with shock. Confusion is present in 55% of patients, and in some, coma or combativeness is manifest (8). Eighty percent of patients have clinical signs of soft tissue infection, such as localized swelling and erythema, which in 70% of patients progressed to necrotizing fasciitis or myositis and required surgical debridement, fasciectomy or amputation (8). An ominous sign is the progression of soft tissue swelling to the formation of vesicles, then bullae, which appear violaceous or bluish. In such patients, emergent surgical exploration should be performed to establish the diagnosis and distinguish GAS infection from other necrotizing soft tissue infections. Among the 20% of patients without soft tissue findings, clinical symptoms include endophthalmitis, myositis, perihepatitis, peritonitis, myocarditis, and overwhelming sepsis. A diffuse, scarlatina-like erythema occurs in only 10% of patients. Nearly 50% of patients may have normal blood pressure (systolic pressure >110 mm Hg) on admission but develop hypotension within the subsequent 4 hours (8).

Laboratory Evaluation of Patients

On admission, renal involvement is indicated by the presence of hemoglobinuria and by serum creatinine values that are, on average, >2.5 times normal. Renal impairment precedes hypotension in 40% to 50% of patients (8). Hypoalbuminemia is associated with hypocalcemia on admission and throughout the hospital course. The serum creatinine kinase level is useful in detecting deeper soft-tissue infections;
when the level is elevated or rising, there is a good correlation with necrotizing fasciitis or myositis. Though the initial laboratory studies demonstrate only mild leukocytosis, the mean percentage of immature neutrophils (including band forms, metamyelocytes, and myelocytes) is striking, reaching 40% to 50%. Blood cultures are positive in 60% of cases (8).

Clinical Course
Shock is apparent at the time of admission or within 4 to 8 hours in virtually all patients (Table 2). In only 10% of patients does systolic blood pressure become normal 4 to 8 hours after administration of antibiotics, albumin, and electrolyte solutions containing salts or dopamine; in all other patients, shock persists. Similarly, renal dysfunction progresses or persists in all patients for 48 to 72 hours in spite of treatment, and many patients may require dialysis (8). In patients who survive, serum creatinine values return to normal within 4 to 6 weeks. Renal dysfunction precedes shock in many patients and is apparent early in the course of shock in all others. Acute respiratory distress syndrome

Table 1. Case definition of streptococcal toxic-shock syndrome (streptococcal TSS) and necrotizing fasciitis*

<table>
<thead>
<tr>
<th>I. Streptococcal TSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Isolation of group A Streptococcus</td>
</tr>
<tr>
<td>1. From a sterile site</td>
</tr>
<tr>
<td>2. From a nonsterile body site</td>
</tr>
<tr>
<td>B. Clinical signs of severity</td>
</tr>
<tr>
<td>1. Hypotension</td>
</tr>
<tr>
<td>2. Clinical and laboratory abnormalities (requires two or more of the following):</td>
</tr>
<tr>
<td>a) Renal impairment</td>
</tr>
<tr>
<td>b) Coagulopathy</td>
</tr>
<tr>
<td>c) Liver abnormalities</td>
</tr>
<tr>
<td>d) Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>e) Extensive tissue necrosis, i.e., necrotizing fasciitis</td>
</tr>
<tr>
<td>f) Erythematous rash</td>
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</tbody>
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Definite Case = A1 + B(1+2)
Probable Case = A2 + B(1+2)

<table>
<thead>
<tr>
<th>II. Necrotizing fasciitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Definite case</td>
</tr>
<tr>
<td>1. Necrosis of soft tissues with involvement of the fascia</td>
</tr>
<tr>
<td>PLUS</td>
</tr>
<tr>
<td>2. Serious systemic disease, including one or more of the following:</td>
</tr>
<tr>
<td>a) Death</td>
</tr>
<tr>
<td>b) Shock (systolic blood pressure &lt;90 mm of Hg).</td>
</tr>
<tr>
<td>c) Disseminated intravascular coagulopathy</td>
</tr>
<tr>
<td>d) Failure of organ systems</td>
</tr>
<tr>
<td>a. respiratory failure</td>
</tr>
<tr>
<td>b. liver failure</td>
</tr>
<tr>
<td>c. renal failure</td>
</tr>
<tr>
<td>3. Isolation of group A Streptococcus from a normally sterile body site</td>
</tr>
<tr>
<td>B. Suspected case</td>
</tr>
<tr>
<td>1. 1 + 2 and serologic confirmation of group A streptococcal infection by a 4-fold rise against:</td>
</tr>
<tr>
<td>a) streptolysin O</td>
</tr>
<tr>
<td>b) DNase B</td>
</tr>
<tr>
<td>2. 1 + 2 and histologic confirmation:</td>
</tr>
<tr>
<td>Gram-positive cocci in a necrotic soft tissue infection</td>
</tr>
</tbody>
</table>

*Streptococcal toxic-shock syndrome (streptococcal TSS) is defined as any group A streptococcal infection associated with the early onset of shock and organ failure. Definitions describing criteria for shock, organ failure, definite cases, and probable cases are included below. Source: reference 61.
occurs in 55% of patients and generally develops after the onset of hypotension (8). Supplemen tal oxygen, intubation, and mechanical ventilation are necessary in 90% of the patients in whom this syndrome develops. Mortality rates vary from 30% to 70% (1,8,24-26). Morbidity is also high; 13 of 20 patients in one series underwent major surgical procedures, which included fasciotomy, surgical debridement, exploratory laparotomy, intraocular aspiration, amputation, or hysterectomy (8).

### Clinical Isolates

Type 1, 3, 12, and 28 have been the most common isolates from patients with shock and multiorgan failure (8,29). Recently, 80% of strains in Sweden from all types of GAS infection have been M type 1 (S. Holm, pers. comm.). Pyrogenic exotoxin A and/or B was found in most cases of severe infection. In the United States, pyrogenic exotoxin A is most frequently associated with these infections (8,23,29-33), while in Sweden and the United Kingdom, exotoxin B has been most common (12,25). Recently, streptococcal superantigen (SSA), a novel pyrogenic exotoxin, was isolated from an M 3 strain, albeit in small concentrations (34). In addition, mitogenic factor (MF) has been demonstrated in many different M types of GAS (35,36).

### Necrotizing Fasciitis

Necrotizing fasciitis, a deep-seated infection of the subcutaneous tissue that progressively destroys fascia and fat but may spare the skin and muscle, can be caused by GAS, Clostridium perfringens, or C. septicum. Necrotizing fasciitis caused by mixed organisms such as aerobic gram-negative bacteria, anaerobes, and microaerophilic streptococci may develop in diabetic patients or patients with open wounds contaminated with bowel contents. Though Meleney called infections caused by hemolytic streptococci “streptococcal gangrene” (37), the process has been renamed necrotizing fasciitis. His patients’ infections began at the site of trivial or inapparent trauma. Within 24 hours of the initial lesion—which frequently was only mild erythema—swelling, heat, erythema, and tenderness rapidly developed. During the next 24 to 48 hours, the erythema changed from red to purple and then to blue, and blisters and bullae, which contained clear yellow fluid, appeared. On days 4 and 5, the purple areas became gangrenous. From day 7 to day 10, the line of demarcation became sharply defined, and the dead skin began to separate at the margins or breaks in the center, revealing an extensive necrosis of the subcutaneous tissue. In more severe cases, the process advanced rapidly until several large areas of skin became gangrenous, and the intoxication rendered the patient dull, unresponsive, mentally cloudy, or even delirious. Meleney was the first to advocate aggressive “bear scratch” fasciectomy and debridement. With this treatment, together with irrigation with Dakains solution, the mortality rate dropped to 20% (37).

These older reports of necrotizing fasciitis (6) differ from reports of current necrotizing fasciitis cases associated with streptococcal TSS (8). First, recent cases have mainly occurred in young healthy persons who had no underlying disease but sustained minor trauma to an extremity. Earlier series describe older patients with multiple medical problems (6). Meleney’s cases (reported from China) were probably among young healthy persons who sustained minor trauma, though the major difference between them and present cases is the low mortality rate (20% vs 20% to 60% in streptococcal TSS) (6,37) before antibiotics were available (37). Analysis of Meleney’s reports also suggests that most of his patients did not have shock or organ failure, nor did they require amputation. In contrast, present cases of necrotizing fasciitis caused by GAS are invariably associated with severe manifestations of systemic illness and high morbidity despite the absence of underlying disease and the use of antibiotics, dialysis, ventilators, intravenous fluids, and improved surgical techniques. In summary, the high mortality rate among current cases of streptococcal necrotizing fasciitis could be due to the emergence of more virulent streptococci (8).

### Streptococcal Myositis

Streptococcal myositis is an extremely uncommon GAS infection. Adams et al. (38) documented only 21 reported cases from 1900 to 1985, and Svane (39) found only four cases in more 20,000 autopsies. Severe pain may be the only early symptom, and swelling and erythema may be the only early physical findings, though muscle compartment syndromes may develop rapidly (8,10,38-41). Distinguishing streptococcal myositis from spontaneous gas gangrene caused by C. perfringens or C. septicum (42) may be difficult, though crepitus or demonstration of gas in the tissue favors clostridial infection (40). Patients with streptococcal TSS may

### Table 2. Complications of group A streptococcal soft-tissue infection

<table>
<thead>
<tr>
<th>Complication</th>
<th>Percentage of Patients</th>
</tr>
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<tbody>
<tr>
<td>Shock</td>
<td>95</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>55</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>80</td>
</tr>
<tr>
<td>Irreversible</td>
<td>10</td>
</tr>
<tr>
<td>Reversible</td>
<td>70</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>60</td>
</tr>
<tr>
<td>Death</td>
<td>30</td>
</tr>
</tbody>
</table>

Source: reference 1.
have both necrotizing fasciitis and myositis (8,38). In published series, the case-fatality rate for necrotizing fasciitis is 20% to 50%, whereas GAS myositis has a fatality rate of 80% to 100% (6). Aggressive surgical debridement is extremely important for establishing a diagnosis and removing devitalized tissue.

Bacteremia

Streptococcal bacteremia has occurred most commonly in the very young and in the elderly (5). Among children, predisposing factors (other than scarlet fever) include burns, varicella, malignant neoplasm, immunosuppression, and age less than 2 years (5). In patients with scarlet fever, the pharynx is the most common source of GAS. Frequently such patients have complications, such as extension of infection into the sinuses, peritonsillar tissue, or mastoids (septic scarlet fever or scarlet fever angina); yet documented bacteremia occurs in only 0.3% of febrile patients (43). Among the children with varicella studied by Bullowa and Wischik (43), GAS bacteremia occurred in only approximately 0.5% of patients.

In elderly patients the source of GAS infection is invariably the skin and is associated with cellulitis or erysipelas (5). GAS sepsis in the elderly (mean age, 50 to 60 years) has also been associated with diabetes, peripheral vascular disease, malignancy, and corticosteroid use. Not surprisingly, mortality rates of 35% to 80% have been described in this patient population. In the past, GAS bacteremia was rare among persons 14 to 40 years of age; puerperal sepsis accounted for most bacteremia in this age group. Recently, intravenous drug abuse has emerged as a leading cause of GAS bacteremia in this age group (5). Martin and Hoiby have comprehensively demonstrated that the prevalence of GAS bacteremia in Norway in the late 1980s increased in all age groups, but the greatest increase (600% to 800%) was in adolescents and young adults (10). Thus, the demographics of invasive streptococcal infections have changed dramatically in the past 4 to 6 years.

Current Hypotheses Regarding Mechanisms of Shock and Tissue Destruction Caused by Virulent Group A Streptococci

Pyrogenic exotoxins cause fever in humans and animals and also help induce shock by lowering the threshold to exogenous endotoxin (5). Streptococcal pyrogenic exotoxins A and B induce human mononuclear cells to synthesize not only tumor necrosis factor-α (TNFα) (44) but also interleukin-1β (IL-1β) (45) and interleukin-6 (IL-6) (45), suggesting that TNF could mediate the fever, shock, and tissue injury observed in patients with streptococcal TSS (8). Pyrogenic exotoxin C has been associated with mild cases of scarlet fever in the United States (author's observations) and in England (46). The roles of two newly described pyrogenic exotoxins, SSA and MF (see section on "Clinical Isolates"), in streptococcal TSS have not been elucidated.

M protein contributes to invasiveness through its ability to impede phagocytosis of streptococci by human polymorphonuclear leukocytes (47). Conversely, type-specific antibody against the M protein enhances phagocytosis (47). After infection with a particular M type, specific antibody confers resistance to challenge to viable GAS of that M type (47). While M types 1 and 3 strains have accounted for most strains isolated from cases of streptococcal TSS, many other M types, including some nontypable strains, have also been isolated from such cases. M types 1 and 3 are also commonly isolated from asymptomatic carriers, patients with pharyngitis, and patients with mild scarlet fever (7,29).

Could streptococcal TSS be related to the ability of pyrogenic exotoxin or M proteins type 1 or 3 to act as "super antigens" (48)? Data suggest that this exotoxin and a number of staphylococcal toxins (toxic shock syndrome toxin-1 [TSST-1] and staphylococcal enterotoxins A, B, and C) can stimulate T-cell responses through their ability to bind to both the Class II major histocompatibility complex of antigen-presenting cells and the Vβ region of the T-cell receptor (48). The net effect would be to induce T-cell stimulation with production of cytokines capable of mediating shock and tissue injury. Recently, Hackett and Stevens demonstrated that pyrogenic exotoxin A induced both TNFα and TNFβ from mixed cultures of monocytes and lymphocytes (49), supporting the role of lymphokines (TNFβ) in shock associated with strains producing that exotoxin. Kotb et al. (50) have shown that a digest of M protein type 6 can also stimulate T-cell responses by this mechanism; however, the role of specific superantigens in this or any other infectious disease has not been proven. Proof would require demonstration of massive expansion of T-cell subsets bearing a Vβ repertoire specific for the putative superantigen. However, quantitation of such T-cell subsets in patients with acute streptococcal TSS demonstrated deletion rather than expansion, suggesting that perhaps the lifespan of the expanded subset was shortened by a process of apoptosis (51). In addition, the subsets deleted were not specific for streptococcal pyrogenic exotoxins A, B, C, or mitogenic factor, suggesting that an as yet undefined superantigen may play a role (51).

Cytokine production by less exotic mechanisms likely contributes as well to the genesis of shock and organ failure. Peptidoglycan, lipoteichoic acid (52), and killed organisms (53,54) are capable of inducing TNFα production by mononuclear cells in vitro.
Exotoxins such as streptolysin O (SLO) are also potent inducers of TNFα and IL-1β. Pyrogenic exotoxin B, a proteinase precursor, has the ability to cleave pre-IL-1β to release preformed IL-1β (56). Finally, SLO and exotoxin A together have additive effects in the induction of IL-1β by human mononuclear cells (49). Whatever the mechanisms, induction of cytokines in vivo is likely the cause of shock, and these two exotoxins, cell wall components, and the like, are potent inducers of TNF and IL-1.

The mere presence of virulence factors, such as M protein or pyrogenic exotoxins, may be less important in streptococcal TSS than the dynamics of their production in vivo. Recently, Cleary et al. proposed a regulon in GAS that controls the expression of a group of virulence genes coding for known virulence factors such as M protein and C5 peptidase (57). When DNA fingerprinting was used, differences were shown between M1 strains isolated from patients with invasive disease and strains from patients with noninvasive GAS infections (58). Finally, genetic information coding for exotoxins A or C may be introduced to strains of GAS by certain bacteriophage; after lysogenic conversion, synthesis of exotoxin A would occur during growth of the streptococcus (31,59,60). Multilocus enzyme electrophoresis demonstrates two patterns that correspond to the M1 and M3 type organisms that produce pyrogenic exotoxin A, a finding that supports epidemiologic studies implicating these strains in invasive GAS infections (33).

The interaction between these microbial virulence factors and an immune or nonimmune host determines the epidemiology, clinical syndrome, and outcome. Since horizontal transmission of GAS in general is well documented, the only explanation for the absence of a high attack rate of invasive infection is significant herd immunity against one or more of the virulence factors responsible for streptococcal TSS. This hypothetical model explains why epidemics have not materialized and why a particular strain of GAS can cause different clinical manifestations in the same community (8,61) (Figure 1).

**Treatment**

**Antibiotic Therapy – Cures and Failures with Penicillin**

*S. pyogenes* continues to be exquisitely susceptible to β-lactam antibiotics, and numerous studies have demonstrated the clinical efficacy of penicillin preparations for streptococcal pharyngitis. Similarly, penicillins and cephalosporins have proven efficacy in treating erysipelas, impetigo, and cellulitis, all of which are most frequently caused by *S. pyogenes*. In addition, Wannamaker et al. (6) demonstrated that penicillin therapy prevents the development of rheumatic fever following streptococcal pharyngitis if therapy is begun within 8 to 10 days of the onset of sore throat. Nonetheless, some clinical failures of penicillin treatment of streptococcal infection do occur. Penicillin treatment of *S. pyogenes* has failed to eradicate bacteria from the pharynx of 5% to 20% of patients with documented streptococcal pharyngitis (62-64). In addition, more aggressive GAS infections (such as, necrotizing fasciitis, empyema, burn wound sepsis, subcutaneous gangrene, and myositis) respond less well to penicillin and continue to be associated with high mortality rates and extensive morbidity (6,8,9,12,15,38,65). For example, in a recent report, 25 cases of streptococcal myositis had an overall mortality rate of 85% in spite of penicillin therapy (38). Finally, several studies in experimental infection suggest that penicillin fails when large numbers of organisms are present (66,67).

**The Efficacy of Penicillin, Compared to Clindamycin, In Fulminant Experimental *S. pyogenes* Infection**

In a mouse model of myositis caused by *S. pyogenes*, penicillin was ineffective when treatment was delayed ≥2 hours after initiation of infection (67). Survival of erythromycin-treated mice was greater than that of both penicillin-treated mice and untreated controls, but only if treatment was begun within 2 hours. Mice receiving clindamycin, however, had survival rates of 100%, 100%, 80%, and 70%, even if treatment was delayed 0, 2, 6, and 16.5 hours, respectively (67,68).

Eagle suggested that penicillin failed in this type of infection because of the "physiologic state of the
organism” (66). This phenomenon has recently been attributed to both in vitro and in vivo inoculum effects (69,70).

**Inoculum Size and the “Physiologic State of the Organism”: Differential Expression of Penicillin-Binding Proteins**

Penicillin and other β-lactam antibiotics are most efficacious against rapidly growing bacteria. We hypothesized that large inocula reach the stationary phase of growth sooner than smaller inocula both in vitro and in vivo. That high concentrations of S. pyogenes accumulate in deep-seated infection is supported by data from Eagle et al. (66). We compared the penicillin-binding protein patterns from membrane proteins of group A streptococci isolated from different stages of growth, i.e., mid-log phase and stationary phase. Binding of radiolabeled penicillin by all penicillin-binding proteins was decreased in stationary cells; however, PBPs 1 and 4 were undetectable at 36 hours (69). Thus, the loss of certain penicillin-binding proteins during stationary-phase growth in vitro may be responsible for the inoculum effect observed in vivo and may account for the failure of penicillin in treatment of both experimental and human cases of severe streptococcal infection.

**The Greater Efficacy of Clindamycin in Experimental S. pyogenes Infections: Mechanisms of Action**

The greater efficacy of clindamycin is likely multifactorial: First, its efficacy is not affected by inoculum size or stage of growth (69,71); secondly, clindamycin is a potent suppressor of bacterial toxin synthesis (72,73); third, it facilitates phagocytosis of S. pyogenes by inhibiting M-protein synthesis (73); fourth, it suppresses synthesis of penicillin-binding proteins, which, in addition to being targets for penicillin, are also enzymes involved in cell wall synthesis and degradation (71); fifth, clindamycin has a longer postantibiotic effect than β-lactams such as penicillin; and lastly, clindamycin causes suppression of LPS-induced monocyte synthesis of TNF (74). Thus, clindamycin’s efficacy may also be related to its ability to modulate the immune response.

**Other Treatment Measures**

Though antibiotic selection is critically important, other measures, such as prompt and aggressive exploration and debridement of suspected deep-seated S. pyogenes infection, are mandatory. Frequently, the patient has fever and excruciating pain. Later, systemic toxicity develops, and definite evidence of necrotizing fasciitis and myositis appears. Surgical debridement may be too late at this point. Prompt surgical exploration through a small incision with visualization of muscle and fascia, and timely Gram stain of surgically obtained material may provide an early and definitive etiologic diagnosis. Surgical colleagues should be involved early in such cases, since later in the course surgical intervention may be impossible because of toxicity or because infection has extended to vital areas impossible to debride (i.e., the head and neck, thorax, or abdomen).

Anecdotal reports suggest that hyperbaric oxygen has been used in a handful of patients, though no controlled studies are under way, nor is it clear that this treatment is useful.

Because of intractable hypotension and diffuse capillary leak, massive amounts of intravenous fluids (10 to 20 liters/day) are often necessary. Pressors such as dopamine are used frequently, though no controlled trials have been performed in streptococcal TSS. In patients with intractable hypotension, vasoconstrictors such as epinephrine have been used, but symmetrical gangrene of digits seems to result frequently (author’s unpublished observations), often with loss of limb. In these cases it is difficult to determine if symmetrical gangrene is due to pressors, infection, or both.

Neutralization of circulating toxins would be desirable; however, appropriate antibodies are not commercially available in the United States or Europe. Two reports describe the successful use of intravenous gamma globulin in treating streptococcal TSS in two patients (75,76). In summary, if a wild “flesh-eating strain” has recently emerged, a major epidemic with a high attack rate would normally be expected. Clearly, epidemics of streptococcal infections, including impetigo, pharyngitis, scarlet fever, and rheumatic fever have occurred in the past. However, in the last decade, subsequent to early reports of streptococcal TSS, we have observed that the incidence has remained relatively low. I hypothesize that large outbreaks have not occurred because 1) most of the population probably has immunity to one or more streptococcal virulence factors (6,25); 2) predisposing conditions (e.g., varicella, and use of NSAIDs) are required in a given patient; and 3) only a small percentage of the population may have an inherent predisposition to severe streptococcal infection because of constitutional factors such as HLA Class II antigen type (77,78), B-cell (79), or specific Vβ regions on lymphocytes. This last hypothesis is further supported by the observation that secondary cases of streptococcal TSS, though reported (80), have been rare.

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