Toxic Shock and Shock-Like Syndrome: The Constant Threat

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Abstract

We present a case of concomitant Streptococcus pyogenes (GAS; Group A Streptococcus) and Methicillin-Resistant Staphylococcus Aureus (MRSA) Toxic Shock Syndrome (TSS) who responded to conservative therapy with adjunctive Intravenous Immunoglobulin (IVIG) and Hyperbaric Oxygen (HBO) therapy. TSS is a devastating illness with a high mortality rate; therefore, we stress the importance of early multidisciplinary approaches including early administration of IVIGT and HBO.

Introduction

Toxic Shock Syndrome (TSS) or Toxic Shock-Like Syndrome (TSLS) is an acute, multisystem, toxin-mediated illness, typically resulting in shock and Multiorgan Failure (MOF) [1-3]. It is a complication of the invasive or non-invasive disease. Streptococcal TSLS occurs most frequently in the setting of infection due to Streptococcus pyogenes (GAS; Group A Streptococcus). Group B, C, and Streptococci have also been associated with TSLS. Staphylococcal, streptococcal pyrogenic exotoxins and host immune response play a central role in the pathogenesis of this syndrome [4]. These pyrogenic toxins can activate the immune system, bypassing the usual antigen-mediated immune response sequence, resulting in the release of large quantities of inflammatory cytokines [interleukin-1 (IL-1), IL-2, Tumor Necrosis Factor (TNF)-alpha, TNF-beta, and Interferon (IFN)-gamma]. These superantigens trigger massive nonconventional T-cell activation, dependent only on the composition of the variable part of the β-chain of the class II Major Histocompatibility Complex (MHC) of the T-cell receptor, with excessive cytokines from both T-cells and Antigen-Presenting Cells (APC) that cause tissue damage, disseminated intravascular disease, and multi-organ dysfunction. The toxins have thus become referred to as superantigens [5-9]. Staphylococcal TSS is currently a nonmenstrual-associated illness. However, tampon use remains a risk factor [10-12]. The decline in cases of menstrual TSS is partly related to the withdrawal of highly absorbent tampons and polyacrylate rayon-containing products from the market. Nonmenstrual TSS has been reported following surgical wound, skin and soft tissue, musculoskeletal, respiratory, endovascular, and gastrointestinal infections frequently in otherwise healthy individuals. The median interval between surgery or menstruation and TSS is two to three days [13]. However, the onset of TSS has been reported as late as 65 days postoperatively [14]. Streptococcal strains can cause a broad spectrum of clinical manifestations. They can cause respiratory, genitourinary, joint, bone, abdominal, central nervous system, bloodstream, and endovascular infections. Streptococcal-TSLS may occur with infection at any site but most often occurs in association with infection of the skin and soft tissues [15,16]. No portal of entry is recognized in up to 45% of patients with GAS-TSS [1]. It can be the result of direct muscle injury or blunt trauma, in the absence of other sources [1]. Streptococcus agalactiae, commonly referred as Group B Streptococcus (GBS), is a cause of fulminate illness like Streptococcus pyogenes-TSLS. However, skin and soft tissue infections are detected in all patients with GBS-TSLS [16]. TSLS develops in up to one-third of patients with the invasive GAS disease [1,17]. Invasive GAS may occur at any age, but mainly encountered in immunocompetent adults >50 years of age [18-20]. The rate of GAS-STLS among patients with necrotizing fasciitis is approximately 50% [1,20,21]. Invasive GBS is emerging as a cause of infection in nonpregnant adults, 65 years or older, with underlying medical conditions [16]. Malignancy, diabetes and splenectomy are the most likely underlying diseases for GBS-TSLS [16].

Case Presentation

A 68-year-old white man was admitted to Pikeville Medical Center in May 2019 with acute severe
left leg pain, erythema and swelling for 24 h with confusion. The left leg was intensely tender with diffuse erythodema and purplish skin discoloration. The patient had central abdominal pain and nausea. The patient’s condition deteriorated to Multiorgan Failure (MOF) with septic shock and respiratory failure that required intubation and mechanical ventilation, intravenous fluids, vaspressors, and broad-spectrum antimicrobial therapy (vancomycin linezolid, and meropenem). Laboratory values were white blood cell count (WBC) =3,700 cells/µL (29% bands), platelets =114,000 cells/µL, creatinine =1.8 mg/dL, total bilirubin levels =2.3 mg/dL, and procalcitonin of 60.20 μg/L. Cytokine kinase levels were normal suggesting no muscle damage. Chest X-ray showed diffuse infiltrates, and Computed Tomography (CT) imaging of the left lower extremity revealed soft tissue swelling, but no evidence of fluid collection or necrotizing fasciitis. Two consecutive sets of blood (each set consisting of aerobic and anaerobic bottles) were drawn for culture on admission before the initiation of antibiotic therapy. The growth of GAS and Methicillin- Resistant Staphylococcus aureus (MRSA) was seen in both the aerobic and anaerobic bottles in less than 24 h. The GAS isolated strain was susceptible to erythromycin, daptomycin, levofloxacin, linezolid, penicillin, vancomycin, and clindamycin. The susceptibility profile was not suggestive of Macrolide-Lincosamide-Streptogramin B (MLSB) resistance. The susceptibility profile was not suggestive of Macrolide-Lincosamide-Streptogramin B (MLSB) resistance. The susceptibility profile was not suggestive of Macrolide-Lincosamide-Streptogramin B (MLSB) resistance. The susceptibility profile was not suggestive of Macrolide-Lincosamide-Streptogramin B (MLSB) resistance.

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Hypotension studies suggest that enterotoxin A may be a cofactor of TSST-1. Compared with 10% of TSST-1-positive strains [32]. Several animal TSS, 50% of individuals infected with a TSST-1-negative strain died, and by 40% to 60% of strains associated with non-menstrual cases between menstrual and non-menstrual cases. TSST-1 is produced (MSSA) and Methicillin-Resistant Toxin production (MHC) class II haplotypes may influence host susceptibility to the it has been suggested that Major Histocompatibility Complex leads to progression from invasive GAS infection to TSS. In addition, illness (e.g., influenza, varicella) [1]. Unawareness of the condition and streptococcal infections from the sites of injection [24-27]. Other use appears to contribute to the expansion of invasive staphylococcal [14]. As the opioid crisis is sweeping the country, intravenous drug cytokine release and inhibit neutrophil function [26]. Furthermore, TSLS in the setting of traumatic injury [1]. It may also serve as an Anti-Inflammatory Drugs (NSAIDs) may delay the diagnosis of 1 and 2) [2,23]. TSS/TSLS should be suspected in patients presenting with shock in the absence of a clear etiology. The use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) may delay the diagnosis of TSLS in the setting of traumatic injury [1]. It may also serve as an independent predisposing factor for necrotizing soft tissue infections and myonecrosis at the site of injury [1]. NSAIDs may augment cytokine release and inhibit neutrophil function [26]. Furthermore, Cyclo-Oxygenase (COX) inhibitors, particularly the nonselective, reduce the efficacy of antibiotics including penicillin or clindamycin [14]. As the opioid crisis is sweeping the country, intravenous drug use appears to contribute to the expansion of invasive staphylococcal and streptococcal infections from the sites of injection [24-27]. Other risk factors are immunosuppressive status (e.g., HIV, malignancy, steroid use), homelessness, recent surgery, obesity, burns, peripheral vascular disease, diabetes, cardiac disease, postpartum state, viral illness (e.g., influenza, varicella) [1]. Unawareness of the condition leads to progression from invasive GAS infection to TSS. In addition, it has been suggested that Major Histocompatibility Complex (MHC) class II haplotypes may influence host susceptibility to the development of TSS [28].

**Toxin production**

Staphylococcal strains, Methicillin-Susceptible S. Aureus (MSSA) and Methicillin-Resistant S. Aureus (MRSA), can produce TSS toxin-1 (TSST-1) and other exotoxins (enterotoxins A, B, C, D, E, and H) [29,30]. There is a discrepancy in TSST-1 production between menstrual and non-menstrual cases. TSST-1 is produced by 90% to 100% of S. aureus strains associated with menstrual-TSS and by 40% to 60% of strains associated with non-menstrual cases [31]. TSST caused by non-TSST-1-producing strains carries a poorer prognosis. In one study of 32 S. aureus isolates from non-menstrual-TSS, 50% of individuals infected with a TSST-1-negative strain died, compared with 10% of TSST-1-positive strains [32]. Several animal studies suggest that enterotoxin A may be a cofactor of TSST-1. TSST-1-producing S. aureus do not provoke a purulent response, which in part may be explained by TNF-induced PMN inhibition [33]. In addition, data suggest that TSST-1 and enterotoxin B block production of other S. aureus exoproteins, which may explain the absence of purulence in S. aureus infections associated with TSS [34]. All GAS strains isolated from invasive infections produce a toxin called NADase (Nga) [35]. About half of these strains are non-typeable and the remaining half are caused by a limited number of GAS M types (1, 3, 4, 6, and 28) [1,36]. Streptococcus pyogenes bacteria (GAS) are known for their production of pyrogenic toxins, notably streptococcal pyrogenic exotoxins (SPEs). Pyrogenic toxins are also recognized in group C and group G streptococci, and in many of these strains their pyrogenic toxins are related to those from group A streptococci [37]. Most recently, we demonstrated that GBS produces novel uncharacterized pyrogenic toxin(s) (different from the known Streptococcus pyogenes SPEs), explaining the ability of GBS to cause TSLS. The GBS pyrogenic toxins do not cross-react immunologically with known SPEs, likely because the protein amino acid sequences differ significantly. Horizontal transfer of DNA-encoding pyrogenic toxins can occur between streptococcal strains. These SPEs can be transferred by bacteriophages contributing to an increased incidence of severe invasive streptococcal diseases [38,39]. Furthermore, GBS can produce menstrual-related TSS in women with vaginal carriage of certain GBS strains. This phenomenon might be attributed to the ability of GBS pyrogenic toxins to cross vaginal mucosa [40].

**Treatment**

Treatment of streptococcal and staphylococcal-induced TSS/ TSLS requires a multidisciplinary approach with immediate supportive measures for septic shock and its complications, appropriate antimicrobial regimen, administration of intravenous immune globulin, and surgical intervention (if warranted). Such cases frequently require coordinated care from a team including individuals with clinical expertise in critical care, surgery, and infectious disease. Meticulous mucocutaneous examination is warranted. In women, vaginal examination should be performed, and any tampon or foreign body removed. As pyrogenic toxins are pivotal in TSS and TSLS, the addition of bacterial synthesis inhibitor to beta-lactams or
vancomycin is important to minimize the severity and mortality of this devastating disease. In a retrospective study including 84 patients with invasive GAS infection, use of clindamycin was associated with lower 30-day mortality (15% vs. 39% among those who did not receive clindamycin) [41]. Subsequently, beta-lactam or vancomycin monotherapy is not recommended in the setting of toxin-producing streptococcal or staphylococcal infections. Unlike beta-lactams, protein synthesis inhibitors enhance the phagocytosis of streptococci and *Staphylococcus* species and do not exhibit reduced efficacy during the stationary phase of growth. Their efficacy is not diminished due to bacterial load [26,27,42-45]. Of additional concern is the potential for increasing rates of resistance expressed by *S. pyogenes* as well as other streptococcal and staphylococcal species. In the United States, clindamycin resistance occurred in 15% of the GAS isolates overall between 2011 and 2015 [48]. Due to the importance of protein synthesis inhibition, it may be reasonable to consider oxazolidinones (linezolid and tedizolid) as initial therapy until susceptibility to clindamycin is confirmed (Figure 3). Targeted antibiotic therapy should be guided by antibiotic susceptibility testing. The optimal duration of antibiotic therapy in streptococcal TSS/TSLS is unknown but ideally at least 14 days especially in the setting of bacteremia. However, the length of antibiotic therapy should be tailored to clinical response and the adequacy of surgical debridement. Therapy is usually continued for 14 days from the last positive culture obtained during surgical debridement. Adjunctive Intravenous Immune Globulin (IVIG) is associated with improved outcome in streptococcal TSLS. Dosing (for adults and children) consists of 1 g/kg on day 1, followed by 0.5 g/kg on days 2 and 3. In a 2018 meta-analysis that included five studies of patients with streptococcal TSLS treated with clindamycin (one randomized and four nonrandomized), the use of IVIG was associated with two-fold-30-day reduction in mortality (33.7% vs. 15.7%) [49]. Adjunctive IVIGT can boost antibody levels via passive immunity, opsonization for phagocytic killing, neutralization of toxins (SPES A, B and C; mitogenic factor MF), inhibition of T-cell proliferation, and inhibition of inflammatory cytokines such as TNF-alpha and interleukin 6. Differences between IVIG neutralizing activities have been observed in different countries. In one study, Vigam-S (obtained from plasma collected from donors in the United States) had consistently high inhibition against all GAS superantigens, while European IVIG preparations had the lowest activity [50]. There is lack of substantive controlled trials to suggest a benefit with IVIG in staphylococcal TSS. Data are limited to case reports and retrospective reviews. However, use of IVIG may be considered in patients with severe staphylococcal TSS who have diminished antibody production to toxin or are unresponsive to other therapeutic measures [51-53]. The utility of hyperbaric oxygen therapy (HBOT) in the treatment of Necrotizing Soft Tissue Infections (NSTIs) and TSS/TSLS has not been proved. The use of HBOT has been reported in a small number of patients with streptococcal TSLS [54]. However, HBOT is not available universally at all medical centers, and there is often considerable delay associated with its initiation [55].

### Table 2: Clinical and laboratory criteria for the diagnosis of staphylococcal toxic shock syndrome [23].

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<th>Clinical Criteria of streptococcal toxic shock syndrome</th>
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<tr>
<td>• Fever: temperature greater than or equal to 102.0°F (greater than or equal to 38.9°C)</td>
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<td>• Rash: diffuse macular erythema (sunburn) involving palms and soles</td>
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<td>• Desquamation: 1-2 weeks after onset of rash</td>
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<td>• Hypotension: systolic blood pressure less than or equal to 90 mmHg for adults or less than fifth percentile for age by age for children aged less than 16 years</td>
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<td>• Multisystem involvement (three or more of the following organ systems):</td>
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<td>o Gastrointestinal: vomiting or diarrhea at onset of illness</td>
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<td>o Muscular: severe myalgia or creatine phosphokinase level at least twice the upper limit of normal</td>
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<td>o Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia</td>
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<td>o Renal: blood urea nitrogen or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria (greater than or equal to 5 leukocytes per high-power field) in the absence of urinary tract infection</td>
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<td>o Hepatic: total bilirubin, alanine aminotransferase enzyme, or aspartate aminotransferase enzyme levels at least twice the upper limit of normal for laboratory</td>
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<tr>
<td>o Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent. Confusion can be presenting symptom of TSS</td>
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### Laboratory Criteria

- **Negative results on the following tests, if obtained:**
  - o Blood or cerebrospinal fluid cultures blood culture may be positive for *Staphylococcus aureus* |
  - o Negative serologies for Rocky Mountain spotted fever, leptospirosis, or measles |

The CDC criteria were established for epidemiologic surveillance and should not be used to exclude a case that is highly suspicious for TSS, even if all criteria are not met.  
*For patients with suspected TSS, blood cultures (at least two sets) should be collected (ideally prior to antibiotic administration). In addition, cultures should be collected from clinically relevant mucocutaneous sites (including the vaginal canal, wound sites, nares, and surgical debridement materials). Any foreign material in the vaginal canal (such as a tampon, contraceptive sponge, or intrauterine device) should be removed if present. Gram stain of involved tissues demonstrating gram-positive cocci in clusters can provide an early diagnostic clue in many cases. Most laboratory tests normalize 7 to 10 days after onset of illness. Detection of *S. aureus* in cultures is not required for the diagnosis of staphylococcal TSS. *Staphylococcus aureus* is recovered from blood cultures in approximately 5% of cases; it is recovered from wound or mucosal sites in 80 to 90% of cases.  

**Case classification:** Diagnosis Staphylococcal TSS should be suspected in otherwise healthy individuals with rapid onset of fever, rash, hypotension, and multorgan system involvement; relevant risk factors include recent tampon use, recent surgery, and recent infection (involving skin or soft tissue or another site).  

**Probable case:** A case which meets the laboratory criteria and in which four of the five clinical criteria described above are present.  

**Confirmed case:** A case which meets the laboratory criteria and in which all five of the clinical criteria described above are present, including desquamation, unless the patient dies before desquamation occurs.
Figure 3: TSS and TSLS: Modified Empiric antibiotic therapy

Clindamycin: (adults: 900 mg orally every eight hours; children: 10 to 13 mg/kg/dose every eight hours [not to exceed adult maximum]).
Oxacillin/Sulbactam (adults: 500 to 1000 mg IV every 8 hours; children: 40 to 60 mg/kg IV every 8 hours). [Note: not to exceed adult dose].
Ceftriaxone: (adults: 2000 mg IV every 24 hours; children: 25 to 50 mg/kg IV every 24 hours).
Linezolid: (adults: 600 mg IV every 12 hours; children: 10 mg/kg IV every 8 hours).
A combination drug containing a penicillin plus beta-lactamase inhibitor (adults: piperacillin/tazobactam, 4.5 g IV every 6 hours; children: 80 mg/kg IV every 8 hours). [Note: not to exceed adult dose].
Vancomycin: (adults: 20 to 25 g IV every 8 hours; children: 15 to 20 mg/kg IV every 8 hours).
Oxacillin or Nafcillin: (adults: 2 to 4 g IV every 6 hours; children: 50 to 100 mg/kg IV every 8 hours).
Ceftriaxone: (1-2 g IV every 12 hours) may be an acceptable alternative for streptococcal TSLS.

Patients with known hypersensitivity to penicillin or cephalosporins may be treated with a fluoroquinolone or a monobactam (aztreonam) plus metronidazole.

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centers, receiving therapy was associated with a significant survival benefit in severely ill patients with NSTIs (mortality of 4% vs. 23%; P<0.01). Use of anti-TNF antibody has been only studied in an animal model of streptococcal TSS with promising results [56].

 Mortality and prognosis

Death associated with TSS usually occurs within the first few days of hospitalization but may occur as late as two weeks after admission. Fatalities have been attributed to refractory cardiac arrhythmias, cardiomyopathy, irreversible respiratory failure, and, rarely, bleeding caused by coagulation defects [57,58]. Mortality due to streptococcal TSS is substantially higher than mortality due to staphylococcal TSS. It is 1.8% for staphylococcal menstrual TSS and 5% for staphylococcal non-menstrual TSS [59]. However, case fatality ranges from 30% to 79% for streptococcal TSS [60-63]. Streptococcal TSS is frequently associated with deep soft tissue infection, so source control can be difficult. In addition, streptococcal TSS occurs more frequently among patients with underlying medical conditions than staphylococcal TSS.

 Conclusion

Implementation of early, well-coordinated, and multidisciplinary approaches involving surgeons, infectious disease and critical care specialists is required to prevent illness progression and death due to the aggressive TSS and TSLS. Staphylococci and Streptococci produce pyrogenic toxins leading to TSS and TSLS. For that reason, empiric antimicrobial therapy should include a protein synthesis inhibitor, preferably linezolid or tedizolid, while awaiting the results of susceptibility testing. Rapid initiation of adjunctive IVIGT promotes neutralization of superantigens and should not be delayed in TSS/TSLS. Use of HBOC in conjunction with current practices for the treatment of TSS/TSLS can be both a cost-effective and life-saving therapy if started appropriately and in a timely fashion. Controlled trials and the efficacy of this multidisciplinary approach should be more investigated.

 References


