BMJ Best Practice

Toxic shock syndrome

Straight to the point of care

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Table of Contents

Summary

Toxic shock syndrome (TSS) is an exotoxin-mediated illness caused by bacterial infection, most commonly group A streptococcus or *Staphylococcus aureus* .

Presenting signs and symptoms can be nonspecific, but the course of the disease is precipitous and toxicity occurs early, resulting in serious life-threatening disease and multiorgan system failure.

Early diagnosis and treatment is essential.

Streptococcal TSS can occur with infection at any site but is more commonly associated with an infected cutaneous site.

Staphylococcal TSS (menstrual or nonmenstrual) is associated with extended tampon use, postpartum infections, and other sites of infection with the organism.

Treatment includes supportive care in an intensive care unit, early empiric antibiotic treatment, and further culture-sensitive antibiotic treatment. Surgical debridement may be needed for deep-seated streptococcal infections.

Definition

Toxic shock syndrome (TSS) is an exotoxin-mediated illness caused by bacterial infection. Organisms commonly responsible include group A streptococcus (*Streptococcus pyogenes*), or methicillin-sensitive (MSSA) or methicillin-resistant (MRSA) *Staphylococcus aureus* .[1] [2] [3]

Although the presenting signs and symptoms can be nonspecific (e.g., fever, chills, myalgias, headache), the course of the disease is precipitous, and shock and multiorgan system failure occur early in the course of the disease.

Staphylococcal TSS can be split into 2 groups: menstrual TSS, which occurs in women during menstruation with extended use of a single tampon or, historically, with highly absorbable tampons; and nonmenstrual TSS, which can result from a variety of staphylococcal postpartum vaginal and cesarean wound infections.[4] [5] [6] [7] [8]

Epidemiology

Staphylococcal toxic shock syndrome

Toxic shock syndrome (TSS) is most frequently caused by gram-positive staphylococcus. In 2019, there were 44 cases of staphylococcal TSS reported in the US.[18] The incidence of menstrual staphylococcal TSS ranges from 0.03 to 0.50 cases per 100,000 women; overall mortality of menstrual staphylococcal TSS is approximately 8%. Nonmenstrual TSS is now more common than menstrual TSS.[19] The incidence of menstrual TSS has declined since the 1990s owing to changes in tampon manufacture and increased public awareness. In the US, nonmenstrual cases may account for approximately 55% of all staphylococcal TSS.[20] [21] Nonmenstrual cases occur more often in nonwhite, older women but can occur in either sex and are associated with a staphylococcal abscess or recent surgery.[4] [20] [22] Postpartum TSS has been recognized occurring after vaginal and cesarean deliveries and also resulting from various postpartum infections.

Most cases of staphylococcal TSS are due to methicillin-sensitive *Staphylococcus aureus* (MSSA). However, the incidence of TSS from the more virulent community-associated MRSA strains is increasing.[23] [24]

In the UK, the average annual incidence of staphylococcal TSS cases is estimated to be 0.07 per 100,000 population.[19]

Streptococcal toxic shock syndrome

Approximately 14,000 to 25,000 cases of invasive group A streptococcal disease are estimated to have occurred each year between 2017 and 2022 in the US.[25] Based on preliminary 2022–2023 data, the Centers for Disease Control and Prevention (CDC) announced in February 2023 that it is looking into an increase in invasive group A streptococcal infections among children in the US.[26] In a March 2023 UK Health Security Agency (UKHSA) report, notifications of invasive group A streptococcal infections in England were higher than the range expected for the time of year.[27] Invasive group A streptococcal infections include streptococcal TSS. Between 2004 and 2014, the reported incidence of streptococcal TSS in the US ranged from 0.06 to 0.12 cases per 100,000 people.[28] There were 416 cases reported in 2019.[18] Some studies suggest rates of TSS are higher among young children and adults aged ≥65 years.[29] [30] However, people of all ages are affected and most do not have underlying diseases.[31]

Approximately 85% of invasive infections occur sporadically in the community, 10% are hospital acquired, 4% occur in residents of long-term care facilities, and 1% occur after contact with an infected person.[32] [33] One population-based study reported a rate of secondary infection of approximately 2.9 cases per 1000 household contacts.[32] Secondary invasive disease in household contacts and hospital personnel has been reported to occur several hours to weeks after the index case.[32] [33] [34] [35] [36] Outbreaks in closed environments such as hospitals, military bases, and nursing homes have been reported.[35] [36] [37] [38] [39]

Etiology

Streptococcal toxic shock syndrome (TSS) is defined as an invasive infection secondary to group A streptococcus (*Streptococcus pyogenes*) associated with shock and multiorgan system failure occurring early in the course of the disease.[1] [2] Invasive streptococcal infections include bacteremia, cellulitis,

meningitis, pneumonia, empyema, peritonitis, septic arthritis, puerperal sepsis, burn wound sepsis, necrotizing fasciitis, or gangrenous myositis.[9] The most common sites of entry of bacteria include the skin, vagina, and pharynx. In many cases of streptococcal TSS, no site of entry is found.[40] The organism is spread through direct contact with mucosa from the nose or throat of infected patients or through contact with infected wounds.

Staphylococcal TSS is an invasive infection secondary to either methicillin-sensitive (MSSA) or methicillin-resistant (MRSA) *Staphylococcus aureus* and is associated with tampon use and postpartum infections but is not restricted to these cases.

- Menstrual TSS occurs in women during menstruation with extended use of a single tampon or, historically, with highly absorbant tampons.
- Nonmenstrual TSS can result from a variety of staphylococcal postpartum vaginal and cesarean wound infections, including mastitis, therapeutic abortions, episiotomy infections, endometritis, and infected abdominal wounds. Sinusitis, septorhinoplasty, osteomyelitis, arthritis, burns, cutaneous infections, soft-tissue infections, enterocolitis, endovascular infections, visceral abscesses, and postinfluenza respiratory infections have also been implicated.[4][5] [6] [7] [8]

TSS with necrotizing fasciitis, caused by *Streptococcus agalactiae*, has also been reported infrequently.[41] Other organisms infrequently associated with TSS include *Streptococcus viridans*, group C *Streptococcus*, group G *Streptococcus*, and *Clostridium sordellii*.[29]

Pathophysiology

Streptococcal TSS is mediated by streptococcal pyrogenic exotoxins (superantigens) and virulence factors (M strains with M proteins 1 and 3) that activate the immune system to release inflammatory cytokines.[42] [43] The cytokines (TNF-alpha, interleukin-1, and interleukin-6) result in shock and multiorgan failure.[44] Streptococcal pyrogenic exotoxins A (SPEA) and B (SPEB) are found in most severe invasive group A streptococcal infections. Streptococcal superantigen (SSA) is associated with TSS.[45] [46] Patients with invasive group A streptococcal infections have significantly lower levels of protective antibodies against M-protein and superantigens, suggesting that lack of humoral immunity against the group A streptococcal virulence factors contributes to susceptibility to invasive infection.[47] [48] [49] [50] Several studies have shown that protective humoral immunity to group A streptococcal virulence factors is important in preventing disease.[47] [48] [49] [50] [51][52] [53]

Group A streptococcal infections with diverse emm genotypes have been isolated from patients with streptococcal infections. More recently, the emm-49 genotype has been associated with more severe invasive streptococcal infections. CsrS gene mutations in severe invasive group A streptococcal infections have been demonstrated.[54]

Staphylococcal TSS from MSSA and MRSA strains is caused by the toxic shock syndrome toxin-1 (TSST-1). This exotoxin is implicated in 90% to 100% of strains associated with menstrual TSS and in 40% to 60% of nonmenstrual cases.[55] [56] [57] Community-acquired MSSA and MRSA strains are more likely to produce enterotoxin B or C.[58] Enterotoxins C, D, E, and H have been implicated less frequently.[59] Antibodies to TSST-1 develop in 90% to 95% of the population by the fourth decade.[13] Patients with clinical TSS lack the antibody to TSST-1 and other staphylococcal enterotoxins and usually do not develop the antibody in the convalescent stage.[60]

Case history

Case history #1

A 32-year-old woman presents to the emergency department with complaints of fever, chills, headache, muscle aches, and shortness of breath over the past 48 hours. Two weeks before her symptoms, she had an uncomplicated vaginal delivery at term. She has no significant past medical history. No one else at home has been recently sick or traveled outside the country. On physical exam she appears toxic with a temperature of 103.1°F (39.5°C). Her pulse rate is 132 bpm and her BP is 100/60 mmHg with a respiratory rate of 34 breaths/minute. A diffuse erythematous rash is noted on the upper and lower extremities. Breath sounds are diminished at the bases. The rest of the exam is noncontributory.

Other presentations

Severe group A streptococcal infections can result in infections including bacteremia, cellulitis, meningitis, pneumonia, empyema, peritonitis, septic arthritis, puerperal sepsis, burn wound sepsis, necrotizing fasciitis, and gangrenous myositis.[9] These infections can present with evidence of toxic shock syndrome (TSS) with shock and multiorgan system failure. Some atypical presentations have been reported, such as secondary infections with group A streptococcus as a result of a primary varicella infection. Although varicella infection is often a self-limited infection in children, it can be associated with serious life-threatening infections in both immunocompetent and immunocompromised patients. Serious bacterial infections caused by group A streptococcal infections are increasing in frequency as a complication of varicella.[10] [11]

Recurrent menstrual and nonmenstrual staphylococcal TSS have been reported, and are seen primarily in those patients who have not been treated with appropriate antistaphylococcal antibiotics or for adequate duration of therapy.[12] [13] [14] [15] Up to one third of patients may have recurrent menstrual TSS, particularly those patients who do not develop a humoral response to the staphylococcal toxin and/or have persistent colonization with a toxigenic strain of *Staphylococcus aureus* .[12] [14] [16] Recurrent nonmenstrual cases can occur when patients do not develop a protective level of antibody in the convalescent phase after the initial infection.[15] Recurrences can occur from days to months after the initial presenting syndrome. In menstrual TSS, recurrences are generally milder than the initial disease.

A variant of staphylococcal TSS has also been described in patients with AIDS, presenting as a subacute illness with desquamation, erythroderma, mucocutaneous infections, and hypotension, all of which persist or recur over several weeks.[17]

Approach

Early diagnosis of TSS is essential, as serious life-threatening infections can develop within 24 to 72 hours. Initial signs and symptoms are usually nonspecific: for example, pain, fever, malaise, gastrointestinal symptoms such as vomiting and diarrhea, and muscle aches. The clinical course of TSS is often precipitous, and requires a high index of suspicion, prompt diagnosis, and early treatment in an intensive care unit.

Choice of antibiotics in treatment of TSS is aided by differentiating between streptococcal and staphylococcal disease, although the two have many similar history and exam factors, and test results. Microbiologic cultures are not always the best differentiating points because of low likelihood of producing a positive culture.

Clinical evaluation

Streptococcal TSS should be considered in a healthy patient from the community who presents with shock, severe pain, and fever, and has a recent history of trauma. TSS should also be considered in patients with a relatively unimpressive focus of infection but evidence of septic shock. In many cases of streptococcal TSS, no site of entry is found, or it is subtle.[40] Invasive streptococcal infections include bacteremia, cellulitis, meningitis, pneumonia, empyema, peritonitis, septic arthritis, puerperal sepsis, burn wound sepsis, necrotizing fasciitis, or gangrenous myositis.[9] Serious bacterial infections caused by group A streptococcal infections are increasing in frequency as a complication of varicella.[10] [11]

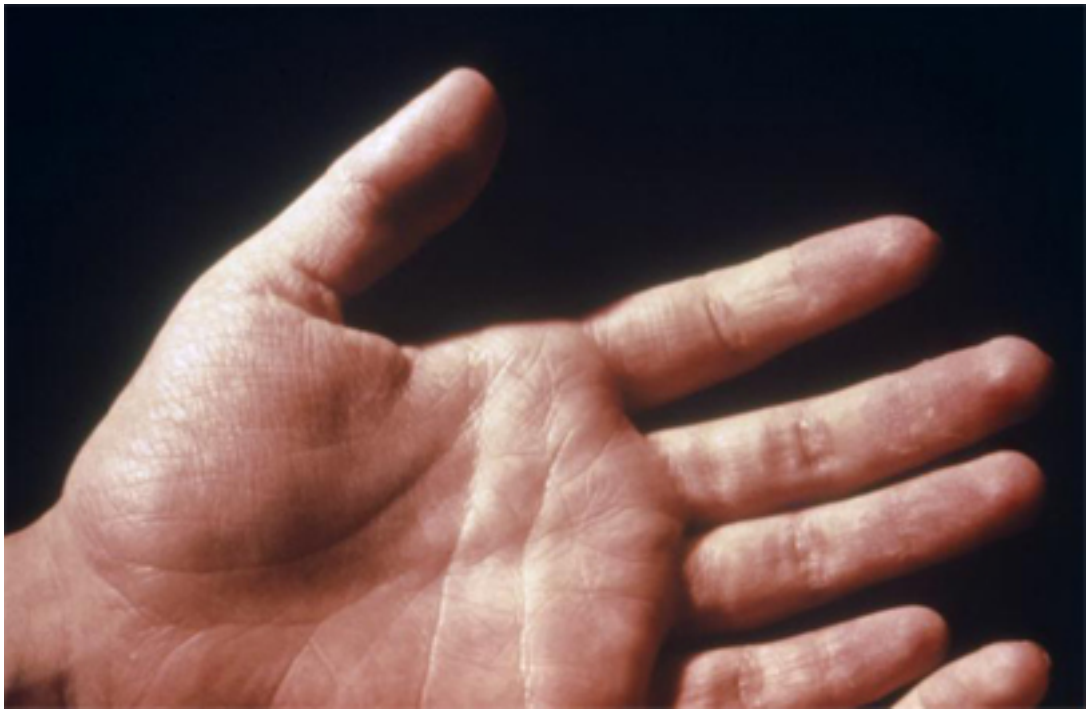
Signs and symptoms

The most common initial presentation of TSS from a group A streptococcal invasive infection is abrupt onset of severe diffuse or localized pain, which often precedes the physical findings of a soft-tissue infection.[62] Extremity pain is the most common complaint, but the pain may mimic peritonitis, pelvic inflammatory disease, pneumonia, myocardial infarction, pericarditis, or cholecystitis.[62] [80] [81] Eighty percent have clinical signs of a soft-tissue infection, with localized swelling or erythema with subsequent ecchymoses and skin sloughing progressing to necrotizing fasciitis or myositis in 70% of cases.[40] Gangrene may also be present.

Staphylococcal TSS should be considered in menstruating patients who have used tampons. However, suspicion should not be limited to only these patients, as nonmenstruating patients can develop staphylococcal TSS.[20][21]

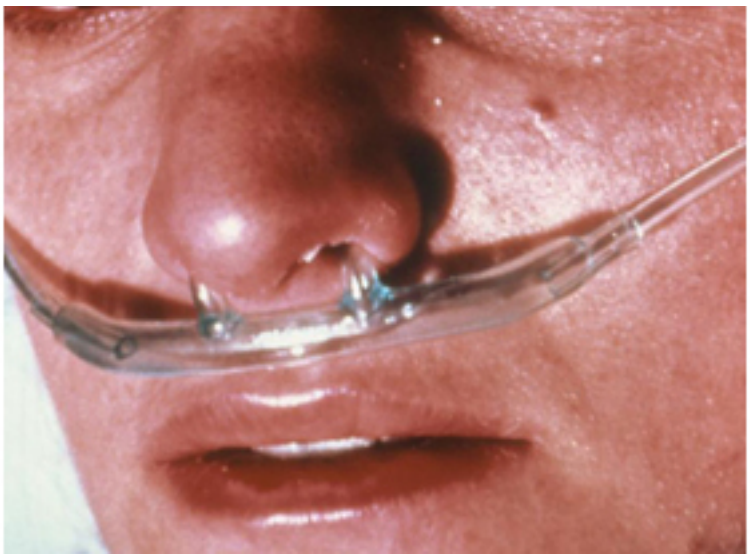
In both streptococcal and staphylococcal infections, fever is the most common presenting sign, although hypothermia can be associated with shock.[62] Nonspecific signs and symptoms on presentation, such as fever, chills, nausea, vomiting, diarrhea, and myalgias, are present in 20% of patients, typically associated with toxin production.[67] A diffuse, erythematous rash develops in 10% of patients with streptococcal TSS. In staphylococcal disease, the maculopapular rash desquamates in 1 to 2 weeks and is often seen initially on the palms and soles. Half of all patients are normotensive on admission, but hypotension and shock will usually develop in the following 4 to 8 hours.[62] Other signs and symptoms of shock and hypoperfusion can be present, such as mental status changes and oliguria.

Myocarditis, peritonitis, and endophthalmitis may be present in both streptococcal and staphylococcal infections. Myocarditis can manifest as chest pain, dyspnea, orthopnea, syncope, fatigue, and palpitations. Findings can include signs of cardiac failure, tachycardias, or arrhythmias. Patients with peritonitis may present with severe abdominal pain with rebound tenderness and guarding on abdominal exam.



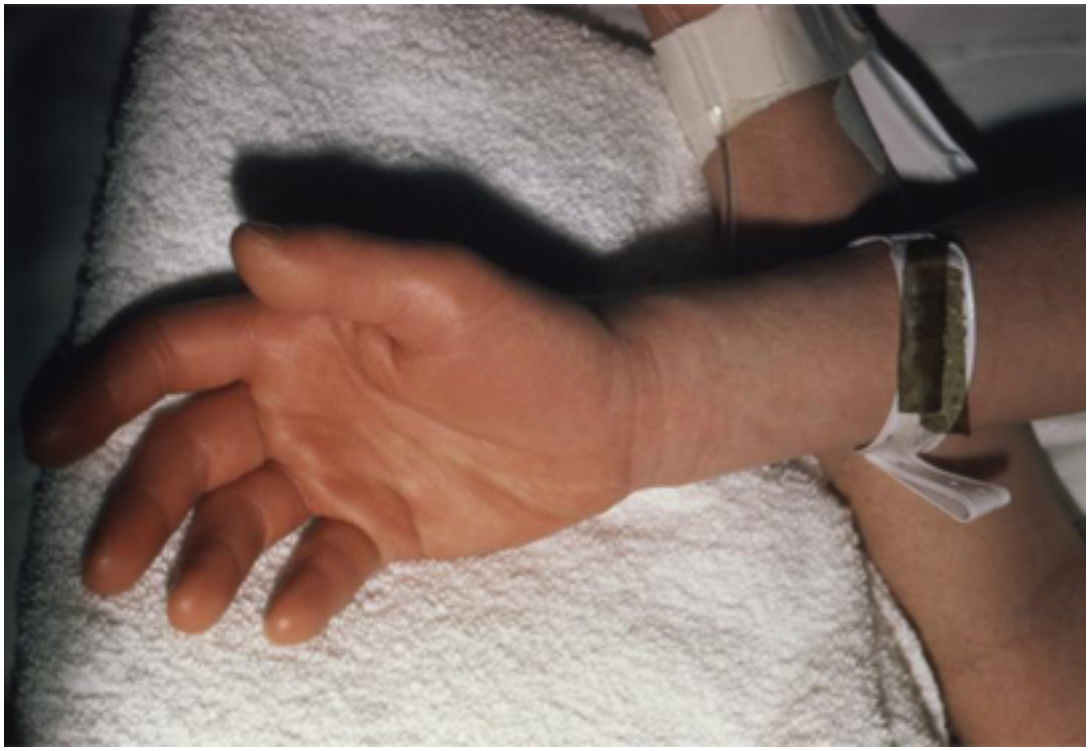
Subtle desquamation of the finger tips of the left hand caused by toxic shock syndrome

From the CDC and the Public Health Image Library



Patient with facial erythematous rash due to toxic shock syndrome

From the CDC and the Public Health Image Library



Rash and subcutaneous edema of the right hand due to toxic shock syndrome

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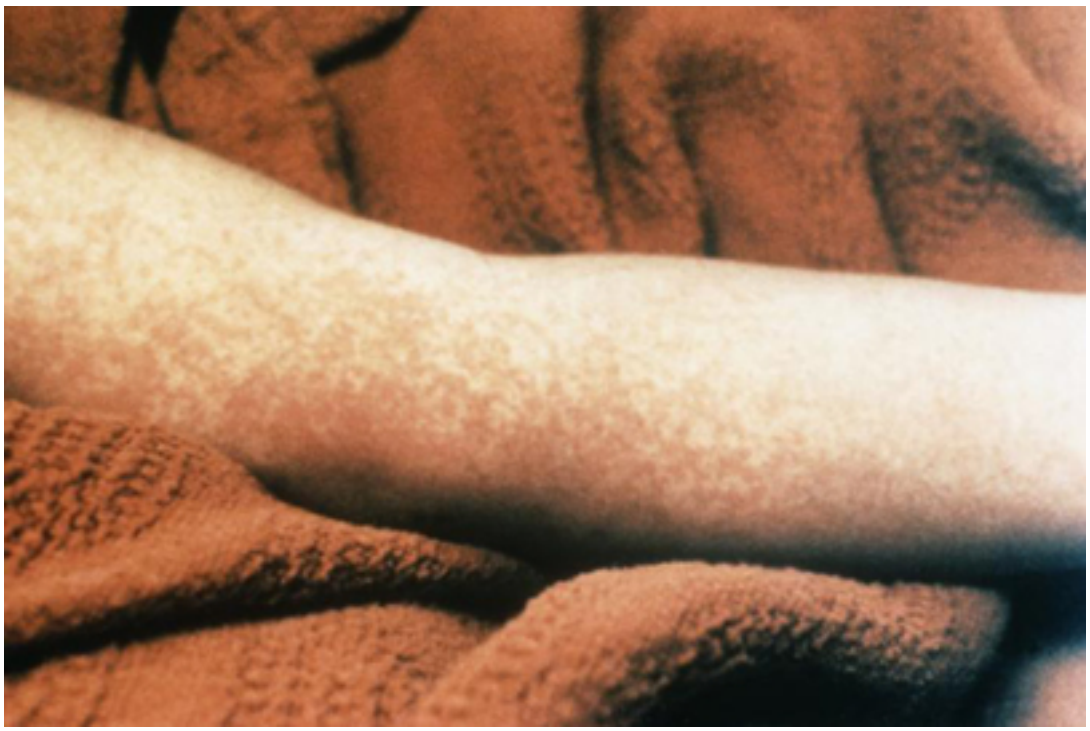
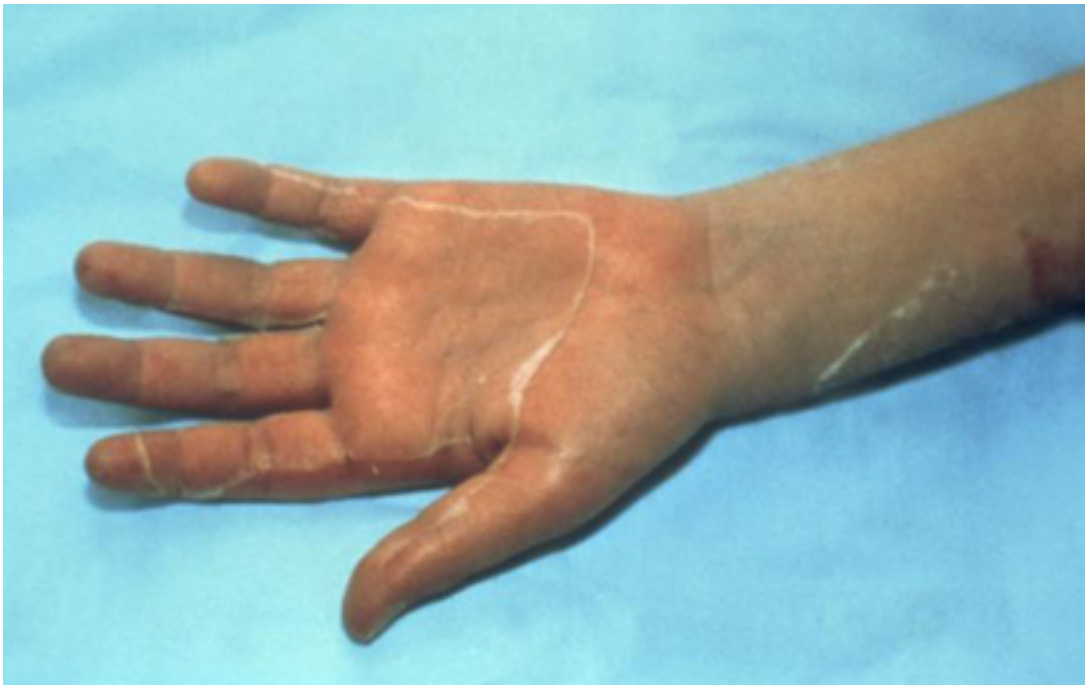


Patient displaying a morbilliform rash (resembling measles) resulting from toxic shock syndrome, 3 to 5 days after onset

From the CDC and the Public Health Image Library



Marked desquamation of the left palm due to toxic shock syndrome, which develops late in the disease

From the CDC and the Public Health Image Library

Risk stratification: identifying patients at risk of deterioration due to organ dysfunction

Early identification of sepsis relies on the systematic evaluation of patients presenting with presumed infection to identify those at risk of deterioration due to organ dysfunction.

Several approaches have been proposed for the quick and pragmatic evaluation of risk of deterioration in everyday clinical practice without the need to await laboratory investigations. Recommendations vary among hospitals and countries. Further research is required to determine the optimal approach, which includes early warning scores (e.g., the National Early Warning Score 2 [NEWS2] developed in the UK or the Modified Early Warning Score [MEWS]), or the use of a risk stratification system as recommended by various guideline groups in the US and UK.[82] [83] [84] [85] [86] These scores typically incorporate physiologic variables such as heart rate and blood pressure, and they can easily be calculated at the bedside. None have been evaluated specifically for TSS.

Investigations

The following investigations should be performed on all patients:

- Microscopy and culture on normally sterile sites (blood, cerebrospinal fluid, pleural or peritoneal fluid, tissue, or throat) may be positive for group A streptococcus or *Staphylococcus aureus* . However, of patients with streptococcal TSS, 60% have positive blood cultures, and of patients with staphylococcal TSS, <5% have positive blood cultures.[40]
- CBC and differential show leukocytosis, anemia, and thrombocytopenia.[62]
- Renal function: elevated BUN, creatinine, and hemoglobinuria are signs of renal failure. Precedes hypotension in 40% to 50% of patients with streptococcal disease.[43]
- Liver function: elevation of bilirubin or transaminases more than twice the normal upper limit.[2]

- Sodium, phosphorus, albumin, and calcium: commonly low on admission with streptococcal disease and throughout the clinical course.
- Lactic acid: elevated in severe sepsis and septic shock.
- Elevated creatine kinase (CK) suggests necrotizing fasciitis or myositis. CK may also be elevated in staphylococcal TSS.
- Coagulation profile: shows increased prothrombin and partial thromboplastin times in staphylococcal disease in conjunction with disseminated intravascular coagulation (DIC); fibrinogen: may be low in the setting of DIC.
- Acute and convalescent staphylococcal antibody testing: positive results may support the diagnosis of staphylococcal TSS.
- Specific testing of streptococcal exotoxin serotypes is possible, but these tests are not routinely available in most hospitals.

Imaging

Chest x-ray should be performed after initial blood and culture workup and may show diffuse bilateral interstitial and alveolar infiltrates consistent with acute respiratory distress syndrome in both streptococcal and staphylococcal disease.

Clinicians should have a low threshold for obtaining definitive imaging to determine the source of infection, because a focus of infection can be subtle in TSS.

History and exam

Key diagnostic factors

severe diffuse or localized pain in an extremity (common)

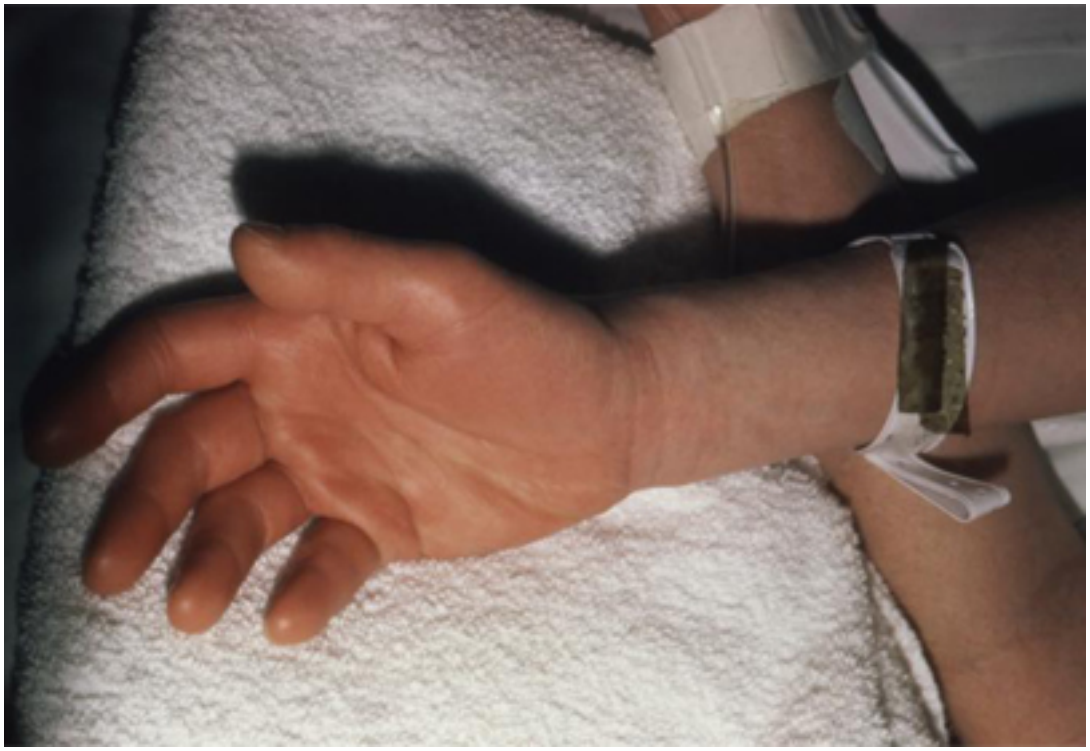
- The most common initial presenting symptom in most patients with streptococcal disease. This is typically out of proportion to the examination and associated with evidence of systemic toxicity.

fever (common)

- The most common early sign of streptococcal and staphylococcal disease, although hypothermia can be seen in patients with shock.[62]

localized swelling or erythema (common)

- Clinical signs of local tissue infection are seen in 80% of patients with streptococcal infections, and 70% of these have subsequent ecchymoses, skin sloughing, and, finally, myositis and necrotizing fasciitis.[40] Gangrene may also develop.
- Diffuse erythroderma involving the skin and mucous membranes may develop within the first 48 hours in staphylococcal disease, particularly of the palms and soles. In postoperative staphylococcal disease, the erythema is often more severe around the surgical wound site, though it may be subtle. In more severe staphylococcal cases, ulcerations, vesicles, and bullae can develop.



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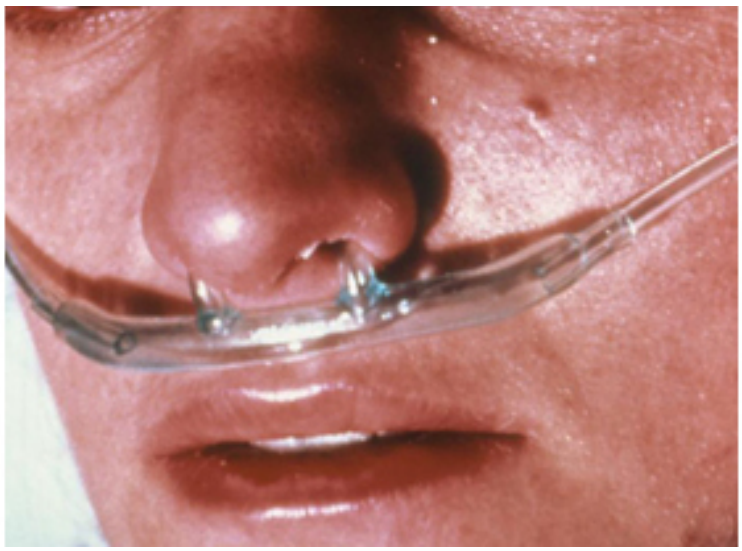


Patient with facial erythematous rash due to toxic shock syndrome

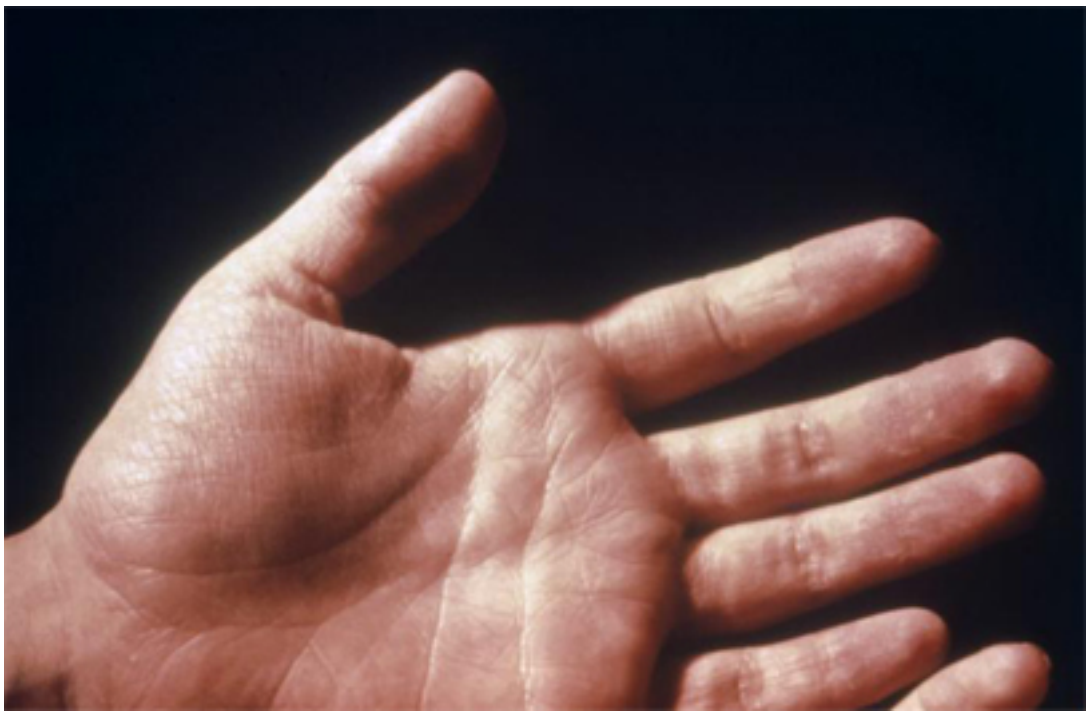
From the CDC and the Public Health Image Library

hypotension (common)

- In streptococcal and staphylococcal infections, half of all patients may be normotensive on admission but develop hypotension in the subsequent 4-8 hours.[62]
- Hypotension reflects hypovolemia, hypoperfusion, and/or severe sepsis with massive cytokine release by the toxins.

diffuse, scarlatina-like erythematous rash (uncommon)

- Seen in 10% patients with streptococcal disease, usually initially of an extremity.[67] Rash may desquamate later.[2]
- In staphylococcal disease, the maculopapular rash desquamates in 1 to 2 weeks and is often seen initially on the palms and soles.



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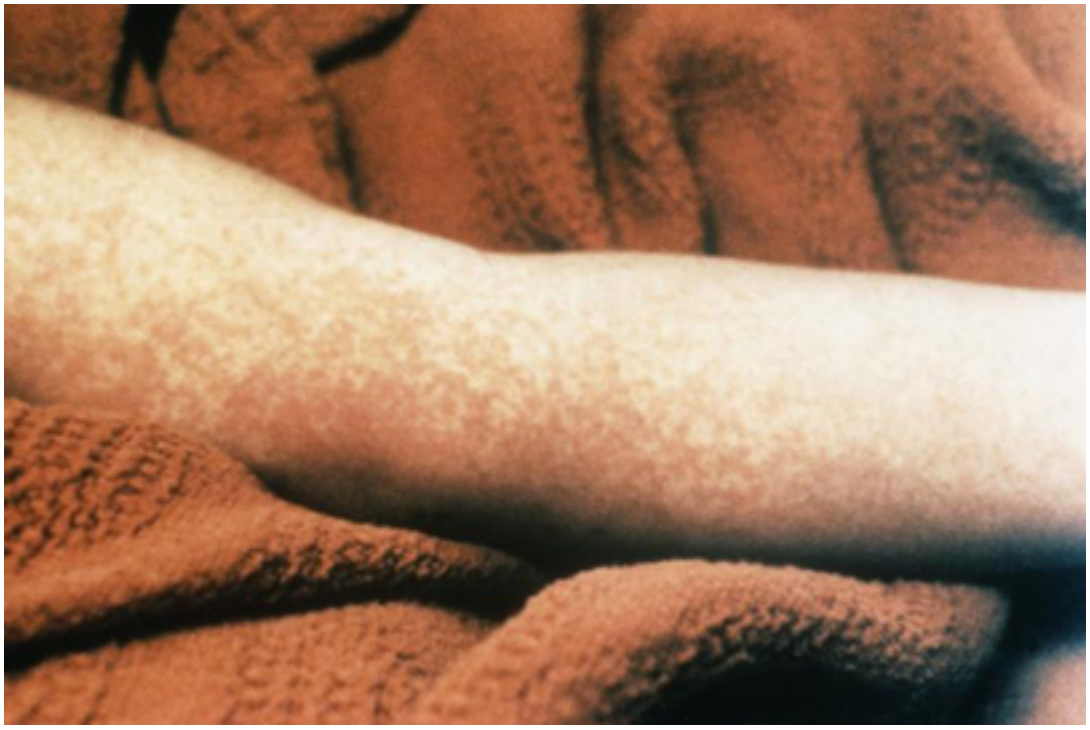

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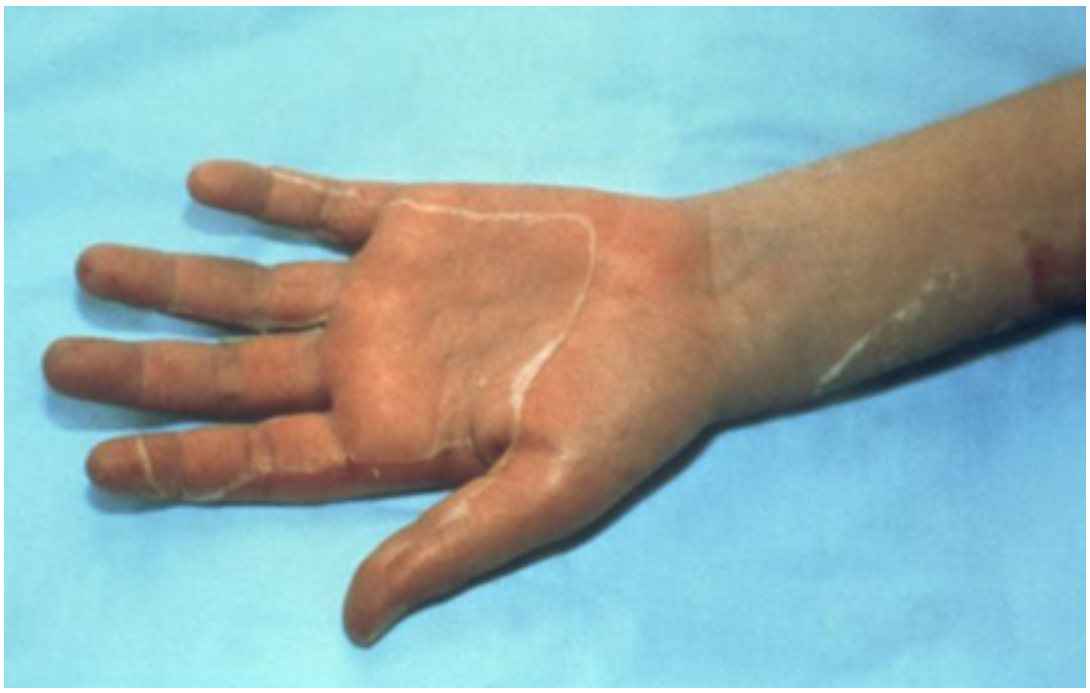

Marked desquamation of the left palm due to toxic shock syndrome, which develops late in the disease

From the CDC and the Public Health Image Library

Other diagnostic factors

acute mental status changes (common)

- Signs of cerebral hypoperfusion and edema with subsequent confusion, agitation, and change in level of consciousness can occur in both streptococcal and staphylococcal infections.

influenza-like symptoms (uncommon)

- Chills, myalgias, nausea, vomiting, and diarrhea are present in 20% at presentation.[67]

muscular tenderness and weakness (uncommon)

- Features of myositis.

gastrointestinal symptoms (uncommon)

- Part of a range of symptoms seen in patients with streptococcal and staphylococcal infections who do not present with soft-tissue findings.
- Patients may present with severe abdominal pain with rebound tenderness and guarding on abdominal exam. Nausea, vomiting, and diarrhea may be present; associated with toxin production.

features of myocarditis (uncommon)

- Part of a range of symptoms seen in patients with streptococcal and staphylococcal infections who do not present with soft-tissue findings.
- Symptoms may include chest pain, dyspnea, orthopnea, syncope, fatigue, and palpitations.
- Findings can include signs of cardiac failure, tachycardias, or arrhythmias.

endophthalmitis (uncommon)

- Part of a range of symptoms seen in patients with streptococcal and staphylococcal infections who do not present with soft-tissue findings.

hypothermia (uncommon)

- Fever is the most common early sign of streptococcal and staphylococcal disease, although hypothermia can be seen in patients with shock.[62]

Risk factors

Strong

diabetes mellitus

- Associated with an increased risk: in a surveillance study performed over 1 year in 4 US states, 21.6% of patients with streptococcal toxic shock syndrome (TSS) had diabetes.[61]

alcohol-use disorder

- Associated with an increased risk: in a surveillance study performed over 1 year in 4 US states, 16.8% of patients with streptococcal TSS reported alcohol misuse.[61]

minor trauma and injuries with bruising, hematoma formation, or muscle strain

- Serve as a portal of entry and predispose to infection.[62]

surgical procedures (e.g., vaginal delivery, breast reconstruction, cesarean section, hysterectomy, liposuction, bunionectomy)

- Case reports demonstrate an association between vaginal deliveries, cesarean deliveries, and breast reconstruction surgery and group A streptococcal infections.[63] [64] [65] [66] [67] Postoperative TSS typically occurs within 10 days of surgery.[68]

prolonged use (>6 hours) of single tampon

- Menstrual staphylococcal TSS is associated with tampon use over 6 hours, overnight use, and failing to follow tampon insertion instructions.[69] [70]
- Tampon use does not increase the likelihood of staphylococcal colonization but increases the risk of staphylococcal TSS by enhancing the production of toxic shock syndrome toxin-1 (TSST-1).

use of highly absorbent tampons

- Although highly absorbent tampons have been withdrawn from the market, tampon use remains a risk factor for staphylococcal TSS.[4][71] [72]
- Tampons containing glycerol monolaurate (GML) reduce *Staphylococcus aureus* exotoxin production. Studies suggest that GML added to tampons provides additional safety relative to menstrual toxic shock.[73]

Weak

nonsteroidal anti-inflammatory drug (NSAID) use

- Association may be from use of NSAIDs for relief of minor trauma, or through inhibition of neutrophils and cytokine release by NSAIDs.[62] [63] [74]

use of contraceptive sponges, diaphragms, and IUDs

- May be risk factors for nonmenstrual staphylococcal TSS.[22]

untreated strep throat

- TSS is a rare complication of streptococcal pharyngitis (strep throat) in adults.[75] Household contacts of young children with group A streptococcal infection are at increased risk of infection.[30] Patients with confirmed strep throat should follow national recommendations to prevent transmission. The Centers for Disease Control and Prevention (CDC) in the US recommends that patients stay at home (from work, school, or daycare) until they are afebrile and at least 12-24 hours after commencing antibiotic treatment.[76] UK guidance recommends that patients with strep throat isolate for at least 24 hours after the start of treatment with an appropriate antibiotic.[77]

Tests

1st test to order

Test	Result
microscopy and culture (blood, wound, fluid, tissue) • Early diagnosis of streptococcal infections in most patients is made with Gram stain of the infected fascia or muscle, obtained by surgical debridement. This reveals gram-positive cocci in pairs and chains. Growth from blood cultures usually occurs in 8-24 hours, and blood cultures are positive in 60% of streptococcal cases.[40] • Bacteremia with positive blood cultures is rare in staphylococcal TSS.[4][40] [87] *S aureus* is isolated from mucus or wound sites in 80% of patients with staphylococcal disease.[12]	**positive for group A streptococcus or *Staphylococcus aureus***
CBC • Increased WBC count and anemia and decreased platelet count are sensitive but not specific for the diagnosis of streptococcal or staphylococcal TSS.	**leukocytosis with a left shift; anemia; thrombocytopenia with platelets <100 x 10^3/microliter**
coagulation profile • Including prothrombin time, partial thromboplastin time, and fibrinogen.	**in staphylococcal disease in conjunction with DIC: prothrombin time/partial thromboplastin time may be prolonged; fibrinogen may be low**
serum BUN and creatinine • Elevated BUN and creatinine, and hemoglobinuria are signs of renal failure. Precedes hypotension in 40% to 50% of patients with streptococcal disease.[43]	**elevated**
urinalysis • Elevated BUN and creatinine, and hemoglobinuria are signs of renal failure. Precedes hypotension in 40% to 50% of patients with streptococcal disease.[43]	**hemoglobinuria**
LFTs • Shows elevation of bilirubin or transaminases more than twice the normal upper limit.	**elevated transaminases and bilirubin**
creatine kinase (CK) • Elevated CK suggests necrotizing fasciitis or myositis. CK may also be elevated in staphylococcal TSS.	**elevated in necrotizing fasciitis or myositis and in some staphylococcal disease**
serum calcium • Hypocalcemia is found on admission and throughout the course of streptococcal disease.	**low in streptococcal disease**
serum sodium • Hyponatremia may be present on admission and throughout the course of streptococcal disease.	**low in streptococcal disease**

Test	Result
serum phosphorus • Hypophosphatemia may be present on admission and throughout the course of streptococcal disease.	**low in streptococcal disease**
serum albumin • Hypoalbuminemia is found on admission and throughout the course of streptococcal disease.	**low in streptococcal disease**
serum lactic acid • Lactic acidosis is seen in sepsis resulting from poor tissue perfusion or diminished oxygenation of blood.	**elevated in severe sepsis and septic shock**

Other tests to consider

Test	Result
Staphylococcus aureus antibody testing • Diagnosis of staphylococcal TSS is supported by acute and convalescent antibody testing.	**presence of *S aureus* in the absence of an acute-phase antibody**
chest x-ray • Consistent with acute respiratory distress syndrome.	**diffuse bilateral interstitial and alveolar infiltrates**

Emerging tests

Test	Result
serotyping • Diagnosis of TSS with presence of phenotypic and genotypic characteristics: M-protein type, serum opacity factor production, protease production, the presence of streptococcal pyrogenic exotoxin (Spe) genes A, B, and C, and in vitro production of SpeA and SpeB. However, these tests are not routinely available in most hospitals.	**evidence of streptococcal exotoxins**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Gram-negative sepsis	• Absence of desquamating rash. • Renal failure more commonly develops subsequent to hypotension.[40]	• Cultures positive for gram-negative organism (e.g., *Escherichia coli* , *Klebsiella pneumoniae* , and *Pseudomonas aeruginosa*).
Rocky Mountain spotted fever (RMSF)	• Severe headache and petechial rash are present in most patients. • Rapid progression of disease.	• Positive serology using indirect immunofluorescence assay detects increased IgM levels at the end of the first week of illness and increased IgG levels by 7-10 days after the onset of illness in RMSF. • Enzyme-linked immunosorbent assay (ELISA), latex agglutination, and dot immunoassays can also be used in the diagnosis of RMSF.
Acute meningococcemia	• Petechial rash, purpura, and meningitis may be seen.	• Cerebrospinal fluid (CSF) or blood culture with *Neisseria meningitides* .
Pneumonia	• Symptoms of respiratory distress and crackles/rales on auscultation.	• Chest x-ray shows infiltration, consolidation, effusions, and cavitation. • Oximetry shows hypoxia and respiratory acidosis.
Meningitis	• Headache and neck stiffness.	• Positive CSF culture.
Leptospirosis	• There may be no difference in signs and symptoms, although patients may be asymptomatic between phases of the disease.	• Sensitivity of blood cultures is low, and culture isolation requires special media and up to 6 weeks of incubation. • Indirect hemagglutination assay and IgM dot ELISA are specific for acute infections from leptospirosis.[88]
Heat stroke	• Nonspecific signs and symptoms such as fever, hypovolemia, hypotension, confusion, and erythema can occur in both entities.	• History of heat exposure is essential to the diagnosis.
Adrenal crisis	• Cutaneous hyperpigmentation,	• Serum cortisol level <20 micrograms/dL (<552

Condition	Differentiating signs / symptoms	Differentiating tests
	refractory hypotension, and hypoglycemia may be present; hyponatremia and hyperkalemia may be present; desquamation is absent.	nanomols/L), followed by adrenocorticotrophic hormone (ACTH) stimulation test.

Criteria

The diagnostic criteria for streptococcal and staphylococcal TSS were established for research purposes, and the sensitivity and specificity of these criteria have not been validated in the clinical setting. Optimizing patient outcomes often requires treatment prior to the patient meeting the CDC case definition.

CDC case definition: streptococcal toxic-shock syndrome (STSS)[2]

Clinical manifestations:

- Hypotension: systolic BP ≤90 mmHg for adults or less than fifth percentile by age for children aged less than 16 years
- Multisystem involvement with 2 or more of the following:
    - renal impairment (creatinine ≥2 mg/dL for adults or greater than or equal to twice the upper limit of normal for age; in patients with pre-existing renal disease, a greater than 2-fold elevation over the baseline level)
    - coagulopathy (platelets ≤100,000/mm^3, or disseminated intravascular coagulation defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products)
    - hepatic impairment (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 pre-existing liver disease, a greater than 2-fold 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 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.

Laboratory criteria:

- Isolation of group A Streptococcus.

Probable case: a case that meets the clinical case definition in the absence of another identified etiology for the illness and with the isolation of group A Streptococcus from a nonsterile site.

Confirmed case: 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 [CSF] or, less commonly, joint, pleural, or pericardial fluid).

CDC case definition: toxic-shock syndrome (TSS) other than streptococcal[3]

Clinical manifestations:

- Fever: temperature ≥102.0°F (38.9°C)
- Rash (diffuse macular erythroderma)
- Desquamation 1 to 2 weeks after onset of rash
- Hypotension: systolic BP ≤90 mmHg for adults or less than fifth percentile by age for children aged less than 16 years
- Multisystem involvement with 3 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 (BUN or creatinine at least twice the upper limit of normal for laboratory, or urinary sediment with pyuria 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 <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 blood or CSF cultures (blood culture may be positive for *Staphylococcus aureus*)
- Negative serologies for Rocky Mountain spotted fever, leptospirosis, or measles.

Probable case: a case which meets the laboratory criteria and in which 4 or 5 of the clinical findings are present.

Confirmed case: a case which meets the laboratory criteria and in which all 5 of the clinical findings are present (including desquamation, unless the patient dies before desquamation).

Approach

The mainstay of treatment for both streptococcal and staphylococcal toxic shock syndrome (TSS) is supportive and is focused on specific management of the complications and sequelae associated with severe sepsis and multiorgan failure.

Supportive therapy

Early and immediate treatment should include aggressive fluid resuscitation, empiric antibiotic therapy, vasopressor support for refractory hypotension, hemodynamics optimization, source control, and surgical debridement. Massive fluid resuscitation is often needed because of the diffuse capillary leak phenomenon and the refractory hypotension. The use of the vasopressor dopamine has been associated with higher mortality and more arrhythmic events compared with norepinephrine administration.[89] Intravenous corticosteroids should be administered for patients with ongoing vasopressor requirements or vasopressor-refractory septic shock.[82]

General intensive care preventive measures include stress ulcer prophylaxis with H2 antagonists or proton-pump inhibitors, deep venous thrombosis prophylaxis with heparin or low-molecular weight heparin, compression stockings, and enteral nutrition.[82] [90] [91] The American Diabetes Association recommends a general glucose goal of 140-180 mg/dL in most critically ill patients with diabetes, preferably by using an insulin infusion protocol; however, more stringent control of blood glucose, in the range of 110-140 mg/dL, may be appropriate in a selected population of critically ill patients (such as critically ill patients undergoing surgery), if that can be achieved without the risk of hypoglycemia.[92] The Surviving Sepsis Campaign recommends the use of validated insulin infusion protocols targeting a blood glucose level of <180 mg/dL.[82]

Patients with evidence of acute respiratory distress syndrome should receive lung-protective ventilation using maximum plateau pressures <30 cm H_2O and permissive hypercapnia to limit pulmonary damage.[93]

The patient should be promptly transferred to an intensive care unit for treatment.

Surgical debridement

Early and immediate surgical debridement should be considered in most patients with streptococcal TSS (i.e., those who present with fever, pain, soft-tissue swelling, and/or vesicle and bullae formation) with an appropriate surgical focus of infection. Aggressive surgical debridement of infected tissue including fascia is imperative and mandatory if a site of potential infection is identified. Repeated and sequential operative and bedside debridements of infected tissue are often needed, particularly if necrotizing fasciitis is present in streptococcal disease.[62]

Source control is mandatory, including drainage of any existing abscesses and removal of the tampon, if present.

Delaying surgery until the patient develops systemic toxicity and definitive evidence of necrotizing fasciitis or myositis increases mortality. In addition to surgical debridements, fasciotomy or amputation may be needed to halt the progression of the disease.

Antibiotic therapy

Definitive randomized, controlled studies on antibiotic therapy for streptococcal and staphylococcal TSS are not available. However, antibiotics remain a key component of therapy.

Suspected TSS

- Antibiotics should be initiated empirically before culture reports.
- Recommended empiric therapy is clindamycin plus 1 of the following: a carbapenem (i.e., imipenem/cilastatin or meropenem); a penicillin with a beta-lactamase inhibitor (e.g., piperacillin/tazobactam); or vancomycin (in patients with penicillin allergies). In patients with suspected staphylococcal TSS, clindamycin plus vancomycin is recommended.

Confirmed streptococcal TSS

- On the basis of animal studies, most experts recommend combination therapy with penicillin G and clindamycin.[94] [95] Beta-lactam antibiotics are effective at treating group A streptococcal (*Streptococcus pyogenes*) infection. Vancomycin may be used in place of penicillin G in patients who are allergic to penicillin.
- Treatment failure with penicillin has been reported, especially when organisms are present in large numbers.[96] Also, more aggressive group A streptococcal infections (i.e., necrotizing fasciitis, empyema, burn wound sepsis, subcutaneous gangrene, and myositis) respond less well to penicillin.[40] [97][98]
- Clindamycin as an alternative to penicillin has some advantages, especially because its efficacy is not affected by the size of the inoculum. It also inhibits protein synthesis and the synthesis of both M protein and streptococcal pyrogenic exotoxins. However, clindamycin should not be used alone because some strains of group A streptococcus are clindamycin resistant.[99] Increasing resistance of group A streptococcal infections to clindamycin has been seen in Europe, but resistance in the US has been reported in <1% of cases.[100] [101]

Confirmed streptococcal TSS: adjunctive therapy

- The addition of intravenous immune globulin (IVIG) may also be considered, but efficacy data are conflicting. Some observational studies suggest modest benefit. However, one small double-blind placebo-controlled trial (prematurely terminated because of slow patient recruitment) and one large retrospective analysis (of patients with debrided necrotizing fasciitis with shock caused by group A streptococcus or *Staphylococcus aureus*) found that adjunctive IVIG was not associated with improved survival.[102] [103] [104] [105] [106] One meta-analysis including five studies found a potential mortality reduction with IVIG in those receiving clindamycin, but the results are controversial due to the inclusion of a randomized controlled trial among observational studies.[107]
- Infectious Diseases Society of America (IDSA) guidelines do not include a recommendation regarding the use of IVIG in patients with necrotizing fasciitis with streptococcal toxic shock syndrome, citing the need for additional efficacy studies.[108]
- Consensus recommendations from the World Society of Emergency Surgery and the Surgical Infection Society Europe advocate consideration of IVIG in patients with necrotizing fasciitis caused by group A streptococcus, while recognizing that the use of IVIG for treating necrotizing soft tissue infections remains controversial.[109] [110]

Confirmed staphylococcal TSS

- Antistaphylococcal antibiotics are needed to eradicate the organism and to prevent recurrences.[12]

- If the organism is identified as methicillin-sensitive *Staphylococcus aureus* , clindamycin plus oxacillin or nafcillin is recommended. Vancomycin may be used in place of oxacillin or nafcillin in patients allergic to penicillin.
- If methicillin-resistant *S aureus* is identified, combination therapy with clindamycin plus vancomycin or linezolid should be given. There is *in vitro* evidence to suggest that linezolid can inhibit, and in some cases stimulate, toxin production by organisms involved in streptococcal or staphylococcal toxic shock syndrome. However, more research is needed to establish the clinical relevance of these findings.[111]
- Treatment with topical mupirocin has been suggested to eradicate a positive nasal culture for *Staphylococcus* , but there are no data to support this practice.

Patients with clinical TSS without confirmed cultures should receive continued empiric therapy. Additional antibiotics may be needed for treating superinfections that may occur.

Treatment duration should be individualized, especially if there is a deep-seated infection. If bacteremic, the patient should be treated for 14 days. Usually treatment is for 14 days after the last positive culture is obtained at surgery.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial		(summary)
suspected toxic shock syndrome		
	1st	**supportive therapies**
	plus	**empiric antibiotic therapy**
	adjunct	**surgical debridement**

Acute (summary)		
confirmed streptococcal toxic shock syndrome		
	1st	**clindamycin + penicillin G or vancomycin**
	plus	**intensive care unit support**
	adjunct	**intravenous immune globulin (IVIG)**
confirmed staphylococcal toxic shock syndrome: methicillin-sensitive		
	1st	**clindamycin + oxacillin or nafcillin or vancomycin**
	plus	**intensive care unit support**
	adjunct	**topical mupirocin**
confirmed staphylococcal toxic shock syndrome: methicillin-resistant		
	1st	**clindamycin + vancomycin or linezolid**
	plus	**intensive care unit support**
	adjunct	**topical mupirocin**
clinical toxic shock syndrome without confirmed cultures		
	1st	**continued empiric antibiotic therapy**
	plus	**intensive care unit support**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial

suspected toxic shock syndrome

1st **supportive therapies**

» Early and immediate treatment should include aggressive fluid resuscitation, empiric antibiotic therapy, vasopressor support for refractory hypotension, hemodynamics optimization, source control, and surgical debridement.

» Massive fluid resuscitation is often needed because of the diffuse capillary leak phenomenon and the refractory hypotension. The use of the vasopressor dopamine has been associated with higher mortality and more arrhythmic events compared with norepinephrine administration.[89] Intravenous corticosteroids should be administered for patients with ongoing vasopressor requirements or vasopressor-refractory septic shock.[82] Consult a specialist for guidance on suitable vasopressor regimens and doses.

» Source control is mandatory, including drainage of any existing abscesses and removal of the tampon, if present.

» The patient should be promptly transferred to an intensive care unit for treatment.

plus **empiric antibiotic therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» clindamycin: 900 mg intravenously every 8 hours

--AND--

» imipenem/cilastatin: 500 mg intravenously every 6 hours
Dose refers to imipenem component.

-or-
» meropenem: 1 g intravenously every 8 hours
-or-
» piperacillin/tazobactam: 4.5 g intravenously every 6 hours
Dose consists of 4 g piperacillin plus 0.5 g tazobactam.

MANAGEMENT

Initial

-or-

» vancomycin: 15-20 mg/kg intravenously every 12 hours

» Antibiotics should be initiated empirically before culture reports.

» Recommended empiric therapy is clindamycin plus 1 of the following: a carbapenem (i.e., imipenem/cilastatin or meropenem); a penicillin with a beta-lactamase inhibitor (e.g., piperacillin/tazobactam); or vancomycin (in patients with penicillin allergies).

» In patients with suspected staphylococcal toxic shock syndrome, clindamycin plus vancomycin is recommended.

» Additional antibiotics may be needed for treating superinfections that may occur.

adjunct **surgical debridement**

Treatment recommended for SOME patients in selected patient group

» Early and immediate surgical debridement should be considered in most patients with suspected streptococcal toxic shock syndrome (i.e., those who present with fever, pain, soft-tissue swelling, and/or vesicle and bullae formation) with an appropriate surgical focus of infection.

» Aggressive surgical debridement of infected tissue including fascia is imperative and mandatory if a site of potential infection is identified. Repeated and sequential operative and bedside debridements of infected tissue are often needed, particularly if necrotizing fasciitis is present in streptococcal disease.[62]

» In addition to surgical debridements, fasciotomy or amputation may be needed to halt the progression of the disease.

Acute

confirmed streptococcal toxic shock syndrome

1st **clindamycin + penicillin G or vancomycin**

Primary options

» clindamycin: 900 mg intravenously every 8 hours

--AND--

» penicillin G sodium: 4 million units intramuscularly every 4 hours

-or-

» vancomycin: 15-20 mg/kg intravenously every 12 hours

» Most experts recommend combination therapy with penicillin G plus clindamycin.[94] [95]

» Vancomycin may be used in place of penicillin G in patients who are allergic to penicillin.

» Additional antibiotics may be needed for treating superinfections that may occur.

» Treatment duration should be individualized, especially if there is a deep-seated infection. If bacteremic, the patient should be treated for 14 days. Usually treatment is for 14 days after the last positive culture is obtained at surgery.

plus **intensive care unit support**

Treatment recommended for ALL patients in selected patient group

» General intensive care preventive measures include stress ulcer prophylaxis with H2 antagonists or proton-pump inhibitors, deep venous thrombosis prophylaxis with heparin or low-molecular weight heparin, compression stockings, and enteral nutrition.[82] [90] [91]

» The American Diabetes Association recommends a general glucose goal of 140-180 mg/dL in most critically ill patients with diabetes, preferably by using an insulin infusion protocol; however, more stringent control of blood glucose, in the range of 110-140 mg/dL, may be appropriate in a selected population of critically ill patients (such as critically ill patients undergoing surgery), if that can be achieved without the risk of hypoglycemia.[92] The Surviving Sepsis Campaign recommends the use of validated insulin infusion protocols targeting a blood glucose level of <180 mg/dL.[82]

Acute

» Patients with evidence of acute respiratory distress syndrome should receive lung-protective ventilation using maximum plateau pressures <30 cm H_2O and permissive hypercapnia to limit pulmonary damage.[93]

» Initial supportive therapy such as aggressive fluid resuscitation, vasopressor support for refractory hypotension, hemodynamics optimization, and surgical debridement initiated before confirmation of the cause must be continued. Massive fluid resuscitation is often needed because of the diffuse capillary leak phenomenon and the refractory hypotension. The use of the vasopressor dopamine has been associated with higher mortality and more arrhythmic events compared with norepinephrine administration.[89] Intravenous corticosteroids should be administered for patients with ongoing vasopressor requirements or vasopressor-refractory septic shock.[82] Consult a specialist for guidance on suitable vasopressor regimens and doses.

» Source control is mandatory, including drainage of any existing abscesses and removal of the tampon, if present.

adjunct **intravenous immune globulin (IVIG)**

Treatment recommended for SOME patients in selected patient group

Primary options

» immune globulin (human): 1 g/kg intravenously on day 1, followed by 0.5 g/kg on days 2 and 3; or 2 g/kg intravenously as a single dose
Dose regimens may vary; consult specialist for further guidance on dose.

» The addition of IVIG may be considered for the treatment of streptococcal toxic shock syndrome, although data on efficacy are conflicting.[108] [109] [110]

confirmed staphylococcal toxic shock syndrome: methicillin-sensitive

1st **clindamycin + oxacillin or nafcillin or vancomycin**

Primary options

» clindamycin: 900 mg intravenously every 8 hours

--AND--

» oxacillin: 2 g intravenously every 4 hours

Acute

-or-
» nafcillin: 2 g intravenously every 4 hours
-or-
» vancomycin: 15-20 mg/kg intravenously every 12 hours

» If the organism is identified as methicillin-sensitive *Staphylococcus aureus* , clindamycin plus oxacillin or nafcillin is recommended.

» Vancomycin may be used in place of oxacillin or nafcillin in patients who are allergic to penicillin.

» Additional antibiotics may be needed for treating superinfections that may occur.

» Treatment duration should be individualized, especially if there is a deep-seated infection. If bacteremic, the patient should be treated for 14 days. Usually treatment is for 14 days after the last positive culture is obtained at surgery.

plus **intensive care unit support**

Treatment recommended for ALL patients in selected patient group

» General intensive care preventive measures include stress ulcer prophylaxis with H2 antagonists or proton-pump inhibitors, deep venous thrombosis prophylaxis with heparin or low-molecular weight heparin, compression stockings, and enteral nutrition.[82] [90] [91] The American Diabetes Association recommends a general glucose goal of 140-180 mg/dL in most critically ill patients with diabetes, preferably by using an insulin infusion protocol; however, more stringent control of blood glucose, in the range of 110-140 mg/dL, may be appropriate in a selected population of critically ill patients (such as critically ill patients undergoing surgery), if that can be achieved without the risk of hypoglycemia.[92] The Surviving Sepsis Campaign recommends the use of validated insulin infusion protocols targeting a blood glucose level of <180 mg/dL.[82]

» Patients with evidence of acute respiratory distress syndrome should receive lung-protective ventilation using maximum plateau pressures <30 cm H_2O and permissive hypercapnia to limit pulmonary damage.[93]

» Initial supportive therapy such as aggressive fluid resuscitation, vasopressor support for refractory hypotension, hemodynamics optimization, and surgical debridement initiated before confirmation of the cause must be

Acute

continued. Massive fluid resuscitation is often needed because of the diffuse capillary leak phenomenon and the refractory hypotension. The use of the vasopressor dopamine has been associated with higher mortality and more arrhythmic events compared with norepinephrine administration.[89] Intravenous corticosteroids should be administered for patients with ongoing vasopressor requirements or vasopressor-refractory septic shock.[82] Consult a specialist for guidance on suitable vasopressor regimens and doses.

» Source control is mandatory, including drainage of any existing abscesses and removal of the tampon, if present.

adjunct **topical mupirocin**

Treatment recommended for SOME patients in selected patient group

Primary options

» mupirocin topical: (2%) apply to nares twice daily for 5 days

» Treatment with mupirocin has been suggested to eradicate a positive nasal culture for *Staphylococcus* , but there are no data to support this practice.

confirmed staphylococcal toxic shock syndrome: methicillin-resistant

1st **clindamycin + vancomycin or linezolid**

Primary options

» clindamycin: 900 mg intravenously every 8 hours

--AND--

» vancomycin: 15-20 mg/kg intravenously every 12 hours

-or-

» linezolid: 600 mg intravenously every 12 hours

» If MRSA is identified, combination therapy with clindamycin plus vancomycin or linezolid should be given.

» Additional antibiotics may be needed for treating superinfections that may occur.

» Treatment duration should be individualized, especially if there is a deep-seated infection. If bacteremic, the patient should be treated for 14 days. Usually treatment is for 14 days after the last positive culture is obtained at surgery.

Acute

plus **intensive care unit support**

Treatment recommended for ALL patients in selected patient group

» General intensive care preventive measures include stress ulcer prophylaxis with H2 antagonists or proton-pump inhibitors, deep venous thrombosis prophylaxis with heparin or low-molecular weight heparin, compression stockings, and enteral nutrition.[82] [90] [91] The American Diabetes Association recommends a general glucose goal of 140-180 mg/dL in most critically ill patients with diabetes, preferably by using an insulin infusion protocol; however, more stringent control of blood glucose, in the range of 110-140 mg/dL, may be appropriate in a selected population of critically ill patients (such as critically ill patients undergoing surgery), if that can be achieved without the risk of hypoglycemia.[92] The Surviving Sepsis Campaign recommends the use of validated insulin infusion protocols targeting a blood glucose level of <180 mg/dL.[82]

» Patients with evidence of acute respiratory distress syndrome should receive lung-protective ventilation using maximum plateau pressures <30 cm H_2O and permissive hypercapnia to limit pulmonary damage.[93]

» Initial supportive therapy such as aggressive fluid resuscitation, vasopressor support for refractory hypotension, hemodynamics optimization, and surgical debridement initiated before confirmation of the cause must be continued. Massive fluid resuscitation is often needed because of the diffuse capillary leak phenomenon and the refractory hypotension. The use of the vasopressor dopamine has been associated with higher mortality and more arrhythmic events compared with norepinephrine administration.[89] Intravenous corticosteroids should be administered for patients with ongoing vasopressor requirements or vasopressor-refractory septic shock.[82] Consult a specialist for guidance on suitable vasopressor regimens and doses.

» Source control is mandatory, including drainage of any existing abscesses and removal of the tampon, if present.

adjunct **topical mupirocin**

Treatment recommended for SOME patients in selected patient group

Primary options

Acute

» mupirocin topical: (2%) apply to nares twice daily for 5 days

» Treatment with mupirocin has been suggested to eradicate a positive nasal culture for *Staphylococcus* , but there are no data to support this practice.

clinical toxic shock syndrome without confirmed cultures

1st **continued empiric antibiotic therapy**

Primary options

» clindamycin: 900 mg intravenously every 8 hours

--AND--

» imipenem/cilastatin: 500 mg intravenously every 6 hours
Dose refers to imipenem component.

-or-
» meropenem: 1 g intravenously every 8 hours
-or-
» piperacillin/tazobactam: 4.5 g intravenously every 6 hours
Dose consists of 4 g piperacillin plus 0.5 g tazobactam.

-or-
» vancomycin: 15-20 mg/kg intravenously every 12 hours

» Patients with clinical toxic shock syndrome without confirmed cultures should receive continued empiric therapy.

» Additional antibiotics may be needed for treating superinfections that may occur.

» Treatment duration should be individualized, especially if there is a deep-seated infection. If bacteremic, the patient should be treated for 14 days. Usually treatment is for 14 days after the last positive culture is obtained at surgery.

plus **intensive care unit support**

Treatment recommended for ALL patients in selected patient group

» General intensive care preventive measures include stress ulcer prophylaxis with H2 antagonists or proton-pump inhibitors, deep venous thrombosis prophylaxis with heparin or low-molecular weight heparin, compression stockings, and enteral nutrition.[82] [90] [91] The

Acute

American Diabetes Association recommends a general glucose goal of 140-180 mg/dL in most critically ill patients with diabetes, preferably by using an insulin infusion protocol; however, more stringent control of blood glucose, in the range of 110-140 mg/dL, may be appropriate in a selected population of critically ill patients (such as critically ill patients undergoing surgery), if that can be achieved without the risk of hypoglycemia.[92] The Surviving Sepsis Campaign recommends the use of validated insulin infusion protocols targeting a blood glucose level of <180 mg/dL.[82]

» Patients with evidence of acute respiratory distress syndrome should receive lung-protective ventilation using maximum plateau pressures <30 cm H_2O and permissive hypercapnia to limit pulmonary damage.[93]

» Initial supportive therapy such as aggressive fluid resuscitation, vasopressor support for refractory hypotension, hemodynamics optimization, and surgical debridement initiated before confirmation of the cause must be continued. Massive fluid resuscitation is often needed because of the diffuse capillary leak phenomenon and the refractory hypotension. The use of the vasopressor dopamine has been associated with higher mortality and more arrhythmic events compared with norepinephrine administration.[89] Intravenous corticosteroids should be administered for patients with ongoing vasopressor requirements or vasopressor-refractory septic shock.[82] Consult a specialist for guidance on suitable vasopressor regimens and doses.

Emerging

Hyperbaric oxygen

There are no controlled studies, but the use of hyperbaric oxygen was reported in a few patients with group A streptococcal infections. It is unclear whether this therapy is useful.[112] [113]

Primary prevention

Streptococcal toxic shock syndrome

The spread of all types of group A streptococcal infections can be reduced by good hand washing, especially after coughing and sneezing and before preparing foods or eating.[77]

Patients with confirmed strep throat should follow national recommendations to prevent onward transmission. The Centers for Disease Control and Prevention (CDC) in the US recommends that patients stay at home (from work, school, or daycare) until they are afebrile and at least 12-24 hours after commencing antibiotic treatment.[76] UK guidance recommends that patients with strep throat isolate for at least 24 hours after the start of treatment with an appropriate antibiotic.[77]

All wounds should be kept clean and observed for possible signs of infection such as redness, swelling, drainage, and pain at the wound site.

National guidelines should be followed for recommendations on chemoprophylaxis. In general, it is not necessary for all people exposed to someone with invasive group A streptococcal toxic shock syndrome (TSS) to receive antibiotic therapy to prevent infection.[78] However, clinicians should alert all close contacts to signs and symptoms of TSS and advise them to seek medical attention if they develop a fever within 30 days of the index patient.

In certain circumstances, antibiotic therapy may be appropriate for a close contact of a confirmed case of invasive group A streptococcal infection, including TSS. A close contact can be defined as:

- Someone who has had prolonged contact with the case in a household-type setting during the 7 days before diagnosis of infection and up to 24 hours after initiation of appropriate antimicrobial therapy in the index case. Examples of such contacts would be those with an overnight stay in the same household (including extended household if the case has stayed at another household), pupils in the same dormitory, intimate partners, or university students sharing a kitchen in a hall of residence[77]
- Those who have had direct contact with mucous membranes or oral or nasal secretions[79]
- Injection drug users who have shared a needle[79]
- Contacts in child care settings, select hospital contacts, and select long-term care facility contacts.[79]

The Centers for Disease Control and Prevention only recommends considering antibiotic prophylaxis for close contacts of patients with streptococcal TSS aged ≥65 years.[78]

Guidelines from the Canadian Paediatric Society recommend that:[79]

- Chemoprophylaxis should only be offered to close contacts of a confirmed case of severe invasive group A streptococcal disease who have been exposed during the period from 7 days before the onset of symptoms in the index case to 24 hours after the index case has initiated antimicrobial therapy.
- Chemoprophylaxis should be started as soon as possible, and preferably within 24 hours of identifying the case. Chemoprophylaxis is still recommended up to 7 days after the last contact with the index case.

UK guidance recommends that:[77]

- Chemoprophylaxis should be offered to high-risk close contacts. High-risk close contacts include those ages ≥75 years or ≤28 days; women during late pregnancy (≥37 weeks) or ≤28 days postpartum;

and those with open chickenpox lesions within 7 days prior to diagnosis of the index case or within 48 hours after the index case has commenced antibiotics, if exposure is ongoing.

- Chemoprophylaxis may be considered for other contacts if multiple cases of confirmed or probable invasive group A streptococcus infection are identified within the same school/other childcare setting, or care home. If there are multiple cases within one household, chemoprophylaxis should be offered to the entire household.

Staphylococcal TSS

Education regarding extended tampon use and the withdrawal of highly absorbent tampons from the market has decreased the incidence of staphylococcal TSS.[69] Lack of seroconversion after an acute staphylococcal illness may be used as a marker for patients at risk for recurrent disease.[15] These patients should be treated for a protracted course with antistaphylococcal antibodies for at least 2 weeks.

Secondary prevention

The risk of secondary cases of invasive disease is low at 2.9 per 1000.[95] Several regimens have been successful in eradicating group A streptococcus from the pharynx of chronic carriers (i.e., rifampin plus intramuscular benzathine penicillin or a 10-day course of a second-generation cephalosporin or clindamycin).[125] However, there are limited data concerning chemoprophylaxis for severe invasive group A streptococcal or staphylococcal infections.

Women who have had toxic shock syndrome (TSS) should avoid the use of tampons while menstruating. If use is unavoidable, tampons should be changed every 4-8 hours.[129]

Patient discussions

Patients should be instructed to recognize symptoms of recurrence and to present to the emergency department if they return.

Women should be reminded to regularly change tampons, if used, during menses.

Monitoring

Monitoring

Patients should be monitored for any longer-term sequelae. Neuropsychiatric complications such as headache, memory loss, and poor concentration can persist in patients after staphylococcal disease.

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
bacteremia	**short term**	**high**
Relatively rare in streptococcal toxic shock syndrome (TSS) but can be seen with aggressive skin and soft-tissue infections.[122] [123] In patients aged ≤40 years, bacteremia is associated with puerperal sepsis, intravenous drug use, and HIV infections.[122] [124] In patients >40 years of age, burns, surgical procedures, nosocomial infections, diabetes, peripheral vascular disease, malignancy, corticosteroid use, immunosuppression, and cardiac disease have been implicated.[125] [126] [127]		
acute respiratory distress syndrome	**short term**	**high**
Secondary to capillary leak and vasodilation. Develops in 55% of patients, usually after the development of shock and hypotension.[40] [62]		
disseminated intravascular coagulation (DIC)	**short term**	**high**
Aggressive treatment of the underlying disorder to remove the triggering factor is the most effective therapy in management of DIC.		
renal failure	**short term**	**high**
A significant number of patients will require dialysis for up to 3 weeks and the serum creatinine will normalize within 4 to 6 weeks. Hypotension, myoglobinuria, and hemoglobinuria can lead to acute renal failure.		
wound sequela requiring major surgical procedures	**short term**	**high**
Fasciotomy, surgical debridements, exploratory laparotomy, amputation, and hysterectomy may be needed in streptococcal infections.[40]		
acute hemorrhagic adrenal insufficiency (Waterhouse-Friderichsen syndrome)	**short term**	**low**
There have been case reports of patients with Waterhouse-Friderichsen syndrome secondary to group A streptococcal TSS.[126][128]		
neuropsychiatric sequelae	**long term**	**medium**
Persistent symptoms including headache, memory loss, and poor concentration can occur in patients with staphylococcal disease.		

Prognosis

Mortality ranging from 30% to 85% has been reported for streptococcal toxic shock syndrome (TSS), despite prompt antibiotic therapy.[32] [33] [40] [45] [46] [62] [98] [114] [115] Death is usually due to cardiac arrhythmias, cardiomyopathy, and respiratory failure.[116] [117] Higher mortality is associated with necrotizing fasciitis and TSS.[62] Shock is the most important predictor of death.[118] Advanced age, hypotension, and multiorgan system failure are significantly associated with increased mortality.[119]

Menstrual staphylococcal TSS has a mortality of approximately 8%.[120] One study in the US found a higher mortality rate in nonmenstrual TSS compared with menstrual TSS.[20] However, a study in the UK reported no difference in mortality between menstrual and nonmenstrual TSS.[19] Mortality may be higher in staphylococcal TSS associated with toxins other than toxic shock syndrome toxin-1 (TSST-1).[118]

Admission physical exam and laboratory values

A retrospective study compared admission physical exam findings and laboratory values of survivors versus those who died. Mortality was significantly higher in patients with:[121]

- Lower mean WBC count ≤10,000 cells/mm³
- Decreased mean platelet count ≤120,000/mm³
- Higher serum creatinine ≥3 mg/dL
- Hypothermia, mean ≤98.6°F (37°C)
- Decreased mean systolic BP ≤90 mmHg.

Treatment guidelines

International

Invasive group A streptococcal disease: management and chemoprophylaxis (https://cps.ca/en/documents) [79]

Published by: Canadian Paediatric Society **Last published:** 2019

Practice guidelines for the diagnosis and management of skin and soft-tissue infections (https://www.idsociety.org/practice-guideline/practice-guidelines) [108]

Published by: Infectious Diseases Society of America **Last published:** 2014

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2021 (https://www.sccm.org/SurvivingSepsisCampaign/Guidelines) [82]

Published by: International Surviving Sepsis Campaign Guidelines Committee **Last published:** 2021

World Society of Emergency Surgery (WSES) and the Surgical Infection Society Europe (SIS-E) consensus conference: recommendations for the management of skin and soft-tissue infections (https://wjes.biomedcentral.com/articles/10.1186/s13017-018-0219-9) [109]

Published by: World Journal of Emergency Surgery **Last published:** 2018

Key articles

- Centers for Disease Control and Prevention. Streptococcal toxic shock syndrome (STSS): 2010 case definition. 2010 [internet publication]. Full text (https://ndc.services.cdc.gov/case-definitions/streptococcal-toxic-shock-syndrome-2010)
- Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med. 2021 Nov 1;49(11):e1063-143. Full text (https://www.doi.org/10.1097/CCM.0000000000005337) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34605781?tool=bestpractice.bmj.com)
- Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59:e10-e52. Full text (http://cid.oxfordjournals.org/content/59/2/e10.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24947530?tool=bestpractice.bmj.com)
- Sartelli M, Guirao X, Hardcastle TC, et al. 2018 WSES/SIS-E consensus conference: recommendations for the management of skin and soft-tissue infections. World J Emerg Surg. 2018;13:58. Full text (https://www.doi.org/10.1186/s13017-018-0219-9) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30564282?tool=bestpractice.bmj.com)

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Images

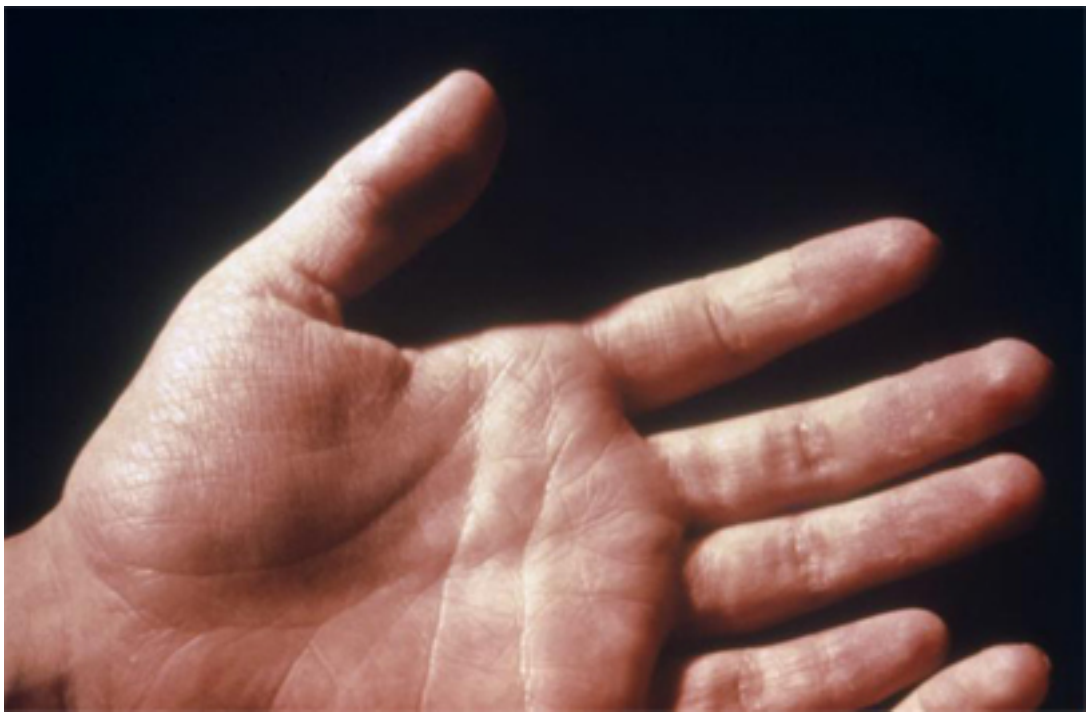

Figure 1: Subtle desquamation of the finger tips of the left hand caused by toxic shock syndrome

From the CDC and the Public Health Image Library

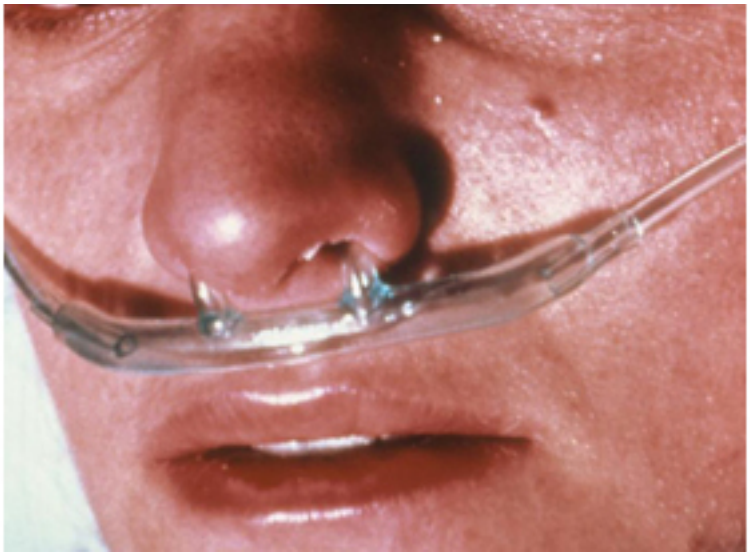

Figure 2: Patient with facial erythematous rash due to toxic shock syndrome

From the CDC and the Public Health Image Library

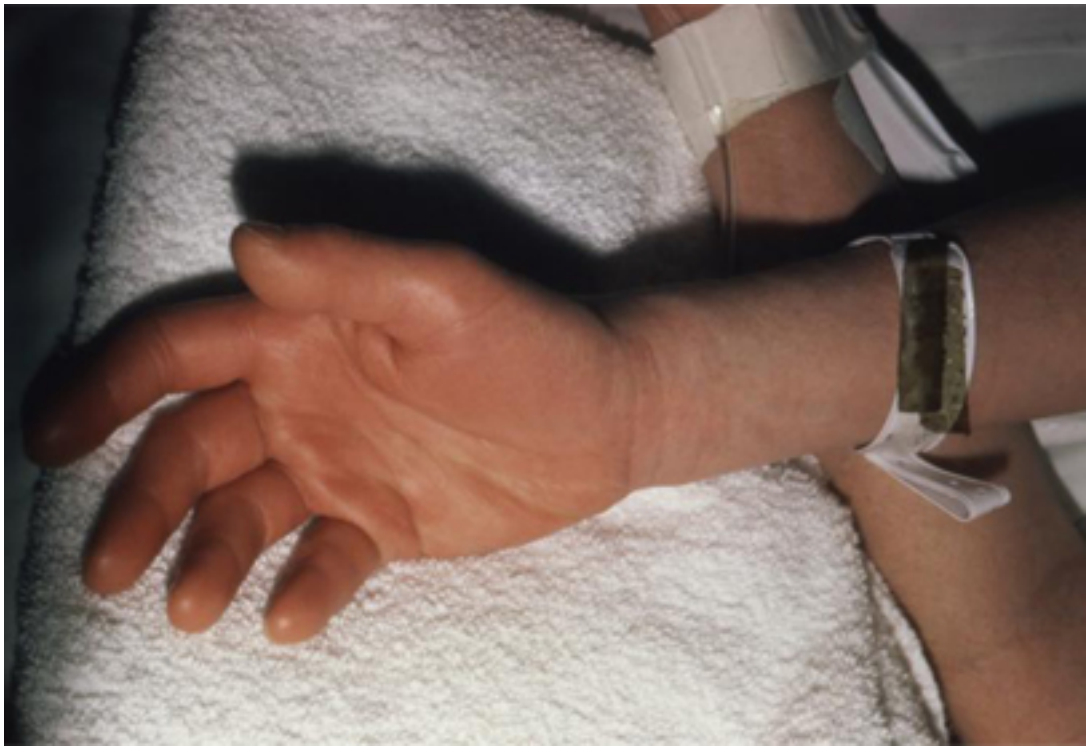

Figure 3: Rash and subcutaneous edema of the right hand due to toxic shock syndrome

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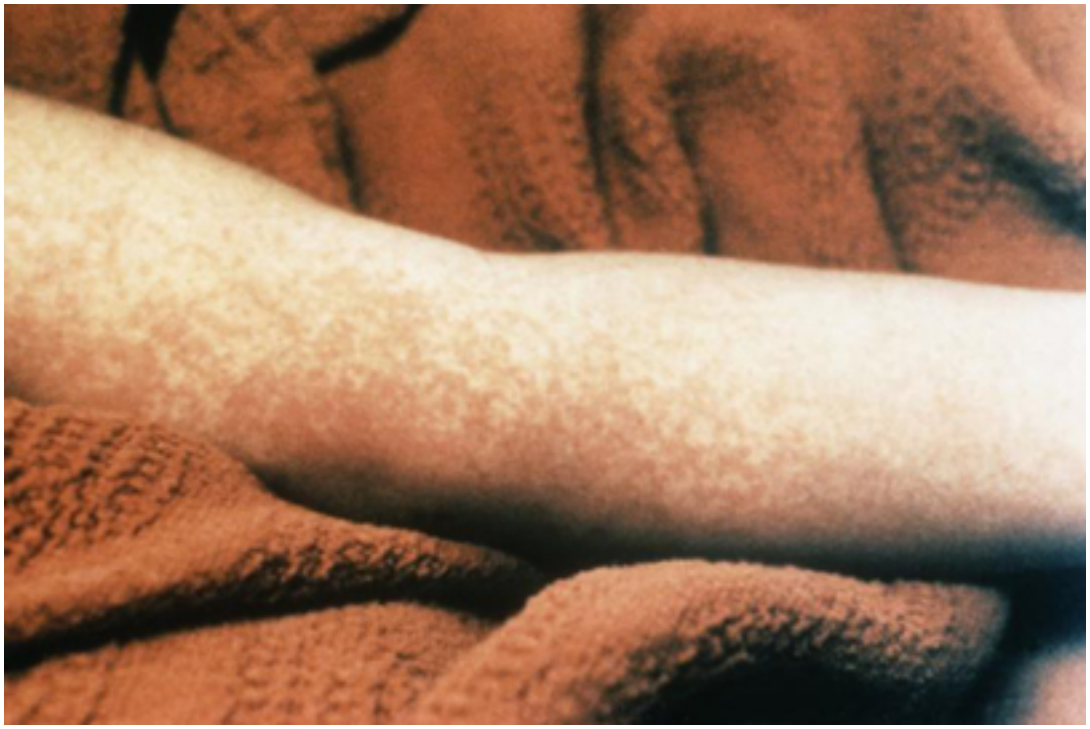

Figure 4: Patient displaying a morbilliform rash (resembling measles) resulting from toxic shock syndrome, 3 to 5 days after onset

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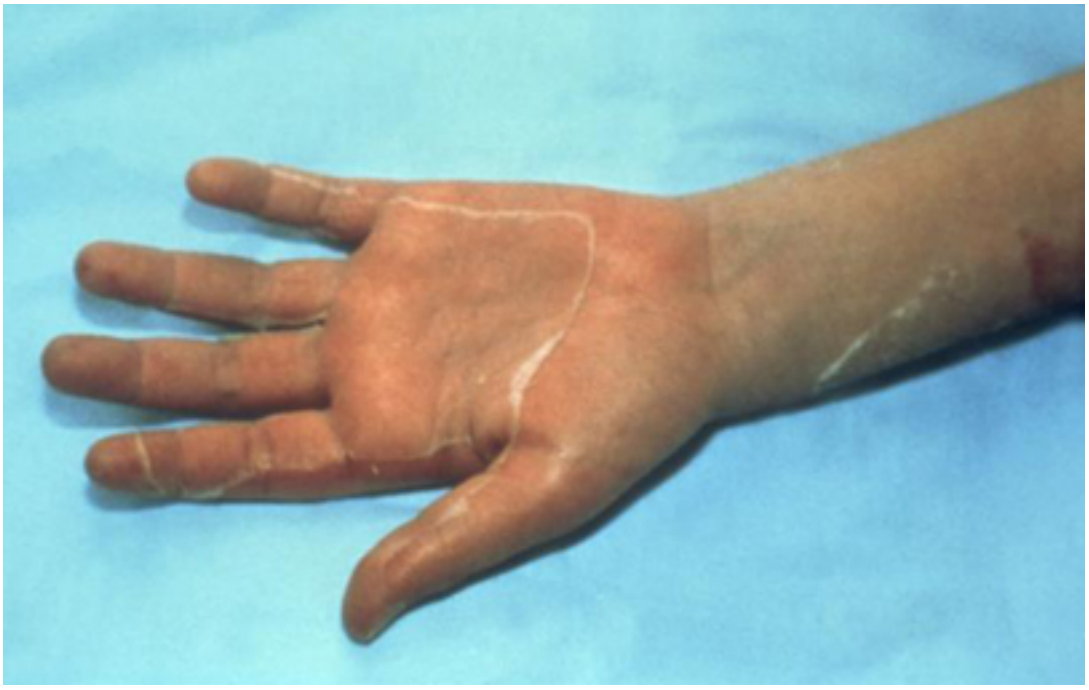

Figure 5: Marked desquamation of the left palm due to toxic shock syndrome, which develops late in the disease

From the CDC and the Public Health Image Library

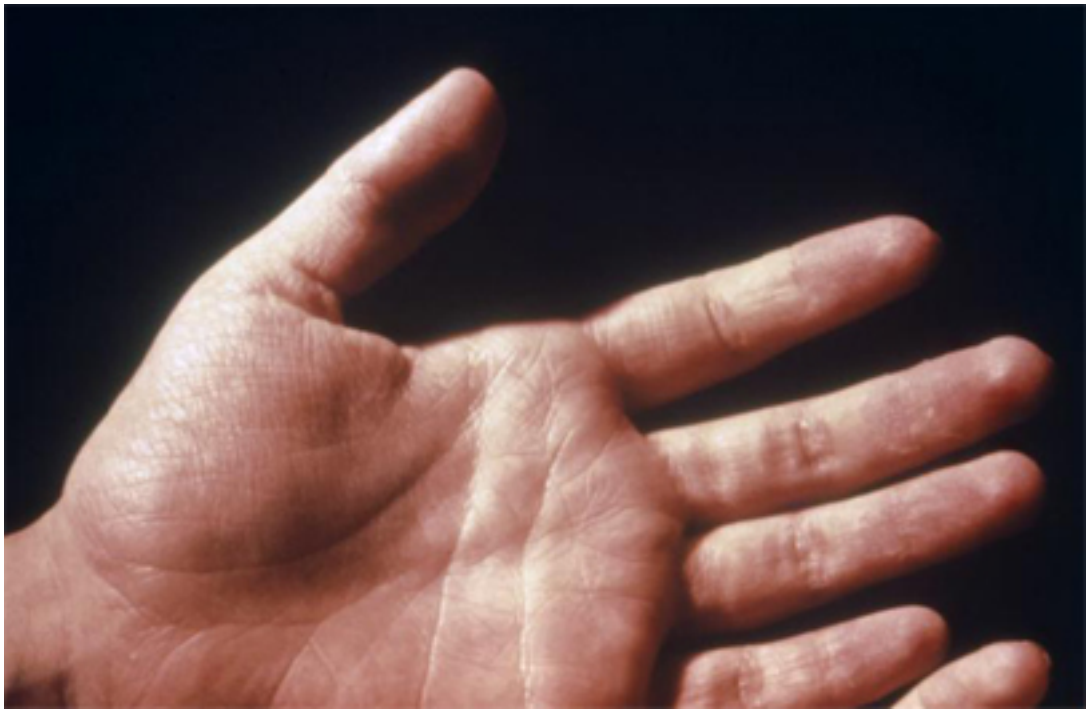

Figure 6: Subtle desquamation of the finger tips of the left hand caused by toxic shock syndrome

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Figure 1 – BMJ Best Practice Numeral Style

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4-digit numerals: 1000

numerals < 1: 0.25

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