

** no patient handout

Toxic shock syndrome

Contributors: Noah Craft MD, PhD, Lindy P. Fox MD, Lowell A. Goldsmith MD, MPH

Synopsis Toxic shock syndrome (TSS) is a severe exotoxin-mediated bacterial infection that is characterized by high fevers, headache, pharyngitis, vomiting, diarrhea, and hypotension. Two subtypes of TSS exist, based on the bacterial etiology: *Staphylococcus aureus* and group A streptococci. Significantly, the severity of TSS can range from mild disease to rapid progression to shock and end organ failure. The dermatologic manifestations of TSS include the following:

- Erythema of the palms and soles that desquamates 1-3 weeks after the initial onset
- Diffuse scarlatiniform exanthem that begins on the trunk and spreads toward the extremities
- Erythema of the mucous membranes (strawberry tongue and conjunctival hyperemia)

TSS was identified in and most commonly affected menstruating young white females using tampons in the 1980s. Current TSS cases are seen in post-surgical interventions in men, women, and children, as well as in other settings, in addition to cases of menstrual TSS, which have declined with increased public education on tampon usage and TSS. One study in Japanese patients found the highest TSS incidence to occur among children with burns, as *Staphylococcus* colonization is high in this subgroup and antibody titers are not yet sufficient to protect children from the exotoxins causing TSS.

Staphylococcal TSS is caused by *S. aureus* strains that can produce the toxic shock syndrome toxin-1 (TSST-1). TSST-1 is believed to cause disease via direct effects on end organs, impairing clearance of gut flora derived endotoxins, with TSST-1 acting as a superantigen leading to massive nonspecific activation of T-cells and subsequent inflammation and vascular leakage. In this form of TSS, risk factors include lack of an antibody to TSST-1, surgical packing, abscesses, surgical mesh, and tampon use. A late 1980s study showed a lower rate of tampon usage among African American and Mexican American women compared to white women, and while this may help explain the lower incidence of TSS in African American women, the authors did not believe the findings were sufficient to explain the discrepancy entirely. They hypothesized that perhaps the erythema of TSS is more difficult to see on darker skin phototypes, thus resulting in clinicians failing to recognize or report TSS because they failed to recognize one of the criteria for diagnosis.

Streptococcal TSS is also caused by exotoxins that cause massive stimulation of T-cells via a superantigen mechanism. Clinically, the most common presenting symptom is severe pain in an extremity with or without underlying soft tissue infection. A prodrome of fever, diarrhea, and myalgias is often seen. The macular exanthem seen in staphylococcal TSS is much less

commonly found in streptococcal TSS. Approximately 48-72 hours after the initial onset, shock and multiorgan failure follow. In this form of TSS, risk factors include varicella infection, bites, and lacerations.

Epidemiological studies from 2000-2004 in the United States show the incidence of invasive group A *Streptococcus* infections, such as streptococcal TSS, are higher among African Americans than other groups. The case fatality rate, however, was not different between groups.

Interestingly, there is an emerging pathogen, *Streptococcus suis*, which can be transmitted from pigs to humans and has been responsible for several large outbreaks of disease, including toxic shock syndrome, in Asia, specifically Thailand and China. The consumption of raw or undercooked pork is the number one risk factor. In one Thai study, 23% of patients with positive cultures developed TSS, and the mortality rate from infection with certain serotypes of *S. suis* has proven to be exceptionally high. Thus, this new pathogen has been cause of great concern worldwide.

All forms of TSS can result in confusion and coma, renal impairment, liver impairment, adult respiratory distress syndrome, and disseminated intravascular coagulation. Supportive measures (eg, intravenous fluids, vasopressors) and appropriate antibiotics are the mainstays of treatment.

Immunocompromised Patient Considerations

Although infections with *S. aureus* are common in human immunodeficiency virus (HIV)-infected people, the complication of TSS is rare. This is thought to be related to the immune deficits and T-helper cell dysfunction in HIV-infected people. However, in cases that have been reported, they tend to present with a recurrent and prolonged disease course. Attributed to delayed antibody production against TSST-1 by HIV-infected individuals, a protracted disease course has been reported in HIV-infected teens, adults, and children.

Codes

ICD10CM:

A48.3 – Toxic shock syndrome

SNOMEDCT:

18504008 – Toxic shock syndrome

Look For

Early diffuse, macular, or scarlatiniform exanthem. Exanthem may initially appear over the trunk but always spreads to arms and legs. Also look for palms and soles with erythema and edema, intense erythema of the mucous membranes, and, 1-2 weeks after onset of illness, diffuse desquamation with sheet-like peeling. Patchy alopecia (reversible) and fingernail shedding have been described.

Note: The exanthema in these areas – flexural areas, palms, and mucous membranes – may be more appreciable on deeply pigmented skin.

Staphylococcal TSS:

- Diffuse macular erythroderma
- Desquamation of palms / soles 1-3 weeks after onset of symptoms
- High grade fever
- Hypotension
- Multiorgan involvement

Streptococcal TSS:

- Severe localized pain in an extremity
- Prodromal symptoms
- Desquamation of palms / soles 1-3 weeks after onset of symptoms
- Hypotension within 48-72 hours of initial onset of symptoms
- Multiorgan involvement

Note that there are significant differences between staphylococcal and streptococcal TSS. They are as follows:

- Diffuse macular erythroderma is commonly seen in staphylococcal but not in streptococcal TSS.
- Soft tissue infections are rare in staphylococcal TSS but common in streptococcal TSS.
- Positive blood cultures are seen in less than 15% of staphylococcal TSS cases but in over 50% of streptococcal TSS.
- Mortality rates are approximately 3% in staphylococcal TSS and 30%-60% in streptococcal TSS.

Group A streptococci can be isolated from blood, cerebrospinal fluid, tissue biopsy, surgical wound, sputum, throat, vagina, and superficial skin lesion.

Diagnostic Pearls

Staphylococcal TSS – Diffuse macular erythroderma (sunburn appearance), fever, hypotension, multiorgan involvement (including vomiting / diarrhea at onset and conjunctival injection). **Note:** The early exanthem is flexurally accentuated. The underlying infection can be

limited and minor in appearance.

Streptococcal TSS – Severe localized pain in an extremity, fever, hypotension, multiorgan involvement. These symptoms are less common in children than in adults. In children, streptococcal TSS can present without an obvious cellulitis / soft tissue infection. Streptococcal TSS can also be observed with pneumonia, pleural empyema, osteomyelitis, or bacteremia.

Differential Diagnosis & Pitfalls

- **Staphylococcal scalded skin syndrome**
- **Drug hypersensitivity syndrome** (DRESS)
- **Exanthematous drug eruption**
- **Drug-induced erythroderma**
- **Toxic epidermal necrolysis** (TEN) – Drug induced, high fevers, skin tenderness, mucosal erosions, and skin detachment about 1-3 weeks after the inciting medication is started.
- **Stevens-Johnson syndrome** – Drug induced, high fevers, skin tenderness, mucosal erosions, and skin detachment about 1-3 weeks after the inciting medication is started.
- **Scarlet fever** – 1-mm erythematous papules, always elevated WBC with left shift, eosinophilia in up to 20% of patients.
- **Erythrodermic psoriasis**
- **Atopic dermatitis with erythroderma**
- **Contact dermatitis**
- **Pemphigus erythematosus**
- **Pityriasis rubra pilaris**
- Sezary syndrome (see **cutaneous T-cell lymphoma**)
- **Erysipelas**
- **Necrotizing fasciitis** – Rapidly progressing necrosis of fascia and subcutaneous fat.
- **Kawasaki disease** – Fever lasting for more than 5 days with oral mucosal changes, conjunctival injection, and cervical lymphadenopathy.
- **Meningococcemia** – Rapid decompensation, characteristic petechial eruption caused by *N. meningitidis*.

- **Rocky Mountain spotted fever** – Characteristic retiform purpura; check for serologies.

Best Tests

The clinical picture and exam are more important than any test and should prompt initiation of therapy as soon as possible. The following tests and findings support the diagnosis:

- Blood cultures
- Culture of any potentially infected site (eg, skin lesions, throat)
- CBC – leukocytosis, occasionally thrombocytopenia and/or anemia
- Electrolyte abnormalities, including azotemia
- Liver function tests – often bilirubin and/or transaminases will be elevated
- Coagulation studies – partial thromboplastin time (PTT) and fibrin split products may be elevated
- Arterial blood gas – metabolic acidosis
- Creatine kinase may be increased
- Urinalysis may be abnormal, with myoglobin or casts
- Serologic testing may be performed to rule out other causes of the clinical findings (Rocky Mountain spotted fever, measles, leptospirosis, syphilis, Epstein-Barr virus, hepatitis B, or antinuclear antibodies).

Depending on the clinical scenario, further testing will be needed to investigate or monitor possible complications and may include:

- ECG / continuous cardiac monitoring
- Invasive hemodynamic monitoring
- Chest radiographs
- Echocardiogram
- Plain films, CT, or MRI of any suspected site of infection
- Lumbar puncture

Management Pearls

Supportive care in a tertiary medical center (if possible) is necessary for a successful outcome.

Precautions: Standard and Contact (Isolate patient, wear gloves and a gown, limit patient transport, and avoid sharing patient-care equipment.)

In the United States, streptococcal TSS is reportable in the District of Columbia and all states and territories **except** American Samoa, CA, CT, MS, OK, PR, TX, WA.

In the United States, TSS other than streptococcal is reportable in the District of Columbia and all states and territories **except** AK, American Samoa, CT, HI, ME, MS, OK, PR, TX, WA.

In the United States, methicillin-resistant *Staphylococcus aureus* (MRSA) infection is reportable in the District of Columbia and all states and territories **except** AL, AK, American Samoa, AZ, AR, FL, ID, KS, LA, MA, MS, NE, NV, NM, NY, NC, OK, RI, TX, VT, VA, WA, WI.

In the United States, vancomycin-resistant *Staphylococcus aureus* (VRSA) infection is reportable in the District of Columbia and all states and territories **except** AL, AK, American Samoa, ID, KS, MA, NM, WA.

In the United States, vancomycin-intermediate *Staphylococcus aureus* (VISA) infection is reportable in the District of Columbia and all states and territories **except** AL, AK, American Samoa, CO, ID, KS, NM, Virgin Islands, WA.

In the United States, vancomycin-resistant enterococci (VRE) infection is reportable in AR, Guam, HI, LA, MN, MS, MO, NV, NH, ND, PR, TN, VT, Virgin Islands, WY.

Therapy

Immediate intervention for shock and systemic antistaphylococcal / streptococcal antibiotics is essential. Aggressive fluid support will be needed. Cardiovascular, pulmonary, and metabolic intervention / support may be necessary.

- Patients with suspected TSS – Clindamycin 600 mg intravenous (IV) every 8 hours plus vancomycin 30 mg/kg divided twice daily
- Patients with confirmed methicillin-susceptible *S. aureus* – Clindamycin 600 mg IV every 8 hours plus either oxacillin IV or nafcillin IV (2 g every 4 hours)
- Patients with confirmed MRSA or penicillin allergy – Clindamycin 600 mg IV every 8 hours plus either vancomycin 30 mg/kg/day IV divided twice daily or linezolid 600 mg IV or by mouth every 12 hours

Continue antibiotics for a total of 10-14 days.

Immune globulin (400 mg/kg over 2-3 hours) contains antibody to TSS and may be used for patients with refractory foci of infection.