Therapeutic Approaches to Streptococcal Toxic Shock Syndrome

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The streptococcal toxic shock syndrome (STSS) is a severe, life-threatening condition characterized by hypotension and multiorgan system dysfunction associated with infection by the group A *Streptococcus* (GAS) or rarely by streptococci of other Lancefield serogroups. It is associated with a soft tissue infection, such as necrotizing fasciitis, in about half of the cases; the remainder are secondary to a variety of other invasive and noninvasive GAS infections. Although the pathophysiology of STSS is not yet fully understood, there are compelling reasons to believe that the syndrome results at least in part from the action of the streptococcal pyrogenic exotoxins, which act as superantigens. Patients with STSS should be admitted to an intensive care unit for support of cardiovascular, respiratory, and renal function as required. In experimental models of overwhelming GAS infection, clindamycin has greater efficacy than penicillin, and therapy with this agent is recommended. Penicillin, to which GAS are uniformly susceptible, may be used in addition to clindamycin. Limited clinical experience, most of which is anecdotal, suggests marked improvement in some STSS patients after administration of intravenous immunoglobulin. Even in the absence of conclusive data, the potential benefits of intravenous immunoglobulin in this highly lethal disease make its use reasonable in life-threatening cases. Other experimental approaches are also discussed, such as the use of anti–tumor necrosis factor monoclonal antibodies and plasmapheresis.

Introduction

The streptococcal toxic shock syndrome (STSS) is a severe, life-threatening condition characterized by hypotensio and multiorgan system dysfunction associated with infection by the group A *Streptococcus* (GAS). STSS is associated with a soft tissue infection such as necrotizing fasciitis, myonecrosis, or cellulitis in about 50% of cases [1,2]. It has, however, followed a variety of other streptococcal infections such as pneumonia, meningitis, sinusitis, endophthalmitis, pancreatitis, peritonitis, puerperal sepsis, septic arthritis, pharyngitis, and retroperitoneal necrotizing fasciitis [2–7]. In as many as 20% of patients, no site of infection is apparent at the time of presentation [3,8•]. Approximately 60% of patients are bacteremic, and in one half of bacteremic patients the source of infection cannot be ascertained [1,2].

The microorganism most frequently isolated and the one classically associated with this condition is the GAS. Most studies have shown that strains of the M-protein serotypes 1 and 3 are those most frequently isolated from patients with STSS [1,8•]. Moreover, among patients experiencing invasive GAS disease, infection with an organism of the M-1 serotype has been associated with an increased risk of developing STSS [8•]. In a recent series, however, these serotypes accounted for only 37.5% of the isolates, with the remaining isolates belonging to multiple other serotypes or being non–M-typable [9]. STSS has also been described after infections with streptococci from the Lancefield groups B, C, and G [10–15] and *Streptococcus suis* [16].

Epidemiology

Extremes of age, HIV infection, cancer, heart disease, diabetes mellitus, lung disease, alcohol abuse, and active varicella infection have been identified as risk factors for invasive GAS disease [17]. Are there specific risk factors for the development of STSS among persons with invasive GAS disease? Population-based studies are at variance on this point. Zurawski *et al.* [9] found no clear differences in age distribution or underlying disease state between patients with or without STSS in metropolitan Atlanta. Eriksson *et al.* [8•] studied invasive GAS disease in Stockholm; multivariate logistic regression analysis revealed alcohol abuse and infection with type M-1 organisms to be significantly associated with STSS. In Ontario, Davies *et al.* [17] found STSS patients to be older, more likely to have an underlying chronic illness, and less likely to have nosocomial disease than others with invasive disease.

Most STSS patients have an obvious percutaneous portal of entry, including surgical and nonsurgical acute wounds, chronic skin ulcers, illicit injection of intravenous drugs [3,9], superinfection of varicella lesions [9,18–20], or rarely even acupuncture [21]. It is believed that most of the other patients acquire the infection via the pharyngeal or the vaginal mucosa [1].

It has been postulated that the use of nonsteroidal anti-inflammatory agents (NSAIDs) might facilitate the progression of streptococcal infections to STSS, since these agents adversely affect granulocyte chemotaxis, phagocytosis, and bacterial killing and enhance the production of tumor necrosis factor (TNF) [22]. However, no such association has been demonstrated in clinical studies [9,23]. Moreover, the issue has been difficult to assess because of the ready availability of NSAIDs and the frequency with which they are employed in patients experiencing fever and pain, two early symptoms of invasive GAS disease and STSS.

Pathogenesis and Pathophysiology

Although the pathogenesis and pathophysiology of STSS are not yet fully understood, there are compelling reasons to believe that the syndrome results in large part from the action of streptococcal toxins, most of which are extracellularly elaborated. Indeed, the very name of this entity proclaims its similarity to the toxic shock syndrome caused by *Staphylococcus aureus*, a disorder known to be toxin mediated. Moreover, certain GAS toxins bear considerable structural and functional similarity to those produced by *S. aureus*.

Of particular interest in regard to STSS are the streptococcal pyrogenic exotoxins (SPE), of which five are currently known. These include SPE-A, SPE-B, SPE-C, mitogenic factor (MF, SPE-F) and streptococcal superantigen (SSA). Most of the SPE function as superantigens [5,26,27], and M protein has also been reported to possess superantigenic activity.

Superantigens are a group of very powerful immunostimulatory molecules produced by bacteria and viruses [25,26]. They induce massive T-cell proliferation by their ability to bind directly to both the major histocompatibility complex (MHC) class II molecule outside the antigen-binding cleft on the antigen-presenting cell and to a specific Vβ region of the T-cell receptor, thus circumventing normal antigen recognition and processing. A superantigen may activate as many as 3% to 10% of the entire T-cell population, often all those expressing the specific Vβ chain to which the superantigen binds [27]. In contrast, conventional antigens, which have to match all five elements of the T-cell receptor (Vα, Jα, Vβ, Dβ, Jβ), activate approximately 0.01% to 0.1% of the body's T cells (Fig. 1) [28].

Such nonspecific stimulation of T lymphocytes results in an unbridled release of cytokines, including TNF-α, TNF-β, interleukin (IL)-1, and IL-6 [29], which may well underlie the hypotension and multiorgan dysfunction seen in STSS. The initial proliferation of T cells in response to superantigens is followed by the rapid depletion of T-cell subsets bearing the specific β subunit through accelerated programmed cell death (apoptosis) [25].

The conventional pathways of antigen presentation and processing also play a role in the development of STSS [30•]. Cytokine production has been induced by pepti-
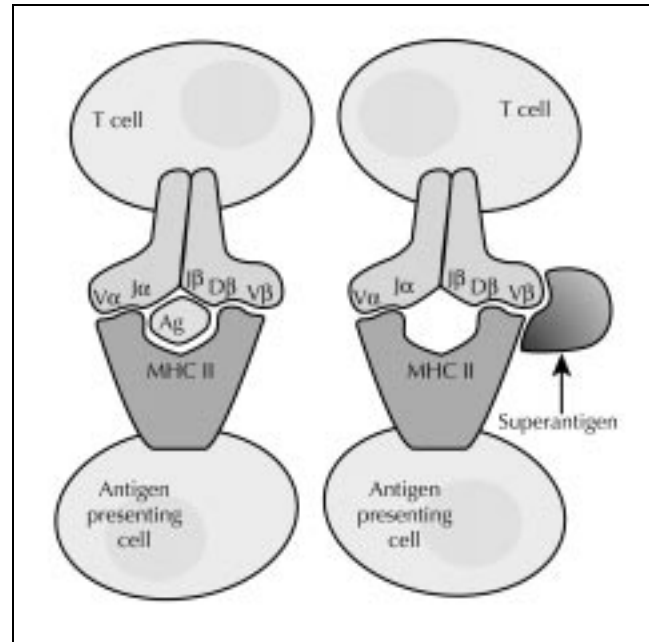

Figure 1. Interaction of antigens and superantigens with the antigen presenting cell and the T lymphocyte. Ag—antigen; MHC—major histocompatibility complex. *Adapted from* Manders [28]; with permission.

doglycan, lipoteichoic acid, exotoxins such as streptolysin O, and killed streptococci [31] by these more common mechanisms. SPE-B is a cysteine protease that has bee shown in mice to be critical for the pathogenicity of invasive GAS disease [32] and to increase the production of IL-1β by cleaving its percursor [33].

The conclusion that TNF plays a central role is supported by the observation that high levels of TNF wer observed in a baboon model of group A streptococcal bacteremia at a point in time when profound hypotension was manifest. In addition, a neutralizing monoclonal antibody against TNF restored normal blood pressure and reduced mortality by 50% in the same model [34].

Noncytokine mechanisms of shock may also pla role. Recently, a cysteine protease produced by group A streptococci was shown to release bradykinin, which is a very potent vasodilator and could be at least partially responsible for the early hypotension seen in STSS [35].

Why certain people infected with virulent toxigenic GAS strains develop STSS, invasive infection without STSS, or carry the same organism asymptomatically (as shown by DNA macrorestriction analysis [36] and by pulsed-field gel electrophoresis [37•]) is not known. It has been postulated that in order to develop STSS, the patient must lack both specific antibodies neutralizing SPE and opsonizing M protein [38–40]

Diagnosis

Streptococcal toxic shock syndrome manifests initially with myalgia, malaise, chills, fever, nausea, vomiting, and diarrhea, followed later by tachycardia, tachypnea, and evidence of

Table 1 Case definition for the streptococcal toxic shock syndrome

Clinical case definition

An illness with the following clinical manifestations occurring within the first 48 hours of hospitalization or, for a nosocomial case, within the first 48 hours of illness:

Hypotension defined by a systolic blood pressure ≤ 90 mm Hg for adults or less than the fifth percentile by age for children aged less than 16 years.

Multiorgan involvement characterized by two or more of the following:

1. Renal impairment: Creatinine ≥ 2 mg/dL (≥ 177 μ/L) for adults or ≥ twice the upper limit of normal for age. In patients with preexisting renal disease, a greater than twofold elevation over the baseline level.
2. Coagulopathy: Platelets ≤ 100,000/mm^3 (≤ 100 x 10^6/L) or disseminated intravascular coagulation, defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products.
3. Liver involvement: Alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels≥ twice the upper limit of normal for the patient's age. In patients with preexisting liver disease, a greater than twofold increase over the baseline level.
4. Acute respiratory distress syndrome: defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in the absence of cardiac failure or by 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.

Laboratory criteria for diagnosis

Isolation of group A *Streptococcus.*

Case classification

Probable: A case that meets the clinical case definition in the absence of another identified etiology for the illness and with isolation of group A *Streptococcus* from a nonsterile site.
Confirmed: A case that meets the clinical case definition and with isolation of group A*Streptococcus* from a normally sterile site (*eg*, blood or cerebrospinal fluid or, less commonly, joint, pleural, or pericardial fluid).

Adapted from Centers for Disease Control and Prevention [42].

shock and organ failure [1]. Included in the clinical picture are also symptoms associated with the primary infection. In the case of necrotizing fasciitis, for example, severe and unrelenting deep pain out of proportion to the cutaneous findings is frequently seen. The diagnosis of STSS is made on clinical and laboratory data according to the case definition proposed by the Working Group on Severe Streptococcal Infections[41] and revised by the Centers for Disease Control and Prevention in September, 1996 (Table 1) [42]

Therapy

Proper antibiotic therapy and aggressive supportive care are essential components in the treatment of invasive GAS disease and toxic shock. If necrotizing fasciitis is present, prompt surgical intervention with radical debridement of all infected tissues is virtually always required and may be life saving [43]. Several other interventions directed towards arresting the immunologic and inflammatory mechanisms responsible for STSS have been proposed to be beneficial in the management of this condition.

Supportive therapy

Patients with STSS should be admitted to an intensive care unit. Resuscitation often requires copious volumes of intravenous fluids. Inotropic agents, blood products, mechanical ventilation, and hemodialysis should be used as indicated by the patient's condition. Invasive hemodynamic monitoring is usually required.

Antimicrobials
Penicillin
Streptococci of Lancefield groups A, B, C, and G are universally susceptible to penicillin [44,45], which remains the drug of choice in the early treatment of invasive as well as noninvasive *Streptococcus pyogene* infections [46]. There is, however, an important caveat. Penicillin exerts its bactericidal activity by binding to certain enzymes (penicillin-binding proteins) involved in bacterial cell wall synthesis. The antimicrobial effect is thus expressed primarily in rapidly replicating bacteria and is greatly attenuated in cultures that have reached the stationary phase of growth. Organisms in such cultures decrease their expression o certain penicillin-binding proteins and become less susceptible to penicillin. This phenomenon (inoculum effect or Eagle effect) [47] has been demonstrated both in vitro and in the GAS myositis mouse model.

Inoculum size is a major factor in determining the efficacy of penicillin in the experimental treatment of deep-seated streptococcal infections [47]. With large inocula, the stationary phase of streptococcal growth in vivo may be reached sooner than with smaller inocula. Therefore, a large inoculum or a delayed treatment increases the probability of failure of penicillin. This is due to a slower growth rate of bacteria in the

infected tissues (analogous to the stationary growth phase of cultures in vitro) and not merely to the bacterial concentration per se [47,48]. In this setting, antimicrobials active at the ribosomal level were more effective than penicillin in decreasing lethality in the mouse myositis model [47,48]

Clindamycin
The efficacy of clindamycin is likely related to its ability to suppress the synthesis of proteins, including M protein and bacterial exotoxins, and to the fact that its mode of action is independent of the phase of bacterial growth [48]. It may also enhance certain host responses to infection such as phagocytosis and intracellular killing [47]. It has been shown that clindamycin has greater efficacy than penicillin in treating experimental myositis caused by two toxin-producing, gram-positive bacterial species, *S. pyogenes* (Fig. 2) and *Clostridium perfringens* [48]. This theoretical advantage, however, has not been validated in any controlled study, and clindamycin is often used in addition to (as opposed to instead of) penicillin or another cell wall–active agent [49]. In in vitro timed-kill studies using clinically relevant antimicrobial concentrations such combinations are neither antagonistic nor synergistic [50•].

Macrolides
Erythromycin is generally recommended as the therapy of choice for common streptococcal throat and skin infections in penicillin-allergic individuals [51]. It has also been found to be more effective than penicillin, although less so than clindamycin, in the GAS myositis mouse model [48]. Moreover, approximately 5% of GAS isolates in the United States are resistant to erythromycin and to other macrolides [45]. This figure is considerably higher in some other countries. At the present time there is no indication for the use of erythromycin or other macrolide congeners in the treatment of STSS.

Vancomycin
Holdsworth *et al.* [52] reported two patients with life-threatening GAS soft tissue infection who failed to respond to intravenous penicillin (even though the microorganisms were fully sensitive in vitro) but who improved dramatically when treated with vancomycin. Only one of the cases was proven bacteriologically to be due to GAS; the diagnosis in the second case was based on the clinical picture and a diagnostic rise in the serum titer of antistreptolysin O.

Vancomycin is an attractive alternative to penicillin because GAS are uniformly susceptible to it, it is bactericidal at therapeutic concentrations, and it has a long half-life and a long postantibiotic effect. Although, like penicillin, vancomycin interferes with cell wall synthesis, it does so by complexing with D-alanyl-D-alanine precursors and not with the penicillin-binding proteins that are the target of penicillin. Despite these theoretical advantages, the dearth of clinical data does not allow a recommendation for the use of vancomycin in STSS.
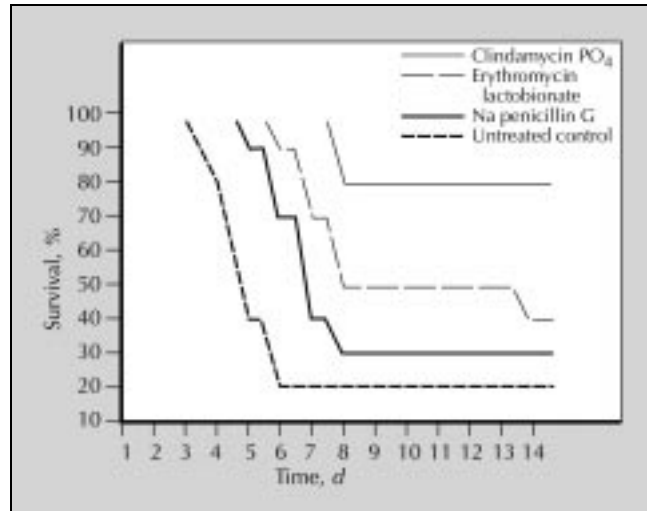

Figure 2. The survival of mice treated 6 hours after infection. Groups of 10 mice received 3.5 x 10^9 log-phase colony-forming units of *Streptococcus pyogenes.* Antibiotics were administered 6 hours after initiation of infection and were continued every 4 hours for a total of 4 doses. Animals were observed for 14 days, and the percent survival was calculated. *Adapted from* Stevens *et al.* [48]; with permission.

Intravenous immunoglobulins
If STSS is indeed a toxin-mediated disorder, then administration of antitoxic antibodies might be efficacious in its therapy. Specific antisera against streptococcal toxins are not available for human use, nor it is known which toxins are most intimately involved in the pathogenesis of thi disease. A possible source of such antitoxic antibodies i intravenous human pooled polyspecific immunoglobulin G (IVIG). There have been a few case reports of dramatic improvement of STSS patients after administration of IVI [19,39,53–56]. In a comparative observational study, the 30-day survival of 21 STSS patients receiving IVIG was 34%, while that of 32 patients not receiving this therapy was 67% (*P*=0.02) [57].

Multiple mechanisms have been postulated to explain a putative favorable effect of IVIG in the management of STSS [58]. IVIG neutralizes the superantigenic effect of the streptococcal toxins [59] and strongly inhibits the production of TNF and interleukins. It reduces blast transformation and inhibits lymphokine production (in particular TNF-β and interferon-γ) by SPE-A–stimulated peripheral blood mononuclear cells in vitro, even when added 24 hours after stimulation [60]. It also inhibits complement-mediated damage by binding to C3b and C4b and might modulate the activity of the reticuloendothelial system by binding to, and functionally blocking, Fc receptors of macrophages and monocytes [58].

Intravenous immunoglobulin is obtained by poolin plasma of thousands (often 15,000) of blood donors and isolating the IgG fraction [58]. The half-life of infused IVIG is similar to that of IgG in normal human serum: 3 weeks in the case of IgG1, IgG2, and IgG4, and 1 week in the case of IgG3 [58]. Its composition resembles the IgG subclass distri-

bution corresponding to that of normal serum. It contains antibodies to a number of toxic substances, including multiple streptococcal superantigens [61]. However, different commercial brands or even different lots of the same IVIG brand exhibit great variability in their neutralizing activity against purified and mixed group A streptococcal superantigens [62], making the standardization of this treatment and the recommendation of a dosage very difficult. Multiple doses may be necessary to neutralize all the potential pyrogenic exotoxins, particularly SPE-A [40,62].

The dosage used in the different case reports ranges from 0.15 to 1.0 g/kg body weight given for 1 to 5 consecutive days [19,39,53–57,63]. At this point, data in support of the use of IVIG are still largely theoretical. Considering the high mortality of full-blown STSS, and while awaiting more definitive data, use of this agent does seem reasonable in life-threatening cases.

Corticosteroids

Steroids may inhibit cytokine production, as well as inhibit the toxic alteration of vascular permeability [64]. Also, about one third of patients at stress have low cortisol values in relation to the stress situation [64]. There are fe reports on the use of corticosteroids in the management of STSS [55,64]. In most cases, these patients were also treated with antibiotics, IVIG, dialysis-plasma exchange, and other therapeutic modalities; they were all uncontrolled. It should be noted, however, that extensive controlled studies in septic shock caused by other bacterial agents have failed to show any benefit for the use these agents. For this reason, corticosteroids cannot be recommended in the treatment of STSS at the present time.

Anti–tumor necrosis factor monoclonal antibodies

There are scant data on the use of monoclonal antibodies (mAB) against TNF-α in the treatment of STSS. In a study of baboons with STSS induced by a strain producing pyrogenic exotoxin A, early treatment with anti-TNF mAB markedly improved arterial blood pressure and tissue perfusion and decreased mortality from100% to 50% [34]. Further studies are needed to clarify the role of anti-TNF mAB in the management of STSS.

Plasmapheresis

In a series of 11 patients with STSS in Sweden [64], seven received plasma exchange therapy. The primary rationale for plasma exchange is the removal of potential toxic substances (*ie*, anaphylotoxins, proteases, cell debris, cytokines, bacterial exo- and endotoxins) from the patient's plasma and replenishment of normal plasma constituents consumed in the inflammatory process [64]. It was found that plasmapheresis patients required less dialysis days (mean 7 days) than those who did not receive plasmapheresis (mean 20 days). These findings, although promising, still need to be confirmed in larger groups of patients.

Immunization

The increase in highly lethal GAS infections such as STSS, the persistence of acute rheumatic fever in the developing world, and the recent resurgence of acute rheumatic fever in the United States have led to renewed interest in the development of a GAS vaccine. Research on such a vaccine has focused primarily on M protein, because type-specific opsonic antibodies to this protein are the basis of acquired human immunity against GAS. Attempts to develop such a vaccine have been impeded by the fact that antibodies to M proteins crossreact with a variety of human tissues, including heart and synovium [65]. The extent to which such antigenic mimicry plays a role in the pathogenesis of acute rheumatic fever remains unknown. Advances in our knowledge of the genetics, structure, and function of the M protein molecule are now making it possible to separate epitopes responsible for immunity from those shared with human tissues. It has also been learned that the distal (variable) portion of the M protein fibrils possesses the epitopes conferring type specificity, while the more proximal (conserved) portions are widely shared among different M protein types. This information has spawned tw different approaches.

The first approach is recombinant, multivalent M protein vaccine. This approach involves constructing recombinant hybrid proteins that contain amino-terminal peptides of multiple different M proteins linked in tandem. Although there are over 90 GAS M protein types, a vaccine composed of approximately a dozen would encompass the great majority of strains currently causing life-threatening invasive and nonsuppurative GAS disease in the United States. This approach is similar to that employed in the 23-valent pneumococcal vaccine. So far, a gene that encodes an octavalent protein has been constructed and proven to elicit type-specific immunity to all eight M types in rabbits [65]

The second approach is non–type-specific M protein. Vaccines formulated from the conserved (so-called C-repeat) portion of the M protein molecule have been linked to cholera toxin B subunit and vaccinia virus as vectors. When administered orally or intranasally, such vaccines have protected mice against colonization and infection with several GAS serotypes. The commensal streptococcal organism, *Streptococcus gordonii*, has been genetically engineered to produce the C-repeat region o the M protein, and when this genetically altered organism is administered orally, it induces a secretory IgA, serum IgG, and T-cell response to the recombinant antigen [65].

Other approaches are also being explored. One of these focuses on C5a peptidase, an enzyme produced by GAS that inactivates complement factor C5a, a potent chemotaxin. Immunization with this enzyme induces high concentrations of salivary IgA and serum IgG in animals, thus inactivating the peptidase and facilitating clearance of the bacteri from tissue sites. If successful, this approach would obviate problems posed both by the multiplicity of GAS M protein types and of cross-reactivity between GAS and human tissues.

Although the group A specific carbohydrate has traditionally been thought not to play a role in human immunity, recent observations have challenged this dogma. If these results are confirmed, they would provide anothe approach to GAS immunization [65].

Prophylaxis of contacts

Several studies have shown the potential for transmission of invasive GAS disease in nursing homes, and from patients to household contacts and health care workers [36,66,67]. In the Ontario study [17], the risk of subsequent invasive disease among household contacts has been estimated to be 2.9 per 1000 (95% CI, 0.8–7.5), a figure almost 200 times the risk in the general population and similar to the risk of secondary meningococcal infection [68•]. This estimation is based on a series that encountered only four subsequent cases from 1360 contacts during a 4-year surveillance [17], numbers that limit the degree to which these results can be generalized. Recently, an expert panel was convened to consider whether sufficient data were available to recommend antimicrobial prophylaxis to prevent subsequent invasive GAS infections among household contacts of index patients [68•]. The limited amount of data precluded a firm recommendation regarding routine prophylaxis. Special consideration might well be given to contacts of patients who have severe GAS disease (STSS or necrotizing fasciitis); those at the extremes of age (>65 years or <1 year of age); and those with chronic cardiac and pulmonary disease, diabetes mellitus, HIV infection, or injection drug users and alcohol abusers, all of whom may be at increased risk for invasive disease.

Certain regimens have proved effective in eradicatin GAS colonization from the oropharyngeal mucosa. It is not known, however, whether these regimens will prevent severe, invasive GAS infections or those occurring through a cutaneous portal of entry [68•].

If chemoprophylaxis is to be given, either empiricall or to culture-positive intimate contacts, it should be recalled that penicillin is relatively ineffective in erradicating asymptomatic pharyngeal GAS carriage. Other agents may be employed, including clindamycin or ampicillin-clavulanate. Recommendations for specific regimens have been published elsewhere [51]. In a recent preliminary report, a 5-day course of azithromycin was highly effective in eradicating GAS from the nasopharynx in schoolmates of a child with invasive GAS disease. There was, however, a marked increase in the proportion of nasopharyngea *Streptococcus pneumoniae* isolates resistant to erythromycin [69].

Conclusions

Streptococcal toxic shock syndrome is a condition associated with high morbidity and mortality. Early recognition and prompt initiation of therapy are of utmost importance. The patients should be aggressively resuscitated and cardiovascular, pulmonary, and renal function supported in an intensive care unit as necessary. Surgical debridement is often necessary and is virtually always needed in the presence of necrotizing fasciitis. Antibiotic therapy should be initiated immediately. Intravenous clindamycin, with or without high-dose penicillin, is the regimen of choice. Even though there is no definitive evidence regarding it effectiveness, the use of IVIG should be considered in severe cases.

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