Toxic Shock Syndrome

Fever, Erythroderma, Conjunctivitis, Shock

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Toxic shock syndrome (TSS) was first described in 1978 [1]. The case series report included seven children and adolescents who had presented with fever, rash, conjunctival hyperemia, headache, confusion, vomiting, and diarrhea. All had evidence of acute renal insufficiency, hepatic insufficiency, coagulopathy, and cardiovascular collapse with prolonged shock. One patient died, one developed gangrene of the toes, and all six survivors eventually developed skin desquamation during convalescence. *Staphylococcus aureus* (*S. aureus*) was isolated from nasopharyngeal, vaginal, or tracheal mucous membranes or from sequestered, localized collections of pus from abscesses or pleural empyema. None of the seven patients described in the initial report had documented bacteremia. The isolates of *S. aureus* were shown to produce an exotoxin which caused a positive Nikolsky sign in the newborn mouse. In the years that followed this case series publication, lay media reports focused substantial attention on the association of TSS with the use of high absorbency tampons. During that period of time, Dr. Todd provided important reminders to both the lay public and to medical personnel that risks were not isolated to the use of tampons speaking of "the myths, partial truths, and gross misconceptions promulgated in the media." Despite the hyperbolic approach used at the time, public media reports ultimately served an important public health education role alerting females to the potential risk for TSS associated with tampon use.

TSS syndrome was subsequently identified as a staphylococcal toxin-mediated disease [2]. The term "superantigen" was coined to describe a stimulus that provokes a substantial expansion and proliferation of T lymphocytes associated with uncontrolled pro-inflammatory cytokine production and release. The ensuing, persistent cytokine storm leads to prolonged and severe shock. Tumor necrosis factor (TNF)-α and interleukin (IL)-1, IL-2, and IL-6 are among the most potent of these pro-inflammatory mediators [3].

The signs and symptoms of TSS are mediated by complex interactions between superantigens expressed by some bacteria and the host's response to their presence. These interactions lead to extensive, uncontrolled immune dysregulation. The pro-inflammatory state results in prolonged shock leading to multi-organ dysfunction. Even with the best available intensive care support, mortality from TSS remains substantial.

Infections caused by strains of bacteria that produce superantigens cause TSS. Superantigens produced by some strains of *S. aureus* include toxic shock syndrome toxin-1 (TSST-1) and staphylococcal enterotoxins B (SEB) and C (SEC). Similarly, some strains of *Streptococcus pyogenes* (*S. pyogenes* or group A beta-hemolytic streptococcus) produce the superantigen streptococcal pyrogenic exotoxin A (SPE-A) [► Call Out Box 27.1].

TSS is an acute systemic illness, characterized by fever, hypotension, and involvement of at least two or more organ systems. Separate case definitions have been established for staphylococcal (► Call Out Box 27.2) and streptococcal TSS (► Call Out Box 27.3).

Call Out Box 27.1

Toxic shock syndrome toxin-1, staphylococcal enterotoxins B and C, and streptococcal pyrogenic exotoxin A are superantigens. When expressed and released by bacteria during infection, these toxins stimulate unchecked expansion and proliferation of host T lymphocytes. The ensuing cytokine storm causes toxic shock syndrome.

Call Out Box 27.2 Case Definition for Toxic Shock Syndrome (Other Than Streptococcal)

Clinical Criteria

An illness with the following clinical manifestations:

- Fever: temperature greater than or equal to 102.0 °F (38.9 °C)
- Rash: diffuse macular erythroderma
- Desquamation: 1–2 weeks after onset of rash
- Hypotension: systolic blood pressure less than or equal to 90 mm Hg for adults or less than fifth percentile by age for children aged less than 16 years
- Multisystem involvement (three or more of the following organ systems):
  - Gastrointestinal: vomiting or diarrhea at onset of illness
  - Muscular: severe myalgia or creatine phosphokinase level at least twice the upper limit of normal
  - Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
  - 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
  - Hepatic: total bilirubin, alanine aminotransferase enzyme, or aspartate aminotransferase enzyme levels at least twice the upper limit of normal for laboratory
  - Hematologic: platelets less than 100,000/mm^3
  - Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

Laboratory Criteria

Negative results on the following tests, if obtained:

- Blood or cerebrospinal fluid cultures. Blood culture may be positive for *Staphylococcus aureus*.
- Negative serologies for Rocky Mountain spotted fever, leptospirosis, or measles.

Case Classification

Probable

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

Confirmed

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

27.1 Pathogenesis

Superantigens (SAgs) are major secreted virulence factors of *S. aureus*. Almost every *S. aureus* strain encodes for and can variably produce superantigens when the opportunity arises.

Call Out Box 27.3 Streptococcal Toxic Shock Syndrome: Clinical Case Definition[a]

- Isolation of group A streptococcus *(Streptococcus pyogenes)*
  - From a normally sterile site (e.g., blood, cerebrospinal fluid, peritoneal fluid, or tissue biopsy specimen)
  - From a nonsterile site (e.g., throat, sputum, vagina, open surgical wound, or superficial skin lesion)
- Clinical signs of severity
  - Hypotension: systolic pressure 90 mm Hg or less in adults or lower than the fifth percentile for age in children

  AND
- Two or more of the following signs:
  - Renal impairment: creatinine concentration 177 µmol/L (2 mg/dL) or greater for adults or at least two times the upper limit of normal for age[b]
  - Coagulopathy: platelet count 100,000/mm^3 or less or disseminated intravascular coagulation
  - Hepatic involvement: elevated alanine transaminase, aspartate transaminase, or total bilirubin concentrations at least two times the upper limit of normal for age
  - Adult respiratory distress syndrome
  - A generalized erythematous macular rash that may desquamate
  - Soft tissue necrosis, including necrotizing fasciitis or myositis, or gangrene

[a]An illness fulfilling criteria IA and IIA and IIB can be defined as a *definite* case. An illness fulfilling criteria IB and IIA and IIB can be defined as a *probable* case if no other cause for the illness is identified

[b]In patients with preexisting renal or hepatic disease, concentrations ≥twofold elevation over patient's baseline

Prevailing clones of community-associated methicillin-resistant *S aureus* such as USA300 rarely produce TSS toxin.

The classic SAg expressed by some strains of *S. pyogenes* is SPE-A; however SPE-C and several other novel streptococcal toxins have also been identified that might also be involved in triggering streptococcal TSS. Streptococcal mitogenic exotoxin Z (SMEZ), SPE-G, SPE-H, SPE-I, and SPE-J all possess typical SAg features. Known streptococcal Sag genes, with the exception of SMEZ, SPE-G, and SPE-J, are found on mobile DNA elements.

Traditional antigens must be bound to and presented by MHC molecules before being recognized by a unique T-cell receptor (TcR). In contrast, SAgs bind directly to a conserved locus on the TcR. Bypassing the hypervariable region of the TcR allows the SAg to activate a polyclonal population of T lymphocytes independent of their intended specificity. In some cases, as many as 20% of T lymphocytes are activated by the presence of a single bacterial SAg. The result is widespread activation of T lymphocytes, and other effector cells create the cytokine storm that is responsible for the clinical symptoms seen in patients with TSS [3].

Host defense against SAg-associated diseases relies on the host's ability to neutralize SAgs. Most individuals are exposed to SAgs early in life, so they develop neutralizing antibodies to these proteins by early adulthood. Serum concentrations of anti-TSST-1 antibody, for example, plateaus by age 40 years. For unknown reasons, 20% of people in the USA never develop antibodies to SAg. Children are more likely than adults to lack preformed protective antibodies against the causative toxins explaining why TSS is most common in this age group [4]. Laboratory experiments have shown that high concentrations of interferon-γ lead to the suppression of B-cell function – an in vitro observation that may help to explain why anti-SAg neutralizing antibodies fail to develop in response to severe illness [5]. Among otherwise healthy individuals, the risk of developing streptococcal TSS is higher among those with low levels of specific antibodies against the infecting bacterial strain and the SAgs it produces.

Another pathway that contributes to the severe manifestations of streptococcal TSS involves the bacterial M protein, a constituent of the streptococcal cell wall. M protein that is released from the bacterial surface can form aggregates in the blood and tissues because of its ability to bind to fibrinogen, a constituent of blood plasma [6]. The activation of circulating neutrophils by M protein–fibrinogen aggregates leads to endothelial cell damage, thereby triggering intravascular coagulation. The concomitant loss of integrity of the endothelial lining contributes to vascular leakage [7].

Substantial controversy exists regarding the potential association between using nonsteroidal anti-inflammatory drugs (NSAIDs) and the development of group A streptococcal TSS. Hypothetically, a predisposition to TSS could be mediated by the use of NSAIDs secondary to their inhibition of neutrophil function and suppression of fever, thus masking presenting symptoms. Any delay in diagnosis and treatment would be associated with an augmentation of cytokine release. NSAIDs have been shown to suppress granulocyte chemotaxis, phagocytosis, oxidative burst, and bactericidal activity. One prospective study, limited to the pediatric population, demonstrated a statistically significant but low associated risk (odds ratio 1:2) between NSAID use and subsequent development of non-necrotizing invasive group A streptococcal infection. A subgroup analysis from the same study suggested that the slight increased risk applied only to children who were receiving both ibuprofen and acetaminophen [8].

27.2 Clinical Manifestations

All of the major clinical manifestations of staphylococcal TSS are listed in ▶ Call Out Box 27.2. The illness is characterized by the abrupt onset of fever and hypotension with evidence of multisystem organ involvement. Profuse watery diarrhea, with or without vomiting, is typical. A generalized macular erythroderma and impressive conjunctival hyperemia give the patient's skin and mucous membranes an "inflamed" appearance.

Approximately 50% of reported cases of staphylococcal TSS occur in menstruating females using tampons, while non-menstrual cases account for the rest. Non-menstrual

cases are described following childbirth or abortion, after surgical procedures, and in association with cutaneous lesions such as burns, cellulitis, or even simple skin abrasions in any age group. Given the dramatic clinical presentation of TSS, it is tempting to assume that a focus of infection will be easy to identify, but an obvious staphylococcal infection may not be appreciated. When an infection is identified, it is typically quite unimpressive. Some examples include small cuts or scrapes, ingrown toenails, recent skin piercings, tattoo sites, and sinusitis [9].

Menstrual cases of TSS are almost universally associated with vaginal colonization by a TSST-1 expressing, toxigenic strain of *S. aureus*. Circumstances that promote bacterial overgrowth and/or cause microscopic abrasions in the vaginal mucosa, such as barrier contraception or tampon use, allow sufficient concentrations TSST-1 to gain access to the bloodstream. In contrast only half of non-menstrual TSS cases are caused by TSST-1. The other half are associated with strains of *S. aureus* that produce staphylococcal enterotoxins, such as SEB and SEC.

Streptococcal TSS (▶ Call Out Box 27.3) usually develops as a result of local soft tissue infection at the site of minor blunt trauma such as a bruise or muscle strain. The local infection at the site of the trauma advances very quickly, progressing to life- and limb-threatening necrotizing fasciitis (NF) and/or myonecrosis within a day or so. Streptococcal NF is associated with a 30–70% mortality rate. The impressive speed with which the infection progresses is responsible for its ugly nickname, "flesh-eating strep."

Varicella infection is a known major risk factor for the development of invasive group A streptococcal infection and streptococcal TSS in children [10–13]. One of the underappreciated benefits of universal immunization against varicella was an associated major decline in reported cases of pediatric group A streptococcal NF. Serious invasive disease including group A streptococcal bacteremia, pneumonia, empyema, osteomyelitis, septic arthritis, and endocarditis can also lead to the development of TSS [14]. Of all cases of invasive group A streptococcal infections in children, fewer than 10% are associated with the development of TSS.

Some cases of streptococcal TSS occur without an identifiable focus of infection, similar to what is seen with the majority of staphylococcal TSS. Accidental or incidental inoculation of *S. pyogenes* into the bloodstream during childbirth, surgical procedures, penetrating trauma, or intravenous drug can be sufficient to lead to TSS.

27.3 Epidemiology

Several general differences are noted between TSS caused by *S. aureus* and *S. pyogenes*. Bacteremia and complications that result in tissue necrosis and gangrene are far more common with streptococcal TSS (~50%), while generalized erythema is less common compared to staphylococcal TSS. In streptococcal TSS, *S. pyogenes* is usually isolated from sterile sites. The same is not true for staphylococcal TSS. Culture results from focal sources of infection can be seen with either form of TSS, but securing a microbiologic isolate has always been more challenging with staphylococcal TSS. As such, the case definition for staphylococcal TSS relies more heavily on the constellation of clinical features seen with the disease process than on culture results.

The incidence of streptococcal TSS is highest among young children and the elderly. Mortality rates are much higher in adults (30–80%) than in children (< 5%) reported with staphylococcal TSS [10, 14–17]. Streptococcal and staphylococcal TSS occur with similar frequency among children. Those with streptococcal TSS are younger than those with staphylococcal TSS (3.8 vs 9.5 years; $p < 0.003$).

27.4 Differential Diagnosis

The rash seen in TSS is a diffuse macular erythroderma, a dermopathy that resembles a sunburn [▶ Call Out Box 27.4].

Skin desquamation, usually of the hands and feet, typically occurs 1–3 weeks later. It's important to mention this to the patient because the peeling, while harmless, can be quite impressive. The broader differential diagnosis for TSS includes other systemic inflammatory and infectious illnesses that are associated with fever, rash, conjunctivitis, and evidence of end-organ injury. Infectious causes to consider include Rocky Mountain spotted fever, leptospirosis, meningococcemia, measles, and milder forms of exotoxin-mediated staphylococcal or streptococcal infection. Noninfectious inflammatory illnesses that should be considered include acute rheumatic fever, Kawasaki disease, erythema multiforme major, radiation injury, and heavy metal poisoning.

TSS cases may be missed because the diagnosis relies on the recognition of a constellation of clinical features. Some of the diagnostic features, such as rash and subsequent desquamation, may be subtle and therefore overlooked. Some cases may be deemed "sepsis" without appreciating the role of SAg toxins in the illness. It is important to understand how the established case definitions contribute to an underestimate of its true incidence. The case definitions are designed to have high specificity at the expense of sensitivity. In particular, hypotension is a late clinical sign in children and may not occur with aggressive and effective early fluid management. Impending

Call Out Box 27.4
The rash seen with toxic shock syndrome is best described as a diffuse macular erythroderma. The patient appears to have an impressive sunburn from head to toe. Other considerations in the differential diagnosis might include exotoxin-mediated infection without toxic shock, heavy metal poisoning, other forms of radiation exposure and injury, some cases of erythema multiforme, and Kawasaki disease.

shock from significant capillary leak in children is heralded by tachycardia and prolonged capillary refill time well before the onset of hypotension [18].

27.5 Treatment

The management approach to TSS caused by *S. aureus* and *S. pyogenes* is similar. Once the airway is deemed patent and breathing assessed as adequate, immediate attention to supporting or restoring adequate circulation is initiated. During aggressive fluid resuscitation and implementation of pharmacologic cardiovascular support with inotropic medications, a whole body survey should be performed in search of an infectious focus. Any identified foreign bodies, such as tampons, nasal packing, or recent surgically implanted medical devices, should be removed immediately. Paronychia or ingrown nails found during examination of the fingers and toes should be addressed without delay. Sites of recent piercings or tattoos should be carefully inspected for drainable collections of pus. If a deep tissue infection is suspected or confirmed based on physical examination findings, immediate and aggressive surgical debridement may be life and limb saving (► Call Out Box 27.5). Drainage and irrigation of accessible sites of purulent infection should be performed as soon as possible. Early, aggressive, and repeat surgical debridement is essential for the treatment of necrotizing fasciitis. Limb amputation may be necessary to preserve life.

Because TSS caused by *S. aureus* and *S. pyogenes* are impossible to distinguish from one another clinically, and the disease process if life-threatening, the initial empiric antimicrobial regimen must include coverage for both. Under these circumstances, a combination of *three* antimicrobial agents is recommended, *oxacillin (or nafcillin), vancomycin, and clindamycin*:

1. *Oxacillin* or *nafcillin* is bactericidal for all *S. pyogenes* isolates and all methicillin-susceptible *S. aureus* isolates. These modified penicillins are stable in the presence of the ubiquitous *S. aureus* β-lactamase, have a wide therapeutic window, and are the most potent anti-staphylococcal antibiotics available for the treatment of methicillin-susceptible isolates. Neither agent is active against methicillin-resistant *S. aureus*.
2. *Vancomycin* is bactericidal for all *S. pyogenes* isolates and virtually all *S. aureus* isolates, including methicillin-resistant strains. It has a narrow therapeutic window, requiring careful monitoring of serum concentrations to optimize its antibacterial activity and to avoid toxicity. Regular therapeutic drug monitoring of vancomycin is especially important in critically ill patients where renal function can change quickly and volumes of distribution are difficult to predict. Its use here is specifically to include coverage against methicillin-resistant *S. aureus* isolates. For the treatment of methicillin-susceptible isolates, vancomycin is inferior to oxacillin, nafcillin, and first-generation cephalosporins (e.g., cefazolin). We use vancomycin when we need it for empiric coverage or definitive treatment of methicillin-resistant *S. aureus* infection, but for susceptible isolates, many other agents simply work better.
3. *Clindamycin* is a bacteriostatic protein synthesis inhibitor. It is added initially in an effort to interrupt the translation of any further bacterial exotoxin. Most *S. pyogenes* and many *S. aureus* isolates are susceptible to clindamycin.

All three antibiotics should be given intravenously, at maximum dosages and at appropriate intervals based on age, weight, and/or renal function. Intravenous antibiotic therapy should be continued at least until the patient is afebrile and hemodynamically stable and has negative blood culture results. Total duration of therapy is dictated by the underlying focal infection, if one is identified, and by the patient's clinical response to treatment over time.

Whenever a causative organism is identified in the microbiology laboratory, and the antimicrobial susceptibilities have been confirmed, the empiric antibiotic regimen should be reassessed to determine whether de-escalation is appropriate either by eliminating some of the agents used initially or by replacing one of more agents with more narrow-spectrum options.

Immune globulin intravenous (IgIV) is an adjunctive therapy for TSS with a strong theoretical rationale, with little evidence from clinical trials to support its use routinely [19]. IgIV contains neutralizing antibodies to staphylococcal and streptococcal SAg toxins, has a beneficial effect on opsonization and phagocytosis, and reduces T lymphocyte production of pro-inflammatory cytokines. Taken together, these neutralizing and anti-inflammatory properties seem to be ideal properties of a medication used for the treatment of TSS. A single randomized clinical trial of IgIV vs placebo for the treatment of TSS in adult patients was terminated prematurely because of difficulties in enrollment [20]. Available data from the partially enrolled cohort suggest that

Call Out Box 27.5 Management of Toxic Shock Syndrome

Early and aggressive fluid management sufficient to maintain adequate cardiac filling pressures and systemic venous return

Monitoring for and supporting evolving multisystem organ failure including medication dosing modifications as needed based on renal or hepatic dysfunction

Parenteral antimicrobial therapy at maximum doses to include:

1. Oxacillin or nafcillin, bactericidal cell wall inhibitors active against methicillin-susceptible *S. aureus and S. pyogenes*
2. Vancomycin, a bactericidal cell wall inhibitor active against methicillin-resistant *S. aureus and S. pyogenes*
3. Clindamycin, a bacteriostatic protein synthesis inhibitor used to interrupt synthesis of toxin
4. Immune globulin intravenous should be considered for infection refractory to several hours of aggressive therapy or in the presence of an undrainable focus or persistent oliguria with pulmonary edema
5. Surgical consultation as necessary for debridement and/or abscess drainage

27

compared to placebo, patients treated with IgIV had reduced mortality, reduced sepsis-related organ failure assessment scores, and more robust SAg neutralization. Results from a 2009 provider survey on TSS management in the pediatric population in the UK indicated that 67% of respondents routinely included clindamycin in the initial empiric antibiotic regimen and 20% used IgIV. Eight pediatric deaths were identified during the survey. None of those who died had been given IgIV [17]. Conversely, an Australian retrospective series of 62 pediatric patients with TSS all survived-clindamycin was included as part of the initial empiric antibiotic regimen in 90% of cases, and adjunctive therapy with IgIV was used in 48% of cases. Approximately half of the patients described in the series had received both clindamycin and IgIV [14]. Results from an active, prospective, statewide surveillance for invasive group A streptococcal infections across Australia suggest that including clindamycin in the treatment regimen of patients with severe infection, including TSS, substantially reduces mortality and that this benefit may be further enhanced with concurrent administration of adjunctive IgIV [21].

The role of adjunctive IgIV therapy in pediatric TSS syndrome remains understudied. While adult data consistently suggest improved survival when IgIV is used, similar data are not likely to emerge for the pediatric population because childhood mortality from TSS is already quite low. Going forward, attempts to measure therapeutic benefits associated with IgIV use for TSS in the pediatric age group should choose outcome measures other than survival [22, 23]. Taken together, existing data appear to support a therapeutic benefit of including IgIV in the treatment of TSS, with the stronger evidence coming from observations in adults. IgIV appears more likely to be beneficial when used early in the course of illness, but the American Academy of Pediatrics Committee on Infectious Disease guidance states that IgIV "may be considered for infection refractory to several hours of aggressive therapy" [24] (▶ Call Out Box 27.5). If used, the optimal dose of IgIV remains unknown [24].

Clindamycin and IVIG are relatively safe treatments, and despite the absence of definitive trials, reasonable evidence and expert opinion support their use as adjunctive therapy for both children and adults with TSS. Given the potential for a significant benefit with limited added risk in a life-threatening disease process, adjunctive therapy with IgIV should probably be given to any patient with suspected or proven TSS. Decisions regarding adjunctive treatment(s) should not detract from the immediate and critical importance of confirming a patent airway, verifying adequate breathing, restoring and supporting circulation, identifying and removing all sources of infection, and starting empiric parental antibiotic therapy.

Household contacts of patients with severe invasive group A streptococcal disease, including TSS, are at somewhat higher risk of developing severe infection compared to the general population. This modest increase in risk is not sufficient to justify routine testing for group A streptococcus pharyngeal colonization. Because of the elevated risk of invasive group A streptococcal disease among certain populations, such as individuals with human immunodeficiency virus infection, varicella, and diabetes mellitus and those who are 65 years and older, providers may choose to offer targeted chemoprophylaxis to some household contacts. Secondary cases of invasive, severe group A streptococcal infections in children are uncommon. Chemoprophylaxis is not currently recommended in schools or child-care facilities in the USA after an index case is identified. Public health recommendations for circumstances that indicate a need for post-exposure chemoprophylaxis of close contacts, based on expert opinion, vary by country [24, 25].

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