Group A Streptococcal Sepsis

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The fulminant nature of group A streptococcal sepsis poses impressive challenges from diagnostic and therapeutic perspectives. Most patients are seen early in the course of infection by primary care providers or emergency department physicians and sent home, only to return in 12 to 24 hours with fully developed group A streptococcal sepsis. Early diagnosis is imperative, but the clinician must have a high index of suspicion. Often, the diagnosis is established only after aggressive interventional management has begun. This review emphasizes salient clinical features and provides general recommendations for critical care management.

Introduction

Shock occurring early in the course of any type of group A *Streptococcus* (GAS) infection is defined as the streptococcal toxic shock syndrome (STSS) [1]. The most common infections associated with STSS are listed in Table 1. The incidence of invasive GAS infection is one to five cases per 100,000 population per year [2], and approximately 20% of these cases are STSS. Most cases are primary and sporadic in nature, although epidemics of invasive GAS infections have been described in specific geographic settings. In 1994, an epidemic of related invasive infections occurred in Winnamango, MN [3], with an annualized prevalence of 24 cases per 100,000 population. Five years later in Missoula, MT, the incidence of invasive infections reached 30 cases per 100,000 population (Stevens, Personal observation). Similarly, from November to December 2002, there was an epidemic of invasive GAS infections among Marine Corp recruits at the San Diego Naval Training Base [4]. In addition to community-based infections, invasive GAS infections have been described in hospitals, convalescent centers, and among hospital employees and family contacts of patients with invasive infections [5–7]. Some of these studies have documented the same M type and identical restriction fragment length polymorphism patterns in strains from primary and index cases [5–8]. Although most invasive GAS infections in institutions have been single and isolated cases, outbreaks have occurred [9–12]. In some epidemics, carriage of GAS by health care personnel has been associated with the spread of life-threatening GAS infections among patients in obstetrics/gynecology and ear-nose-throat wards of US hospitals [13].

Thus, since the mid-1980s, reports have documented the presence of these GAS invasive infections and STSS in all areas of the world, all races, both sexes, and all age groups. The current case definition can be found in Table 2. Invasive GAS infections associated with STSS continue to be reported globally, and recent active surveillance data suggest that the incidence may be higher (five cases/100,000 population/year) than in the early 1990s. Alternatively, the latter data could be higher because of better prospective, population-based studies or better recognition by reporting physicians.

The Clinical Course of Streptococcal Sepsis

Streptococcal sepsis is a fulminant process that can progress to shock and organ failure within 48 to 96 hours after acquisition of virulent strains of GAS. Initially, the signs and symptoms of infection are mild and nonspecific. Twenty percent of patients have an influenza-like syndrome characterized by fever, chills, myalgia, nausea, vomiting, and diarrhea [14]. Pain—the most common initial symptom of STSS—is abrupt in onset and severe [14], and may precede tenderness or physical findings. The pain commonly involves an extremity but may mimic peritonitis, pelvic inflammatory disease, pulmonary embolus, pneumonia, acute myocardial infarction, or pericarditis [14]. Fever is the most common sign early in the course of STSS [14]. STSS is frequently misdiagnosed at this stage; the most common erroneous diagnoses are food poisoning, viral gastroenteritis, pulmonary embolus, deep vein thrombophlebitis, pericarditis, pneumonia, muscle strain, simple cellulitis/wound infection, and sunburn with dehydration. Confusion is present in 55% of patients, and in some, coma or combativeness are manifest [14]. Eighty percent of patients develop clinical signs of soft tissue infection such as localized swelling and erythema that progress to necrotizing fasciitis or myositis in 70% of cases, requiring surgical debridement, fasciotomy, or amputation [14]. Of the 20% of cases without soft tissue findings, a variety of clinical presentations were observed, including endophalmitis, myositis, perihepatitis, peritonitis, myocarditis, and overwhelming sepsis [14]. A diffuse, scarlatina-like erythema is uncommon, occurring in only 10% of cases. Late in the course of

Table 1. Types of group A *Streptococcus* infections associated with streptococcal sepsis

Bacteremia
Lymphangitis
Invasive infections of the respiratory tract
Peripharyngeal abscesses
Mediastinitis
Pneumonia
Empyema
Postpartum sepsis
Necrotizing soft tissue infections
Necrotizing fasciitis
Myositis/myonecrosis

infection, patients may have hypothermia as a consequence of profound shock.

Clinical clues for the diagnosis of streptococcal sepsis

Portal of entry of group A Streptococcus is defined: the "outside-in" diagnosis of streptococcal sepsis

A defined portal of entry can be established in 50% of patients with streptococcal sepsis [14,15]. Often, insect bites, splinters, burns, abrasion, and lacerations have been associated with severe soft tissue infection resulting in STSS. Surgical procedures (*eg*, suction lipectomy, hysterectomy, episiotomies, bunionectomy, bone pinning) and virus infections (*eg*, varicella, influenza) have also provided portals of entry [14]. Rarely, patients with symptomatic pharyngitis develop STSS. A defined portal with local inflammation may raise early suspicion of streptococcal infection. Thus, these patients are more likely to exhibit symptoms earlier, and clinicians have an important clue that infection is present. This type of presentation is in stark contrast to the one detailed in the following text.

A portal of entry is not defined: the "inside-out" presentation

A defined portal cannot be defined in the remaining 50% of patients with STSS [14]. In these patients, there is ample evidence that life-threatening GAS infection begins at the exact site of minor nonpenetrating trauma resulting in muscle tear, hematoma, or deep bruise [14]. Severe pain associated with fever may be the only early manifestations in these patients. Diagnosing infection in these patients, especially STSS, often is exceedingly difficult. Many of these patients are seen two or three times in emergency departments for severe pain by the time they finally experience shock and organ failure 48 to 96 hours later.

It is probable that these patients develop a transient asymptomatic bacteremia (perhaps from occult throat colonization) that seeds the site of injury (*eg*, muscle strain). Thus, the infection begins "inside" or in the deep tissues. Although fever and pain are invariably present, cutaneous findings frequently do not develop until later, when shock and organ failure are obvious. Further confusion arises because these patients frequently are prescribed nonsteroidal anti-inflammatory drugs, opioid analgesics, or corticosteroids, which may further confound the diagnosis by masking the symptoms and signs of infection [14].

Table 2. Defining the streptococcal toxic shock syndrome*

Symptoms
Early symptoms are vague
Viral-like prodrome
Severe pain with or without cutaneous evidence of infection
Mental confusion
Signs
Hypotension, systolic
Fever > 38° C
Soft tissue swelling
Tenderness
Respiratory failure, rales, cyanosis, and tachypnea
Laboratory features
Hematologic
Marked left shift
Decline in hematocrit
Thrombocytopenia
Renal
Azotemia (2.5 × normal on admission)
Hematuria
Hypocalcemia
Hypoalbuminemia
Creatinine phosphokinase elevation
Pulmonary abnormalities
Pulmonary infiltrate on chest radiograph
Hypoxia

*An acute, febrile illness that begins with a mild viral-like prodrome and involves minor soft tissue infection that may progress to shock, multiorgan failure, and death.

The rapidity with which shock and multiorgan failure can progress is impressive, and many patients may die 24 to 48 hours after hospitalization [14]. Shock was apparent at the time of admission or within 4 to 8 hours in virtually all patients. Systolic blood pressure became normal 4 to 8 hours after administration of antibiotics and intravenous fluids in only 10% of patients. Renal dysfunction preceded shock in many cases and was apparent on admission in 80% of patients. Renal failure progressed or persisted in all patients for 48 to 72 hours, and several patients required dialysis for 10 to 20 days [14]. In patients who survived, serum creatinine values returned to normal within 4 to 6 weeks. Acute respiratory distress syndrome (ARDS) occurred in 55% of patients and generally developed after the onset of hypotension [14]. Because of its severity, supplemental oxygen, intubation, and mechanical ventilation were necessary in 90% of patients who developed ARDS [14]. Mortality rates have varied from 30% to 70% [14,16,17]; however, morbidity is also high. Thirteen of 20 patients in one study underwent major surgical procedures, which included fasciotomy, surgical debridement, exploratory laparotomy, intraocular aspiration, amputation, or hysterectomy [14].

Laboratory evaluation of patients with streptococcal toxic shock syndrome

The serum creatinine phosphokinase (CPK) level is useful in detecting the presence of deeper soft tissue infections, and when the level is elevated or rising, there is a good correlation with necrotizing fasciitis or myositis [14]. Although the initial laboratory studies may demonstrate only mild leukocytosis, the mean percentage of immature neutrophils (including band forms, metamyelocytes, and myelocytes) is striking, reaching 40% to 50% [14]. The presence of hemoglobinuria and elevated serum creatinine values is evidence of renal involvement. It is important to note that renal impairment precedes hypotension in 40% to 50% of patients [14]. Hypoalbuminemia and hypocalcemia occur early and become profound 24 to 48 hours after admission.

Management of Streptococcal Sepsis

Source control

Figure 1 shows the management of patients with GAS sepsis. Table 1 lists the types of GAS infections associated with streptococcal sepsis and STSS. Identification of the site and appropriate surgical intervention to remove necrotic infected foci is extremely important, and infectious disease specialists and intensive care unit physicians play a huge role in orchestrating a timely approach. Computed tomography and magnetic resonance imaging scans are very helpful in locating the site of primary infection, but because GAS does not form gas or frank abscess, a radiologist's interpretation is often not definitive. A scan demonstrating swelling or edema in the deep tissues in a patient who is toxic may be the best indication of deep-seated infection. Laboratory tests demonstrating marked left shift, elevated creatinine, and high CPK should provide further impetus to encourage surgical evaluation. Although this approach to source control is much easier for infections on an extremity, the stakes get higher and the problem more difficult for GAS infection involving the abdomen, thorax, head, or neck. For example, in postpartum sepsis caused by *Clostridium perfringens*, there is extensive gas in the uterus, and the decision to operate is easy. In postpartum sepsis caused by GAS, the uterus may only appear to be modestly edematous according to computed tomography or magnetic resonance imaging, a condition difficult to distinguish from the normal uterus 2 to 4 days postpartum. Surgical intervention may not be possible in some cases because of shock or anatomic location of the infection. Surgically obtained specimens with Gram stain and culture provide a definitive diagnosis and provide direction for future source control issues.

Antibiotic therapy: importance of the mechanism of action

Streptococcus pyogenes remains exquisitely susceptible to β-lactam antibiotics, and penicillin has excellent efficacy in the treatment of erysipelas, impetigo, and cellulitis and in the prevention of acute rheumatic fever. Clinical failures of penicillin treatment of streptococcal infection occur, and penicillin fails to eradicate bacteria from the pharynx of patients with documented streptococcal pharyngitis in 5% to 20% of cases [18–20]. Aggressive GAS infections (*eg*, necrotizing fasciitis, empyema, burn wound sepsis, subcutaneous gangrene, and myositis) do not respond as well to penicillin and continue to be associated with high mortality and extensive morbidity [14,21–26]. A recent report of 25 cases of streptococcal myositis reported an overall mortality of 85% despite penicillin therapy [21].

Studies in experimental infection have demonstrated that penicillin fails when large numbers of organisms are present [27,28]. In a mouse model of myositis caused by *S. pyogenes*, penicillin was ineffective (0% survival) when treatment was delayed 2 hours or more after initiation of infection [28]. However, mice administered clindamycin had survival rates of 100%, 100%, 80%, and 70% when treatment was delayed 0, 2, 6, and 16.5 hours, respectively [28,29]. Eagle [27] suggested that penicillin failed because of the "physiologic state of the organism." This phenomenon recently has been attributed to inoculum effects, in vitro and in vivo [30,31]. Early in the stages of infection, organisms grow rapidly in vivo but are present in rather small numbers. Higher concentrations of GAS accumulate with delays in treatment [27], and growth begins to slow to a stationary phase.

To investigate the mechanism responsible for loss of penicillin's efficacy in this setting, we compared the penicillin-binding protein (PBP) patterns from membrane proteins of group A streptococci isolated from different stages of growth (*ie*, early and midlog phase vs stationary phase). Binding of radiolabeled penicillin by all PBPs was decreased in stationary cells. PBPs 1 and 4 were undetectable at 36 hours [30]. Thus, the loss of certain PBPs 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 experimental and human cases of severe streptococcal infection.

Factors that contribute to the greater efficacy of clindamycin in patients with severe GAS infections include: clindamycin's efficacy is unaffected by inoculum size or stage of growth [30,32]; clindamycin suppresses bacterial toxin synthesis [33,34]; clindamycin facilitates phagocytosis of *S. pyogenes* by inhibiting M protein synthesis [34]; clindamycin suppresses synthesis of penicillin-binding proteins that, in addition to being targets for penicillin, are enzymes involved in cell wall synthesis and degradation [32]; clindamycin has a longer postantibiotic effect than β-lactams such as penicillin; and we have recently shown that clindamycin suppresses lipopolysaccharide-induced monocyte synthesis of tumor necrosis factor alpha (TNF-α) [35]. Thus, clindamycin's efficacy may be related to its ability to modulate the immune response to GAS infection. In a recent retro-

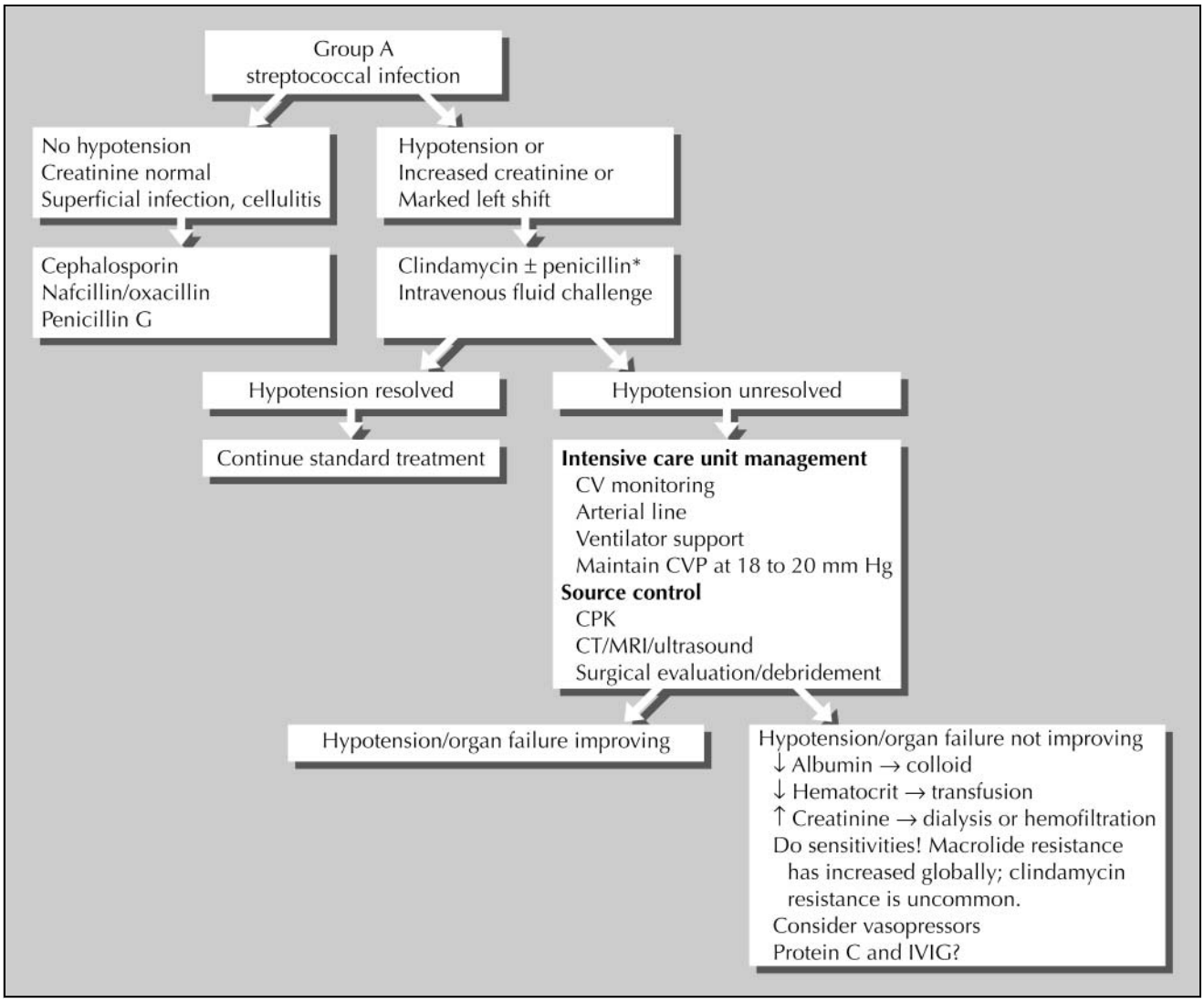

Figure 1. Management of patients with group A streptococcal sepsis. *Asterisk* denotes no additive, synergistic, or antagonistic effects in vitro [27]. CPK—creatinine phosphokinase; CT—computed tomography; CV—cardiovascular; CVP—central venous pressure; IVIG—intravenous immunoglobulin; MRI—magnetic resonance imaging.

spective analysis of STSS cases, Zimbelman *et al.* [36] demonstrated significantly improved survival in patients administered clindamycin compared to those treated with β-lactam antibiotics.

Should a combination of penicillin and clindamycin be administered? There is no evidence to suggest that this combination has additive, synergistic, or antagonistic effects in vitro [37]. The rationale for the empiric use of penicillin and clindamycin is based on the high rate of erythromycin resistance that has been described in Finland, Japan, Sweden, and Pittsburgh, PA. Luckily, most strains of GAS remain sensitive to clindamycin, although erythromycin and clindamycin resistance is common in Italy. When sensitivities are available, there is not much justification for continuing penicillin. Knowledge of the susceptibility patterns of GAS in your region is important. The rationale for choices in antibiotic treatment is summarized in Figure 2.

Fluid resuscitation

If several liters of crystalloid intravenous fluid challenge does not rapidly improve blood pressure (mean arterial pressure > 60 mm Hg) or tissue perfusion, invasive monitoring is indicated. The goal should be to maintain a pulmonary artery occlusion pressure of 12 to 16 mm Hg [38•]. If this goal is reached but hypotension persists, serum albumin concentration and hematocrit should be obtained because profoundly low albumin levels are common and because hemolysins produced by GAS can cause dramatic drops in the circulating red cell mass. Thus, transfusion with packed red blood cells with or without albumin may be useful.

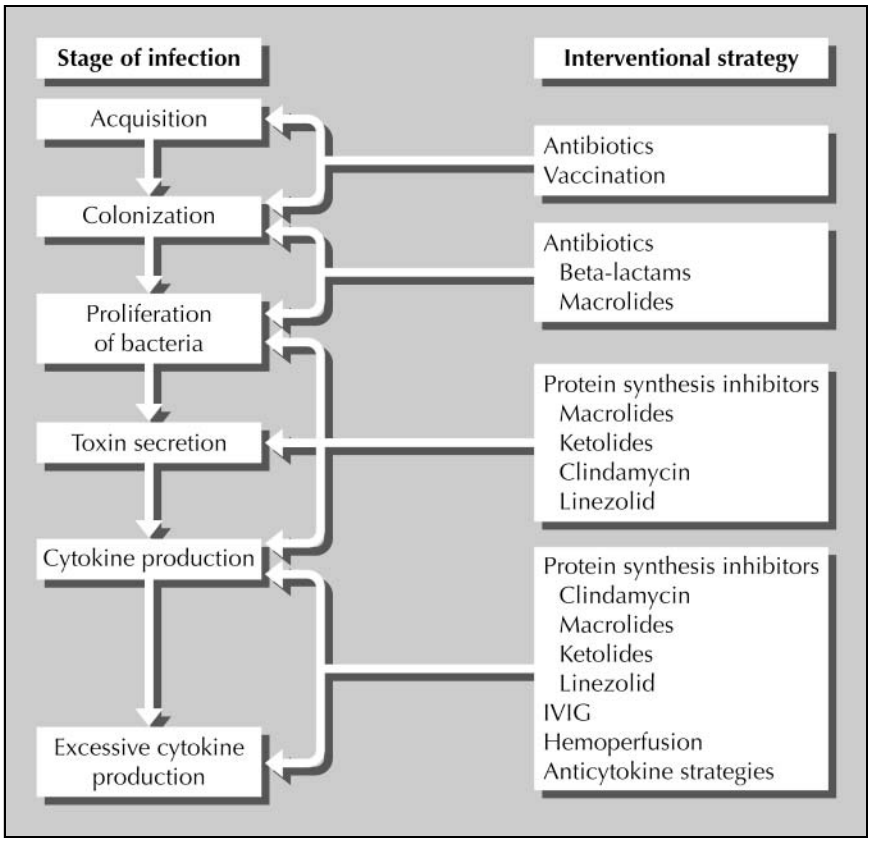

Figure 2. Choices for antibiotic treatment of group A streptococcal sepsis. IVIG–intravenous immunoglobulin.

Management in the intensive care unit: the need for mechanical ventilation, vasopressors, and invasive monitoring of cardiovascular parameters

Monitoring of cardiac outputs is mandatory in patients with persistent hypotension. These patients generally require intubation and mechanical ventilation because of the high incidence of ARDS in STSS [14]. Because of intractable hypotension and diffuse capillary leak, massive amounts of intravenous fluids (10–20 L/day) are often necessary and approximately 10% of patients experience rapid clinical improvement. Pressors such as dopamine are used frequently, although no controlled trials have been performed in STSS. In patients with intractable hypotension, vasoconstrictors such as epinephrine have also been used, but symmetrical gangrene of digits often results (Stevens, Personal observation). Loss of all digits on both hands and feet, or loss of both arms and both legs, has occurred in this setting. It is difficult to determine if symmetrical gangrene is caused in these cases by pressors, coagulopathy, or both. In a small study of five patients with toxic shock syndrome caused by *Staphylococcus aureus*, dobutamine (30 mg/kg body weight initially followed by 15 mg/kg every 6 hours for 24 hours) significantly improved cardiac output and improved mean arterial blood pressure [39].

Strategies to reduce or neutralize circulating toxins

The most important ways to reduce toxin expression are to make an early diagnosis, administer an antibiotic that suppresses toxin production (*See* Antibiotic therapy: importance of the mechanism of action), and maximize source control. Strategies to specifically neutralize circulating toxins are also a desirable therapeutic modality, yet specific preparations analogous to hyperimmunoglobulin for tetanus are not commercially available in the United States or Europe. Intravenous gamma globulin preparations have been shown to have antibodies against some toxins, such as SpeA and SpeB, and to have opsonic antibody against some M types of GAS [40]. However, there is batch-to-batch variation, and standardization is sorely needed. Case reports [41,42] and one nonrandomized clinical trial [40] report that commercial intravenous immunoglobulin (IVIG) is useful for treating STSS. A double-blind study using IVIG in Scandanavia may provide a definitive answer to this question. In contrast, Sriskandan *et al*. [43] have demonstrated that animals immunized with recombinant SpeA have a higher mortality when challenged with an SpeA-producing strain of GAS than animals that are sham-immunized [43]. The reason for this phenomenon is unexplained.

Dialysis and hemoperfusion also may nonspecifically reduce circulating toxins [17]. Renal failure is the most common form of organ failure associated with STSS [14] and dialysis is necessary in more than 50% of patients. A study from Sweden by Stegmayr *et al.* [17] using hemofiltration realized the lowest mortality ever recorded (14%).

A polystyrene superantigen-absorbing device was developed in Japan and has shown to be highly efficacious in absorbing pyrogenic exotoxin A and toxic shock syndrome toxin-1 from plasma, and when used extracorporally in animals, it infused with toxic shock syndrome toxin-1, and lipopolysaccharide improved mortality from 100% to 50% [44•].

The role of tumor necrosis factor alpha neutralization in experimental streptococcal sepsis

Because cytokines are important mediators of shock in patients with STSS, strategies to inhibit or neutralize their effects may provide useful treatments. Recently, a monoclonal antibody against TNF-α showed promising efficacy in a baboon model of STSS [45].

Hyperbaric oxygen

Anecdotal reports suggest that hyperbaric oxygen may be helpful. However, no controlled studies are underway, and it is unclear if this treatment is useful.

Prevention

Prophylaxis and the risk of secondary cases of streptococcal toxic shock syndrome

Clusters of GAS invasive infections have been described in nursing homes [11,12,46], in health care workers [10,47], and among family members [10,46]. In addition, patients may acquire GAS from hospital personnel. This was best demonstrated by Semmelwise in Vienna in 1861 and Holmes in the United States in 1892, although even today such transmission is well-documented [10,47,48]. It has been estimated that the risk of secondary cases of STSS may be approximately 50 to 200 times greater than the risk among the general population [49]. However, because of the low frequency of primary cases (one to five cases/100,000 population/year), the risk of secondary invasive GAS infection is still very low (*ie*, 50 to 1000 cases/100,000 population/year). GAS is a highly infectious agent, and transmission of GAS from person to person is very common. This is exemplified by studies of pharyngitis and rheumatic fever conducted over several centuries showing that GAS is quickly and efficiently transmitted from index cases to susceptible individuals. Depending on the era, the strain of GAS, and the geographic region, such transmission has resulted in many clinical conditions, including asymptomatic colonization, pharyngitis, scarlet fever, rheumatic fever, or more recently, invasive GAS infections. Recently, 25 hospital personnel in San Francisco who cared for one patient with streptococcal sepsis caused by an M-1 strain of GAS became colonized with an identical strain within 5 days of the patient's admission to the hospital. Although some patients developed mild pharyngitis, none developed invasive GAS infection, and most were merely colonized.

Epidemiologic investigation of clusters of cases is important, and treatment of contacts may be necessary despite the low risk of secondary invasive infection [50]. Primary care physicians must consider the extent of exposure, the type of exposure, and the risk factors for the contact. For example, a contact of a patient with STSS with risk factors such as chicken pox, leukemia, burns, recent childbirth, recent surgery, or any open skin lesion should receive prophylaxis with penicillin, erythromycin, or clindamycin [50].

Vaccines

The main goal of vaccine development is to prevent all GAS infections, including pharyngitis [51]. For the past 30 years, research has centered on M protein as an immunogen. However, problems have emerged. Antibodies directed against the conserved region of M protein can crossreact with cardiac tissue and potentially cause rheumatic fever among vaccinees. This observation has stimulated M protein research into three separate areas. One strategy uses the hypervariable region of the M protein molecule, which obviates the induction of crossreactive antiheart antibodies. The drawback is that there are more than 150 different hypervariable regions because this is the primary immunologic determinant for M type. Immunity is related to the induction of opsonophagocytic antibody. A cassette of peptides representing many different hypervariable regions is being evaluated in humans for production of opsonic antibody. Such a vaccine may require changing the peptides in the cassette to reflect temporal changes in prevalent M types.

The second strategy is to express the conserved region of M protein in *Streptococcus gordonii*. Oral inoculation will elicit production of secretory immunoglobulin A antibody but not systemic production of immunoglobulin G antibody. Thus, the proposed vaccine would provide broad spectrum protection against GAS colonization in the pharynx without stimulating crossreactive immunoglobulin G antiheart antibodies.

A third strategy uses a conformationally constrained 12-amino acid peptide from the C repeat region of M protein conjugated with diphtheria toxin. This toxoid induced production of opsonic antibody against several different M types, and actively immunized animals were protected against challenge with an M-6 strain of GAS [52•].

Another surface component, the fibronectin binding protein (SfbI), has been used to actively immunize mice and provides 80% and 90% protection against homologous and heterologous intranasal challenge with viable GAS, respectively [53]. Other strategies that use surface components of GAS as immunogens are in earlier stages of development and include the C5A peptidase and the group A carbohydrate conjugated to carrier protein.

Extracellular toxins such as SpeA and SpeB have been proposed as targets, but it is doubtful that these strategies

would provide protection broad enough for the population because not all strains produce these toxins. Thus, the goal is to protect against STSS and not pharyngitis. Because of the low incidence of STSS, this may not be economically feasible.

Passive immunization

Before the discovery of penicillin, a horse serum vaccine was prepared against culture supernatants from GAS strains isolated from patients with scarlet fever. Scarlet fever could be prevented and, if established, attenuated. Lederle Pharmaceuticals (Madison, NJ) ceased development because of the availability of penicillin and the inevitable adverse reaction of serum sickness. The technology to develop high-titer humanized monoclonal antibodies that neutralize a variety of streptococcal virulence factors is ready and awaits production.

Conclusions

There has been a worldwide increase in invasive GAS infections resulting in sepsis, necrotizing fasciitis, STSS, and bacteremia. These aggressive infections are associated with the early onset of shock and organ failure. Overproduction of cytokines and the direct effect of multiple streptococcal exotoxins and somatic components combine to cause dramatic cardiovascular events resulting in mortalities of 30% to 70% and extensive morbidity.

Earlier suspicion and recognition will be necessary if we are to reduce mortality and the need for disfiguring surgeries. Unfortunately, the latter remains a major factor in treatment. When patients manifest GAS sepsis, invasive cardiovascular monitoring, aggressive fluid resuscitation, ventilator support, dialysis, and surgical debridement usually are required. Administration of antibiotics that suppress toxin production (*eg*, clindamycin) has reduced mortality in experimental and human studies. Hemoperfusion, toxin-removing devices, and IVIG research is promising, but definitive clinical studies are needed.

Acknowledgments

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