PUBLIC HEALTH REFERENCE SHEET
Toxic Shock Syndrome (TSS)

Name	INCLUDES: Streptococcal TSS and non-streptococcal TSS Streptococcal TSS: *Streptococcus pyogenes* (Group A Strep) Non-streptococcal: Often caused by *Staphylococcus aureus*
Reservoir & Transmission	Humans Transmission is through large respiratory droplets or entry of the bacterium through a compromised barrier (such as a skin injury) or through mucus membranes. The bacteria then spread to deep tissues and eventually to the bloodstream.
Incubation Period	The incubation period for STSS varies depending on site of entry. Once initial symptoms occur, hypotension generally develops within 24 to 48 hours. Variable; menstrual TSS usually occurs during the last 2 days of menstruation.
Common Symptoms	Streptococcal TSS often begins with influenza-like symptoms, including fever, chills, myalgia, nausea, and vomiting. These symptoms often quickly progress to sepsis with hypotension, tachycardia, tachypnea, and signs and symptoms suggestive of specific organ failure, including of the following organ systems: kidney, liver, lung, and blood.
Gold Standard Diagnostic Test	Cultures
Risk Groups	STSS can occur in anyone, but risk factors can include adults 65 years of age or older and people with skin injury or breakdown. Predisposing conditions for severe infection are drug abuse, diabetes mellitus, chronic renal failure (especially patients on dialysis), and rheumatoid arthritis. Use of steroids and other immunosuppressive agents also increases susceptibility. Although almost all early cases of TSS occurred in women during menstruation, and most with vaginal tampon use, only about half of the cases now reported are associated with menses. Other risk factors include use of contraceptive diaphragms and vaginal contraceptive sponges and infection following childbirth or abortion.
Geographic Significance	Worldwide

What is toxic shock syndrome?

Streptococcal toxic shock syndrome (STSS) is a disease defined as an infection with *Streptococcus pyogenes*, which are also called group *A Streptococcus* (group A strep). When production of bacterial exotoxins and virulence factors occur in the deep tissues and bloodstream, the induction of the cytokine cascade can occur. Massive cytokine cascades contribute to the development of shock or organ failure, accompanied by the following clinical manifestations:

- Hypotension defined by a systolic blood pressure less than or equal to 90 mm Hg for adults or less than the fifth percentile by age for children less than 16 years old.
- Multi-organ involvement characterized by two or more of the following:
    - Renal impairment: Creatinine greater than or equal to 2 mg/dL (greater than or equal to 177 ìmol/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.

- Coagulopathy: Platelets less than or equal to 100,000/mm^3 or disseminated intravascular coagulation, defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products.
- 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.
- 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, which is manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia.
- A generalized erythematous macular rash that may desquamate.
- Soft-tissue necrosis, including necrotizing fasciitis or myositis, or gangrene.

In STSS production of superantigen, exotoxins directly stimulate a large proportion of circulating T cells, leading to massive cytokine release. Streptococcal pyrogenic exotoxin A is the most commonly implicated superantigen; it is produced by 80% of Group A Streptococcal (GAS) strains causing STSS.

Non-streptococcal TSS is an illness caused by strains of *Staphylococcus aureus* capable of producing pyrogenic toxins, called superantigens. Superantigens activate up to 20% of all T cells simultaneously, which leads to an overwhelming inflammatory response with the following clinical manifestations:

- Fever: temperature greater than or equal to 102.0°F (greater than or equal to 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 less than 16 years old
- 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

What is the occurrence of toxic shock syndrome?
Streptococci have been implicated as a long-standing cause of invasive infection in immunocompromised individuals. However, in the 1980s, STSS was discovered to be affecting young, otherwise healthy individuals as well. The majority of cases are sporadic. It can occur worldwide. The highest incidence of skin and soft tissue infection is in areas where hygiene conditions are suboptimal, and people are crowded together. It is common among children. The disease occurs sporadically and as small epidemics in families, sport teams, and summer camps, with various members developing recurrent illness due to the same bacterial strain.

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Menstrual TSS was first reported in 1978 and has declined with the withdrawal of highly absorbent tampons from the market.

How is toxic shock syndrome transmitted?

Any group A strep infection may progress to STSS. Disease occurs with entry of the bacterium through a compromised barrier (such as a skin injury) or through mucus membranes. The bacteria then spread to deep tissues and eventually to the bloodstream. The main sites of entry for streptococci leading to toxic shock syndrome include vagina, pharynx, mucosa, or skin/soft tissue. Any skin injury or breakdown, including surgical wounds, may provide a site of entry for the bacteria. Unfortunately, route of entry remains unknown for up to 50% of cases. Secondary cases among close contacts or healthcare workers are rare, although have been known to occur. Contaminated objects can also serve as sources of infection. Airborne spread is rare but has been demonstrated in patients with associated viral respiratory disease.

Who is at risk for toxic shock syndrome?

STSS can occur in anyone, but risk factors can include:

- Age: STSS is more common in adults 65 years of age or older.
- Skin injury or breakdown: Recently having surgery, a viral infection that causes open sores (like varicella), or other skin injury increases risk for developing STSS.
- Chronic illnesses: Having alcohol use disorder or diabetes can also increase risk for developing STSS.
- Additionally, strains of group A strep that produce certain virulence factors and exotoxins, particularly streptococcal pyrogenic exotoxins, are more likely to cause STSS and other severe infections.
- Use of non-steroidal anti-inflammatory drugs (NSAIDs) may also increase risk, although evidence for this is limited.

Although almost all early cases of TSS occurred in women during menstruation, and most with vaginal tampon use, only about half of the cases now reported are associated with menses. Other risk factors include use of contraceptive diaphragms and vaginal contraceptive sponges and infection following childbirth or abortion.

What are the signs and symptoms of toxic shock syndrome?

STSS often begins with influenza-like symptoms, including fever, chills, myalgia, nausea, and vomiting. These symptoms often quickly progress to sepsis with hypotension, tachycardia, tachypnea, and signs and symptoms suggestive of specific organ failure, including of the following organ systems: kidney, liver, lung, and blood.

S. aureus can produce toxins that act distant from the site of bacterial infection or colonization. Although infrequent, TSS is reviewed as it is a particularly severe manifestation and hard to diagnose. TSS is a severe illness characterized by sudden onset of high fever, vomiting, profuse watery diarrhea, myalgia, and rash, accompanied by hypotension, edema, and—in severe cases—shock. Menstrual and nonmenstrual TSS can be distinguished. Menstrual TSS is associated with the use of high-absorbency tampons where certain *S. aureus* strains find favorable conditions for toxin production. In nonmenstrual TSS, bacteria can colonize virtually all body sites, including surgical wounds.

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What are the potential complications of toxic shock syndrome?
Despite aggressive treatment, the mortality rate for STSS ranges from 30% to 70%. Mortality from STSS is substantially lower in children than adults. Known complications of shock and organ failure can occur, including tissue necrosis and loss of extremities.

How is toxic shock syndrome diagnosed?
Toxic shock syndrome is typically confirmed by isolation of the organism in culture and alternatively by polymerase chain reaction methods. Most strains of staphylococci can be characterized through the antibiotic resistance profile and molecular methods, such as spa typing or whole-genome sequencing.

- The differential diagnosis of patients in the early stages of STSS is broad, including other viral or bacterial infections (such as staphylococcal toxic shock); therefore, patients are often misdiagnosed. Diagnosis of STSS is made based on the Nationally Notifiable Diseases Surveillance System 2010 case definition (see definition for STSS under the section, “what is toxic shock syndrome?”)
- Laboratory criteria for STSS diagnosis: Isolation of group A Streptococcus.
- Case classification:
    - Probable: 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 nonsterile site.
    - Confirmed: A case that meets the clinical case definition and with isolation of group A Streptococcus from a normally sterile site (e.g., blood or cerebrospinal fluid or, less commonly, joint, pleural, or pericardial fluid).

- Diagnosis of non-streptococcal TSS is made based on the Nationally Notifiable Diseases Surveillance System 2011 case definition for Toxic Shock Syndrome (Other Than Streptococcal) (TSS) (see definition for non-streptococcal TSS under the section, “what is toxic shock syndrome?”)
- Laboratory criteria for diagnosis of non-streptococcal TSS: 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.

How is toxic shock syndrome treated?
- Hospitalization is required. Standard treatment of shock and organ failure, such as fluid resuscitation, is imperative as the first step in treatment. Antibiotic therapy is critical. Know your facility’s existing guidance for diagnosing and managing sepsis. If you suspect sepsis, start antibiotics as soon as possible, in addition to other therapies appropriate for the patient. Once STSS is confirmed, antibiotics can be tailored. Penicillin and clindamycin are used in conjunction as first-line antibiotic choices for STSS. Removal of the source of infection, if possible, is important in the management of STSS, and surgical debridement of deep tissue infection may be necessary. The use of intravenous immunoglobulin has been

used for severely ill patients early in the clinical course; however, more evidence is needed to determine the potential efficacy of this therapy.

- Treatment of TSS is largely supportive with fluid replacement and concomitant respiratory and inotropic support. Efforts should be made to eradicate potential foci of *S. aureus* infection through drainage of wounds, removal of vaginal tampons or other foreign bodies (e.g., wound packing), and use of anti-staphylococcal drugs. Clindamycin may help to reduce toxin production.

How can toxic shock syndrome be prevented?

- There is currently no vaccine to prevent group A strep infections. Screening and antibiotic prophylaxis for household contacts of STSS patients is not recommended for household members under age 65 years, as the risk of secondary cases in these individuals is low. However, the risk of a secondary case in the 30 days following exposure to the index case is highest among household contacts who are 65 years of age or older; thus, antibiotic chemoprophylaxis should be considered for household contacts aged ≥65 years old.
- The spread of group A strep can be reduced by standard infection control practices, including good hand hygiene and respiratory etiquette (e.g., covering your cough or sneeze).
- Menstrual TSS can be prevented by avoiding use of highly absorbent vaginal tampons; risk may be reduced by using tampons intermittently (i.e., not all day and all night throughout the period) and using less absorbent tampons.

What are some Public Health considerations?

- When reporting cases of TSS in the Disease Reporting System Internet (DRSi) system, specify the clinical form of the disease.
- CDC tracks invasive group A strep infections through the Active Bacterial Core surveillance (ABCs) program at https://www.cdc.gov/abcs/index.html.

References:

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