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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 HBOT.

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

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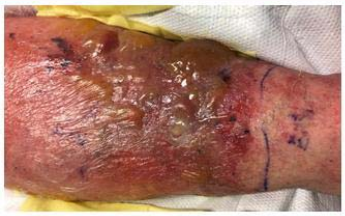
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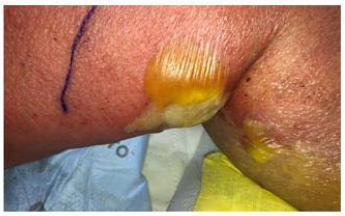
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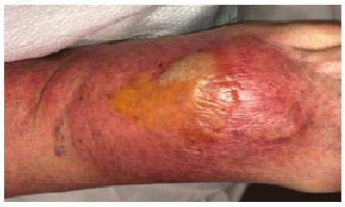
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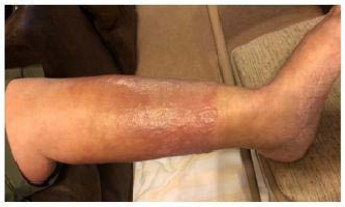
Figure 2

Figure 1: Extensive skin and soft tissue involvement with skin discoloration and bullous lesions affecting the left lower extremity.
Figure 2: Remarkable decrease in the intensity of redness and resolution of bullous lesions without surgical interventions after 4 weeks.

left leg pain, erythema and swelling for 24 h with confusion. The left leg was intensely tender with diffuse erythroderma 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, vasopressors, 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 mg/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 *Streptococcus pyogenes* (GAS) 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 patient was successfully extubated and weaned off pressors on day 3. Antimicrobial therapy was changed to the combination of linezolid 600 mg IV every 12 h and ceftriaxone 2 grams IV daily. The patient developed hives secondary to linezolid and subsequently switched to clindamycin 900 mg IV every 8 h. Throat, urine, respiratory and rectal cultures were negative for GAS and MRSA. The patient was transferred to the floor on day 5 of hospitalization. The leukocytosis, thrombocytopenia, acute kidney injury, coagulopathy, and liver dysfunction had completely resolved on day 7. However, by that point, he had developed multiple areas of extensive skin erythema and non-hemorrhagic bullae over his entire left lower extremities (Figure 1). Aerobic and anaerobic cultures of specimens that obtained in a sterile fashion from aspiration of the bullous lesions demonstrated heavy growth of GAS and Methicillin- Resistant *Staphylococcus aureus* (MRSA). The MRSA isolated strain was susceptible to erythromycin, daptomycin, linezolid, trimethoprim/sulfamethoxazole, rifampin, tetracycline, vancomycin (minimum inhibitory concentration of 1 μg/ml), and clindamycin. The susceptibility profile was not suggestive of Macrolides, Lincosamides, and Streptogramin B (MLS_B) resistance. To boost passive immunity and expedite the clearance of the skin and soft tissue infection, adjunctive intravenous immunoglobulin therapy (IVIGT) (1 g/kg on day 1, followed by 0.5 g/kg on days 2 and 3) and Hyperbaric Oxygen Therapy (HBOT) for 10 days were given. He did not require surgical intervention. On day 14 the left lower extremity erythema had decreased by 50% and antibiotic therapy was switched to oral clindamycin and doxycycline for additional 2 weeks. Generalized erythematous macular rash or desquamation did not occur. After 4 weeks of antimicrobial therapy, the outcome was favorable, and the patient was discharged home with almost complete healing of the left lower extremity skin and soft tissue infection (Figure 2).

Clinical manifestations

The symptoms and signs of TSS/TSLS develop rapidly within 48 h. Clinical manifestations of staphylococcal TSS include fever/chills, hypotension, dermatologic manifestations (diffuse macular erythroderma, followed by desquamation one to two weeks later), and multiorgan system involvement. The disease is more devastating in the setting of streptococcal infection. Altered mental status occurs in about half of cases of GAS-TSLS [22-24]. An influenza-like syndrome characterized by fever, chills, myalgia, nausea, vomiting, and diarrhea occurs in about 20% of patients [25]. Signs of toxicity and a rapidly progressive clinical course are characteristic, and the case fatality rate may exceed 50%. Most commonly, patients with GAS-TSLS present with pain at the site of minor trauma (such as a bruise, strained muscle, or sprained ankle). The discomfort typically precedes physical findings of infection. Subsequently, clinical manifestations include localized swelling and erythema, followed by ecchymoses and sloughing of skin. Deep infection (such as necrotizing fasciitis or myonecrosis) may develop within 24 h to 72 h. Clinical signs of skin soft tissue infections consistent with localized swelling, erythema, and tenderness were observed in all patients with GBS-TSLS, while ecchymoses, bulla formation, and sloughing of the skin were observed in 25% of the cases. TSLS due to GBS initially presents as soft tissue pain in an extremity or the back, an influenza-like syndrome characterized by fever, chills, myalgia, nausea, vomiting, and diarrhea and a change in the mental status.

Diagnosis

The diagnosis of staphylococcal and streptococcal TSS is established based on the clinical criteria and culture findings (Table

Table 1: Clinical and Laboratory Criteria for the Diagnosis of Streptococcal Toxic Shock Syndrome (STSS) [1-3].

A-Clinical Criteria of *streptococcal* toxic shock syndrome*
• Hypotension defined by a systolic blood pressure less than or equal to 90 mm Hg for adults or less than the fifth % ile by age for children aged less than 16 years.
• Multi-organ involvement characterized by two or more of the following:
o Renal impairment: Creatinine greater than or equal to 2 mg/dL (greater than or equal to 177 µmol/L) for adults or greater than or equal to twice the upper limit of normal for age. In patients with preexisting renal disease, a greater than twofold elevation over the baseline level.
o Coagulopathy: Platelets less than or equal to 100,000/mm^3 (less than or equal to 100 × 10^6/L) or disseminated intravascular coagulation, defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products.
o Liver involvement: Alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels greater than or equal to 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.
o 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.
o A generalized erythematous macular rash that may desquamate^.
B-Laboratory Criteria$^{\Psi}$
o Isolation of group A *Streptococcus* from a normally sterile site (e.g., blood or cerebrospinal fluid or, less commonly, joint, pleural, or pericardial fluid).
o Isolation of group A *Streptococcus* from a non-sterile site (e.g., throat, vagina, skin lesion).

*Clinical manifestations do not need to be detected within the first 48 h of hospitalization or illness, as specified in the 1996 case definition. The specification of the 48-h time constraint was for purposes of assessing whether the case was considered nosocomial, not whether it was a case or not.

^A diffuse, scarlatina-like erythema occurs in about 10% of cases.

$^{\Psi}$For patients with suspected invasive *streptococcal* infection, blood cultures (at least two sets) should be obtained (ideally prior to antibiotic administration). In addition, cultures should be collected from clinically relevant sites (such as wounds, debrided surgical materials, endometrial specimens, throat exudates, sputum and pleural specimens). Recovery of GAS from blood cultures usually takes 8 h to 24 h. Gram stain of involved tissues demonstrating *gram-positive cocci* in pairs and chains can provide an early diagnostic clue in many cases.

Case classification:

Probable case: 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 non-sterile site.

Confirmed case: A case that meets the clinical case definition and with isolation of group A *Streptococcus* from a normally sterile site.

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]. TSS 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

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

A-Clinical Criteria of streptococcal toxic shock syndrome
• Fever: temperature greater than or equal to 102.0°F (greater than or equal to 38.9°C)
• Rash: diffuse macular erythroderma (sunburn) involving palms and soles
• Desquamation: 1-2 weeks after onset of rash
• Hypotension: systolic blood pressure less than or equal to 90 mmHg for adults or less than fifth % ile by age for children aged less than 16 years
• Multisystem involvement (three or more of the following organ systems):
o Gastrointestinal: vomiting or diarrhea at onset of illness
o Muscular: severe myalgia or creatine phosphokinase level at least twice the upper limit of normal
o Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
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
o Hepatic: total bilirubin, alanine aminotransferase enzyme, or aspartate aminotransferase enzyme levels at least twice the upper limit of normal for laboratory
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
B-Laboratory Criteria$^{\Psi}$
• 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 be not be used to exclude a case that is highly suspicious for TSS, even if all criteria are not met.

$^{\Psi}$For patients with suspected TSS, blood cultures (at least two sets) should be obtained (ideally prior to antibiotic administration). In addition, cultures should be collected from clinically relevant muco-cutaneous 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 multiorgan 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.

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 *staphylococci* 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 the loss of efficacy of erythromycin and clindamycin due to increasing rates of resistance expressed by *Streptococci* and *Staphylococci* [46,47]. The constitutive or inducible Macrolide-Lincosamide-Streptogramin B (MLSB) phenotype is mediated by the erythromycin ribosomal methylation (erm) gene and has been previously identified in certain strains of *Streptococcus 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% to 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 IVIGT 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]. At HBO-capable

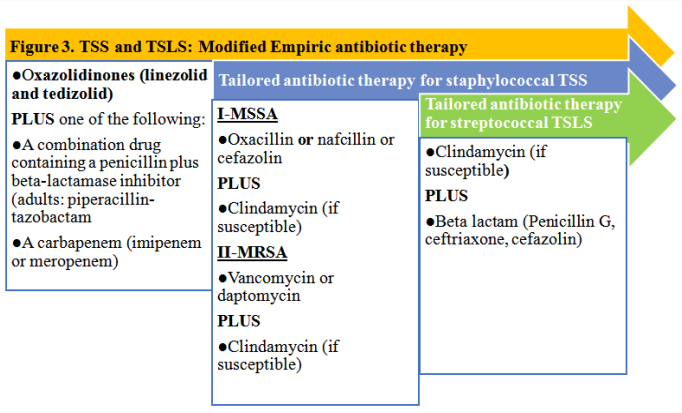

Figure 3: TSS and TSLS: Modified Empiric antibiotic therapy.
Clindamycin: (adults: 900 mg orally every eight hours; children: 10 to 13 mg/kg/dose every eight hours [not to exceed adult maximum]).
Oxazolidinones: Linezolid (adults: 600 mg IV every 12 hours; children: 10 mg/kg per day IV every eight hours; children >12 years old: 10 mg/kg every 12 hours [not to exceed adult dose]) or tedizolid (adults: 200 mg IV daily; <18 years: Safety and efficacy not established).
Carbapenems (adults: imipenem 500 mg IV every six hours or meropenem 1 g IV every eight hours; children: imipenem 15 to 25 mg/kg/dose every 6 hours [maximum 4 g per day] or meropenem 25 mg/kg/dose every 8 hours [maximum 1 g per dose]).
Combination drug containing a penicillin plus beta-lactamase inhibitor (adults: piperacillin-tazobactam 4.5 g every 6 hours; children: 80 mg/kg piperacillin/kg/dose IV every 6 hours or 100 mg/kg piperacillin/kg/dose IV every 8 hours [maximum 16 g piperacillin per day]).
Vancomycin (adults: 15 to 20 mg/kg/dose every 8 to 12 hours, not to exceed 2 g per dose; children: 60 mg/kg per day IV in four divided doses) or daptomycin (adults: 6 mg/kg IV daily) (until bacteremia is excluded).
Daptomycin (adults: 4 to 6 mg/kg/dose every 24 hours; children <17 years: 5-10 mg/kg).
Oxacillin or nafcillin (adults: 2 g IV every four hours; children: 150 to 200 mg/kg per 24 hours IV in four divided doses).
Cefazolin (2 g IV every eight hours) or **ceftriaxone** (1-2 grams IV daily) is 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.

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 HBOT 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

1. Stevens DL, Tanner MH, Winship J, Swarts R, Ries KM, Schlievert PM, et al. Severe group A streptococcal infections associated with a toxic shock-like syndrome and scarlet fever toxin A. N Engl J Med. 1989;321(1):1-7.
2. Defining the group A streptococcal toxic shock syndrome. Rationale and consensus definition. The Working Group on Severe Streptococcal Infections. JAMA. 1993;269(3):390.
3. Karakousis PC, Page KR, Varello MA, Howlett PJ, Stieritz DD. Waterhouse-Friderichsen syndrome after infection with group A *streptococcus*. Mayo Clin Proc. 2001;76(11):1167-70.
4. Spaulding AR, Salgado-Pabón W, Kohler PL, Horswill AR, Leung DY, Schlievert PM. Staphylococcal and streptococcal superantigen exotoxins. Clin Microbiol Rev. 2013;26(3):422-47.
5. Herman A, Kappler JW, Marrack P, Pullen AM. Superantigens: mechanism of T-cell stimulation and role in immune responses. Annu Rev Immunol. 1991;9:745-72.
6. Llewelyn M, Cohen J. Superantigens: microbial agents that corrupt immunity. Lancet Infect Dis. 2002;2:156-62.
7. McCormick JK, Yarwood JM, Schlievert PM. Toxic shock syndrome and bacterial superantigens: an update. Annu Rev Microbiol. 2001;55:77-104.
8. Schlievert PM. Role of superantigens in human disease. J Infect Dis. 1993;167(5):997-1002.
9. Kum WW, Laupland KB, Chow AW. Defining a novel domain of staphylococcal toxic shock syndrome toxin-1 critical for major histocompatibility complex class II binding, superantigenic activity, and lethality. Can J Microbiol. 2000;46:171-9.
10. DeVries AS, Lesher L, Schlievert PM, Villaume LG, Danila R, Lynfield R, et

al. Staphylococcal toxic shock syndrome 2000-2006: epidemiology, clinical features, and molecular characteristics. PLoS One. 2011;6:e22997.

11. Smit MA, Nyquist AC, Todd JK. Infectious shock and toxic shock syndrome diagnoses in hospitals, Colorado, USA. Emerg Infect Dis. 2013;19:1855.

12. Sharma H, Smith D, Turner CE, Game L, Pichon B, Hope R, et al. Clinical and Molecular Epidemiology of Staphylococcal Toxic Shock Syndrome in the United Kingdom. Emerg Infect Dis. 2018;24.

13. Tofte RW, Williams DN. Toxic shock syndrome. Evidence of a broad clinical spectrum. JAMA. 1981;246:2163.

14. Bartlett P, Reingold AL, Graham DR, Dan BB, Selinger DS, Tank GW, et al. Toxic shock syndrome associated with surgical wound infections. JAMA. 1982;247:1448.

15. Vainio H. Public health and evidence-informed policy-making: The case of a commonly used herbicide. Scand J Work Environ Health. 2019.

16. AL Akhrass F, Abdallah L, Berger S, Hanna R, Reynolds N, Thompson S, et al. Streptococcus agalactiae Toxic Shock-Like Syndrome: Two Case Reports and Review of the Literature. Medicine (Baltimore). 2013;92(1):10-4.

17. Ekelund K, Skinhøj P, Madsen J, Konradsen HB. Reemergence of emm1 and a changed superantigen profile for group A *streptococci* causing invasive infections: results from a nationwide study. J Clin Microbiol. 2005;43:1789.

18. Keefer CS, Ingelfinger FJ, Spink WW. Significance of hemolytic *streptococcic bacteremia*; A study of two hundred and forty-six patients. Arch Intern Med. 1937;60:1084.

19. Ispahani P, Donald FE, Aveline AJ. *Streptococcus pyogenes* bacteraemia: an old enemy subdued, but not defeated. J Infect. 1988;16:37.

20. Darenberg J, Luca-Harari B, Jasir A, Sandgren A, Pettersson H, Schalén C, et al. Molecular and clinical characteristics of invasive group A streptococcal infection in Sweden. Clin Infect Dis. 2007;45:450.

21. Kaul R, McGeer A, Low DE, Green K, Schwartz B. Population-based surveillance for group A streptococcal necrotizing fasciitis: Clinical features, prognostic indicators, and microbiologic analysis of seventy-seven cases. Ontario Group A Streptococcal Study. Am J Med. 1997;103:18.

22. Wharton M, Chorba TL, Vogt RL, Morse DL, Buehler JW. Case definitions for public health surveillance. MMWR Recomm Rep. 1990;39(RR-13):1-43.

23. Case definitions for infectious conditions under public health surveillance. Centers for Disease Control and Prevention. MMWR Recomm Rep. 1997;46:1.

24. Sierra JM, Sánchez F, Castro P, Salvadó M, de la Red G, Libois A, et al. Group A streptococcal infections in injection drug users in Barcelona, Spain: epidemiologic, clinical, and microbiologic analysis of 3 clusters of cases from 2000 to 2003. Medicine (Baltimore). 2006;85(3):139-46.

25. Okumura K, Schroff R, Campbell R, Nishioka L, Elster E. Group A streptococcal puerperal sepsis with retroperitoneal involvement developing in a late postpartum woman: case report. Am Surg. 2004;70:730.

26. Hamilton SM, Bayer CR, Stevens DL, Bryant AE. Effects of selective and nonselective nonsteroidal anti-inflammatory drugs on antibiotic efficacy of experimental group A streptococcal myonecrosis. J Infect Dis. 2014;209:1429.

27. Böhlen LM, Mühlemann K, Dubuis O, Aebi C, Täuber MG. Outbreak among Drug Users Caused by a Clonal Strain of Group A *Streptococcus*. Emerg Infect Dis. 2000;6:175-9.

28. Kotb M, Norrby-Teglund A, McGeer A, El-Sherbini H, Dorak MT, Khurshid A, et al. An immunogenetic and molecular basis for differences in outcomes of invasive group A streptococcal infections. Nat Med. 2002;8:1398.

29. Durand G, Bes M, Meugnier H, Enright MC, Forey F, Liassine N, et al. Detection of new methicillin-resistant *Staphylococcus aureus* clones containing the toxic shock syndrome toxin 1 gene responsible for hospital- and community-acquired infections in France. J Clin Microbiol. 2006;44:847.

30. Fey PD, Saïd-Salim B, Rupp ME, Hinrichs SH, Boxrud DJ, Davis CC, et al. Comparative molecular analysis of community- or hospital-acquired methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother. 2003;47(1):196-203.

31. Schlievert PM, Jablonski LM, Roggiani M, Sadler I, Callantine S, Mitchell DT, et al. Pyrogenic toxin superantigen site specificity in toxic shock syndrome and food poisoning in animals. Infect Immun. 2000;68:3630.

32. De Boer ML, Kum WW, Pang LT, Chow AW. Co-production of staphylococcal enterotoxin A with toxic shock syndrome toxin-1 (TSST-1) enhances TSST-1 mediated mortality in a D-galactosamine sensitized mouse model of lethal shock. Microb Pathog. 1999;27:61.

33. Schlievert PM. Role of superantigens in human disease. J Infect Dis. 1993;167(5):997-1002.

34. Vojtov N, Ross HF, Novick RP. Global repression of exotoxin synthesis by staphylococcal superantigens. Proc Natl Acad Sci U S A. 2002;99:10102.

35. Stevens DL, Salmi DB, McIndoo ER, Bryant AE. Molecular epidemiology of nga and NAD glycohydrolase/ADP-ribosyltransferase activity among Streptococcus pyogenes causing streptococcal toxic shock syndrome. J Infect Dis. 2000;182:1117.

36. Stevens DL. Invasive group A streptococcus infections. Clin Infect Dis. 1992;14:2.

37. Igwe EI, Shewmaker PL, Facklam RR, Farley MM, Van Beneden C, Beall B. Identification of superantigen genes speM, ssa, and smeZ in invasive strains of beta-hemolytic group C and G *streptococci* recovered from humans. FEMS Microbiol Lett. 2003;229:259-64.

38. Bessen DE, Hollingshead SK. Allelic polymorphism of emm loci provides evidence for horizontal gene spread in group A *streptococci*. Proc Natl Acad Sci U S A. 1994;91(8):3280-4.

39. Broker G, Spellerberg B. Surface proteins of *Streptococcus agalactiae* and horizontal gene transfer. Int J Med Microbiol. 2004;294:169-75.

40. Begley JS, Barnes RC. Group B streptococcus toxic shock-like syndrome in a healthy woman: a case report. J Reprod Med. 2007;52:323-5.

41. Carapetis JR, Jacoby P, Carville K, Ang SJ, Curtis N, Andrews R. Effectiveness of clindamycin and intravenous immunoglobulin, and risk of disease in contacts, in invasive group a streptococcal infections. Clin Infect Dis. 2014;59:358.

42. Coyle EA, Cha R, Rybak MJ. Influences of linezolid, penicillin and clindamycin alone and in combination, on streptococcal pyrogenic exotoxin A release. Antimicrob Agents Chemother. 2003;47:1752-5.

43. Gemmell CG, Ford CW. Virulence factor expression by gram-positive cocci exposed to sub-inhibitory concentrations of linezolid. J Antimicrob Chemother. 2002;50:665-72.

44. Gemmell CG, Peterson PK, Schmeling D, Kim Y, Mathews J, Wannamaker L, et al. Potentiation of opsonization and phagocytosis of *Streptococcus pyogenes* following growth in the presence of clindamycin. J Clin Invest. 1981;67:1249-56.

45. Sendi P, Johansson L, Norrby-Teglund A. Invasive group B Streptococcal disease in non-pregnant adults: a review with emphasis on skin and soft-tissue infections. Infection. 2008;36:100-11.

46. Phares CR, Lynfield R, Farley MM, Mohle-Boetani J, Harrison LH, Petit S, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999–2005. JAMA. 2008;299:2056-65.

47. Leclercq R, Courvalin P. Bacterial resistance to macrolide, lincosamide and streptogramin antibiotics by target modification. Antimicrob Agents Chemother. 1991;35:1267-72.

48. DeMuri GP, Sterkel AK, Kubica PA, Duster MN, Reed KD, Wald ER. Macrolide and Clindamycin Resistance in Group a *Streptococci* isolated from Children With Pharyngitis. Pediatr Infect Dis J. 2017;36:342.

49. Parks T, Wilson C, Curtis N, Norrby-Teglund A, Sriskandan. Polyspecific Intravenous Immunoglobulin in Clindamycin-treated Patients with Streptococcal Toxic Shock Syndrome: A Systematic Review and Meta-analysis. Clin Infect Dis. 2018;67:1434.

50. Schrage B, Duan G, Yang LP, Fraser JD, Proft T. Different preparations of intravenous immunoglobulin vary in their efficacy to neutralize streptococcal superantigens: implications for treatment of streptococcal toxic shock syndrome. Clin Infect Dis. 2006;43:743.

51. Cone LA, Woodard DR, Byrd RG, Schulz K, Kopp SM, Schlievert PM. A recalcitrant, erythematous, desquamating disorder associated with toxin-producing staphylococci in patients with AIDS. J Infect Dis. 1992;165:638.

52. American Academy of Pediatrics. *Staphylococcus aureus*. In: Red Book: 2018 Report of the Committee on Infectious Diseases, 31st ed. Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. American Academy of Pediatrics, Itasca, IL 2018. p.733.

53. Keller MA, Stiehm ER. Passive immunity in prevention and treatment of infectious diseases. Clin Microbiol Rev. 2000;13(4):602-14.

54. Bisno AL, Stevens DL. Streptococcal infections of skin and soft tissues. N Engl J Med. 1996;334(4):240-5.

55. Shaw JJ, Psoinos C, Emhoff TA, Shah SA, Santry HP. Not Just Full of Hot Air: Hyperbaric Oxygen Therapy Increases Survival in Cases of Necrotizing Soft Tissue Infections. Surg Infect (Larchmt). 2014;15:328-35.

56. Stevens DL, Bryant AE, Hackett SP, Chang A, Peer G, Kosanke S, et al. Group A streptococcal bacteremia: the role of tumor necrosis factor in shock and organ failure. J Infect Dis. 1996;173:619.

57. Larkin SM, Williams DN, Osterholm MT, Tofte RW, Posalaky Z. Toxic shock syndrome: clinical, laboratory, and pathologic findings in nine fatal cases. Ann Intern Med. 1982;96:858.

58. Paris AL, Herwaldt LA, Blum D, Schmid GP, Shands KN, Broome CV. Pathologic findings in twelve fatal cases of toxic shock syndrome. Ann Intern Med. 1982;96:852.

59. Hajjeh RA, Reingold A, Weil A, Shutt K, Anne Schuchat A, Perkins BA. Toxic shock syndrome in the United States: surveillance update, 1979 1996. Emerg Infect Dis. 1999;5:807.

60. Stevens DL, Tanner MH, Winship J, Swarts R, Ries KM, Schlievert PM, et al. Severe group A streptococcal infections associated with a toxic shock-like syndrome and scarlet fever toxin A. N Engl J Med. 1989; 321(1):1-7.

61. Stegmayr B, Björck S, Holm S, Nisell J, Rydvall A, Settergren B. Septic shock induced by group A streptococcal infection: clinical and therapeutic aspects. Scand J Infect Dis. 1992;24:589.

62. Ekelund K, Skinhøj P, Madsen J, Konradsen HB. Reemergence of emm1 and a changed superantigen profile for group A *streptococci* causing invasive infections: results from a nationwide study. J Clin Microbiol. 2005;43:1789.

63. Demers B, Simor AE, Vellend H, Schlievert PM, Byrne S, Jamieson F, et al. Severe invasive group A streptococcal infections in Ontario, Canada: 1987-1991. Clin Infect Dis. 1993;16:792.

64. Hasegawa T, Hashikawa SN, Nakamura T, Torii K, Ohta M. Factors determining prognosis in streptococcal toxic shock-like syndrome: results of a nationwide investigation in Japan. Microbes Infect. 2004;6:1073.