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Staphylococcal Toxic Shock Syndrome: Mechanisms and Management

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Abstract Staphylococcal toxic shock syndrome is a rare complication of *Staphylococcus aureus* infection in which bacterial toxins act as superantigens, activating very large numbers of T cells and generating an overwhelming immune-mediated cytokine avalanche that manifests clinically as fever, rash, shock, and rapidly progressive multiple organ failure, often in young, previously healthy patients. The syndrome can occur with any site of *S. aureus* infection, and so clinicians of all medical specialties should have a firm grasp of the presentation and management. In this article, we review the literature on the pathophysiology, clinical features, and treatment of this serious condition with emphasis on recent insights into pathophysiology and on information of relevance to the practicing clinician.

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Introduction

Staphylococcal toxic shock syndrome (TSS) is a rare complication of infection with *Staphylococcus aureus*, specifically toxin-producing strains. Although the precipitating infection may appear minor, toxins, the most commonly implicated of which is TSS toxin-1 (TSST-1), act as superantigens, generating a disproportionately exuberant immune response and cytokine avalanche. This brings about a rapidly progressive clinical syndrome of multiple organ dysfunction virtually indistinguishable from septic shock and associated with a significant mortality.

It is critical that all clinicians appreciate the pathophysiology and management of this potentially life-threatening condition, given the multiple clinical presentations of staphylococcal infection and the rise in prevalence of gram-positive infections, including hospital- and community-acquired methicillin-resistant *S. aureus* (MRSA) infection.

TSS should be considered in the differential diagnosis of any patient with severe systemic inflammatory response syndrome of unclear etiology, but particularly in the situation of an overwhelming systemic response to a relatively minor source of gram-positive infection.

Epidemiology

TSS was first described in 1978 [1], and reports were published during the 1980s in previously healthy young women in association with the introduction of highly absorbent tampons. Following identification of these tampons as a risk factor for TSS, and their subsequent removal from the market, the incidence declined steadily in the United States between 1980 and 1996 from a peak of 6 to 12 cases per 100,000 inhabitants per year [2]. Changes to the case definition, and a reliance on physicians to report the disease, have made accurate incidence figures difficult to obtain, with between 71 and 101 cases per year reported to the US Centers for Disease Control and Prevention in the past 5 years [3]. In one active surveillance area in Minneapolis-St. Paul, MN, the incidence was reported to have increased from 0.9 to 3.4 cases per 100,000 in the period from 2000 to 2003 [4]; however, more recent figures from the same surveillance program suggest an incidence of 2.1 per 100,000.

Colonization of upper respiratory tract, skin, and genital tract mucosa with *S. aureus* is common even in healthy individuals, with persistent nasal carriage in up to 27% of the population [5] and vaginal colonization in just under 10% of adult females [6]. Overall, only a small proportion (<10%) of *S. aureus* isolates carry *tst,* the gene encoding TSST-1 [7], and the prevalence of vaginal carriage of a toxigenic strain of *S. aureus* is in the order of 1% to 3% of the adult female population [8]. The events that culminate in the shift of *S. aureus* from colonization to infection are unclear. TSS may develop from staphylococcal infections in any site, although in many cases no focal source of infection is identified.

MRSA strains are an increasingly common problem, in the community as well as the hospital population, and geographic spread of TSST-1–producing MRSA strains was reported in Europe and Japan [9, 10], although the status of these strains in the United States is unclear. Although the existence of TSST-1–producing MRSA strains is of concern, conflicting evidence exists as to a possible association between methicillin resistance and superantigen production [7, 11–13].

Given the nonspecific clinical features and lack of widely available rapid diagnostic tools, it is likely that many cases of staphylococcal TSS go undiagnosed or are coded as septic shock. Available figures may well underestimate the true incidence.

Pathophysiology

S. aureus produces a range of protein exotoxins that are key to understanding the pathogenesis of TSS. These bacterial toxins include the staphylococcal enterotoxins (SEs), TSST-1, and the staphylococcal enterotoxin-like toxins (SEIs) (so-called because their emetic potential remains unproven) [14••]. All are virulence factors acting as superantigens to trigger excessive and nonconventional T-cell activation with potentially catastrophic overamplification of the inflammatory cytokine cascade. The term “superantigen” was first used in the late 1980s to describe the mechanism behind the powerful T-cell–stimulating properties of streptococcal enterotoxin B [15].

Superantigens bypass normal mechanisms regulating antigen presentation and processing, in which peptide fragments are presented to the T cell via a specific peptide-binding groove of the major histocompatibility complex (MHC) type 2 molecule on the antigen-presenting cell (APC). This conventional process allows T-cell responses only when both the class 2 molecule and specific antigen fragment are recognized. Superantigens directly stimulate T cells by binding as unprocessed, intact proteins directly to the T-cell receptor (TCR) and MHC class 2 molecule in combination and at locations remote from the conventional peptide binding area [16]. This cross-linking mechanism involves the variable portion of the TCR β chain and can induce a clonal expansion of T cells possessing the corresponding TCR Vβ pattern. Many superantigens are thought to interact with selected TCR Vβ regions, and identification of this characteristic Vβ pattern or signature may be diagnostically useful. However, a recent French study showed that although each Vβ signature analyzed was stimulated by at least one staphylococcal superantigen, there was considerable overlap and redundancy in superantigen-induced Vβ populations, with some, but not all, superantigens having characteristic Vβ patterns [17•]. The list of superantigens with unique signatures included TSST-1, SEA, SEG, SEH, SEIJ, SEIK, SEIL, SEIN, SEIM SEIO, SEIQ, SER, SEIU, and SEIV. The mitogenic potential of a particular superantigen appears to correlate directly with the binding affinity between the TCR and the superantigen [18]. Superantigens are capable of stimulating more than 20% of host T cells, far in excess of that caused by conventional antigen presentation, and with intense potency (femtogram concentrations of superantigen are all that is required in vitro) [14••].

T-cell activation by superantigens leads to a massive, uncoordinated release of proinflammatory cytokines responsible for the clinical picture of TSS. Experimentally, cytokine release is biphasic, with an initial rise in interleukin-2 (IL-2), tumor necrosis factor-α (TNF-α), and IL-6, followed by a more gradual increase in IL-12 and interferon-γ (IFN-γ) [19]. Cytokine activation seems to be linked to induction of the transcription factor nuclear factor-κB (NF-κB), which plays a key role in the expansion of the inflammatory response [20]. In vitro studies demonstrated

that the early cytokine burst is responsible for lethality and is mediated via TNF-α, rather than the underlying helper T-cell (Th1) response [19].

Recently, it was shown that superantigens have the ability to up-regulate monocytic toll-like receptor 2 (TLR2) expression through MHC class 2 signaling [21]. TLR2 is one of many recognition receptors involved in the detection of gram-positive organism components (so-called pathogen-associated molecular patterns [PAMP]) such as lipoteichoic acid, and the production of a subsequent immune response [22•]. Although enhanced TLR2 expression was demonstrated clinically in patients with Group A streptococcal TSS (but not staphylococcal TSS), there does not seem to be a linear relationship between expression and TLR2 signaling, especially in critical illness. Toll-like receptor signaling is considered proinflammatory because their activation coordinates both the innate and adaptive immune responses. However, it seems counterproductive to the survival and growth of an invading organism to induce such a marked inflammatory reaction that either the organism or the host, or both, will be killed. It was recently hypothesized that staphylococcal cell wall peptidoglycans that bind TLR2 can actually downregulate superantigen-induced T-cell activation via IL-10 (generated by APCs) and cause apoptosis of monocytes and macrophages [23•]. The authors, interestingly, suggest that *S. aureus* may use TLR2 signaling to dampen the exotoxin-induced host immune response, and so enhance its chances of survival. In addition to benefiting the organism, this immunomodulation reduces the risk of TSS in the host, and may explain in part why TSS is not more common in patients with staphylococcal infection. It is likely that the exact mechanisms underlying TLR2-mediated immunomodulation differ depending on the *S. aureus* strain and organism load (perhaps immunomodulation is more likely with low organism loads), the tissue site, and the responding immune cells [24••]

Not all *S. aureus* isolates will produce superantigens; 50% to 80% of *S. aureus* isolates are positive for at least one superantigen gene [23•]. Toxin-encoding genes are often contained within mobile genetic elements such as prophages, plasmids, and pathogenicity islands. These are not uniformly distributed between isolates, and horizontal transfer can occur between strains, leading to genetic diversification [14••]. A worrying study from Japan that examined more than 250 *S. aureus* samples from hospital in patients showed that MRSA isolates harbored more superantigenic toxin genes than the methicillin-sensitive *S. aureus* (MSSA) isolates.

The most clearly apparent superantigen-disease relationship is between menstrual TSS and staphylococcal TSST-1. This toxin was implicated in more than 95% of cases, presumably because of the toxin's ability to traverse mucosal barriers. Staphylococcal cytolysin α-toxin induces a strong proinflammatory response in vaginal mucosal cells, promoting release of IL-6, IL-1β, and TNF-α, and disrupting the mucosal surface to enhance penetration of TSST-1 [25]. Although the incidence of menstrual TSS is in decline, TSST-1 was also associated with nonmenstrual TSS in about 50% of cases, the remainder being primarily from the enterotoxin SEB and, less often, SEC, SEG, and SEI.

Host factors are also critical in disease development. Deficient host immunity remains a major factor in the development of menstrual TSS; one early study demonstrated that only 9.5% of patients with menstrual TSS had developed antibodies to TSST-1 in acute-phase sera in the first week of illness, and the subsequent rate of seroconversion remained low [26]. This failure to acquire immunity may result from a lack of Th2 response and the ability of TSST-1 to induce T-cell–dependent apoptosis of B cells. The host genetic profile may also alter disease trajectory, with evidence suggesting that HLA haplotype can also impact clinical susceptibility to the toxic effects of individual superantigens. Most staphylococcal enterotoxins preferentially bind HLA-DR rather than HLA-DQ, and it was recently observed that SEA binding to HLA-DR4 and HLA-DR15 is markedly greater than binding to HLA-DR11, suggesting haplotype-specific binding variation. In contrast, differences of SEB binding to various HLA-DR molecules were small [27]. The role of HLA class 2 polymorphisms may well have a greater significance in the progression of streptococcal TSS than staphylococcal TSS. Polymorphism within genes encoding inflammatory or coagulation cascade products may also translate into altered disease expression in response to exposure to superantigenic material.

Clinical Features, Investigations, and Diagnosis

TSS is multisystem disease that usually presents with rapid onset of fever, hypotension, and progressive multiorgan failure over the course of several hours, often without a very obvious septic focus. Although the largest proportion of TSS is menstrual related, other reported sources of toxigenic *S. aureus* include surgical wounds, soft-tissue infections including infected burns, postpartum infections, intrauterine devices, nasal packs, and pneumonia. Postoperative TSS most commonly occurs on the second postoperative day and may be associated with a benign-looking wound [28]. Carriage of TSST-1–producing *S. aureus* strains was recently identified in a significant proportion of patients with chronic rhinosinusitis [29], and a recent review of 76 cases of pediatric TSS found evidence of acute rhinosinusitis without other sources of infection in

17 cases (21%), suggesting that this may be a common and under-recognized source of toxigenic *S. aureus* [30].

A prodromal influenza-like illness—consisting of fever, chills, myalgia, and often gastrointestinal disturbance including nausea, vomiting, and diarrhea—is frequently present for 1 to 2 days before medical assistance is sought.

At presentation, patients are often profoundly unwell with high fever, tachycardia, vasodilatation, tachypnea, incipient or actual hypotension, dizziness, confusion, or decreased level of consciousness. A widespread macular erythrodermic rash may be present, although this is not invariable and may be transient and limited in extent. Desquamation of palmar and plantar surfaces may occur, but is usually not diagnostically useful at presentation because it often occurs 1 to 2 weeks after disease onset.

Progression to multiple organ failure is usual over the course of 6 to 12 h, with fluid-unresponsive hypotension from vasodilatation and massive capillary leak, acute kidney injury, disseminated intravascular coagulation (DIC), acute respiratory distress syndrome, and hepatic dysfunction developing in the course of the illness in a manner indistinguishable from septic shock. A consensus definition of TSS is given in Table 1 [31].

In addition to the clinical features of TSS, evidence of a precipitating staphylococcal infection may provide a useful diagnostic clue and opportunity for therapeutic intervention to reduce bacterial and toxin load.

Making a clinical diagnosis of TSS is often difficult, particularly in patients with comorbidities and in the postoperative setting. A high index of suspicion is vital if the diagnosis is to be made early, and TSS must be considered, particularly in young female patients during menstruation, in the postpartum period, in patients with nasal packs in situ following nasal surgery, or manifestations of sinusitis, and in patients who develop features of systemic inflammatory response syndrome out of proportion to a minor skin or soft tissue infection. Vaginal examination should be performed to exclude infection, foreign body, or tampon.

The differential diagnosis is wide, comprising the many and varied causes of gram-positive and gram-negative shock, particularly where the characteristic rash is absent or difficult to detect (eg, in non-Caucasian patients). Differential diagnoses (in addition to conventional septic shock) include streptococcal toxic shock, meningococcal septicemia, scarlet fever, Rocky Mountain spotted fever (in at-risk areas), and leptospirosis.

Investigations are used to exclude alternative diagnoses, to identify and track progression of organ dysfunction, and to provide supportive evidence for a diagnosis of TSS.

Hematologic investigations will commonly reveal a neutrophilic leucocytosis and evidence of DIC (elevated prothrombin and activated partial thromboplastin times and decreased platelet count). A transient leukopenia has occasionally been observed, which was attributed to neutrophil sequestration in lymph nodes and spleen [32]. Biochemical analysis will demonstrate multiorgan injury and may show increased urea and creatinine concentrations, elevated hepatic transaminases and bilirubin, hypoalbuminemia, and abnormal electrolyte concentrations. Cultures and Gram staining of any likely sites of infection are mandatory, with vaginal swabs positive for *S. aureus* in more than 90% of menstrual-related cases, even in the absence of overt vaginal infection. In contrast to streptococcal TSS, blood cultures may be positive for *S. aureus* in less than 5% of cases. Chest radiograph findings are likely

Table 1 Staphylococcal toxic shock syndrome case definition

1. Fever ≥38.9°C
2. Rash–diffuse, macular erythrodermic
3. Desquamation, especially of palms and soles, 1–2 wk after onset of illness
4. Hypotension–systolic blood pressure <90 mm Hg in adults
5. Multisystem involvement–three or more of the following:
   a) Gastrointestinal–vomiting or diarrhea at onset of illness
   b) Muscular–severe myalgia or elevated creatine phosphokinase
   c) Mucous membranes–vaginal, oropharyngeal, or conjunctival hyperemia
   d) Renal–blood urea nitrogen or creatinine twice upper limit of normal
   e) Hepatic–serum bilirubin twice upper limit of normal
   f) Hematologic–platelet count $<100\times10^{9}$ L^{-1}
   g) CNS–disorientation or alteration in consciousness without focal neurologic signs
6. Negative results on the following tests:
   a) Blood, throat, or CSF culture (blood culture may be positive for *S. aureus*)
   b) Rise in titer to Rocky mountain spotted fever, leptospirosis, or measles

Case definition:

Probable–case with five of six clinical criteria present

Confirmed–case with all six clinical criteria present

CNS central nervous system, *CSF* cerebrospinal fluid

(*Adapted from* Wharton et al. [31])

to be those of acute respiratory distress syndrome, although a staphylococcal pneumonia or empyema may be the infective source. Other radiologic investigations (including CT and MRI) may be indicated to exclude alternative diagnoses or occult infective foci.

Although the diagnosis is usually made on the basis of compatible clinical features with or without evidence of staphylococcal infection, correlative laboratory testing is available in some centers. Polymerase chain reaction–based detection of staphylococcal superantigen genes may provide prompt support for the diagnosis [33]. Anti–TSST-1 antibody assays may also provide supportive data, with antibody deficiency serving as a marker of susceptibility [34]. Flow cytometric analysis of T-cell populations may be rapidly available and provide corroborative diagnostic information: it may be possible to detect characteristic Vβ T-cell responses to staphylococcal superantigens (classically transient T-cell depletion followed by massive expansion of a Vβ2-positive T-cell subset for TSST-1), and this can help to differentiate TSS from staphylococcal septic shock [35]. A diagnostic approach using this test to complement clinical criteria was shown to reduce the time to diagnosis and anecdotal evidence supports its use [35, 36]. If the local prevalence of individual staphylococcal strains and their association with toxin production and antibiotic resistance is known, identification of a staphylococcus with a particular resistance pattern can be used to infer toxin-producing potential [37•].

Treatment

Treatment of staphylococcal TSS comprises supportive measures, targeted antibiotic therapy, and adjunctive immunomodulatory therapy. In addition, several potentially useful therapies are under development.

Most patients require admission to an intensive care unit for invasive monitoring and physiologic support, although resuscitative measures should not be delayed pending admission. Principles for the initial resuscitation of a patient with staphylococcal TSS are those applicable to any patient with septic shock, and key aspects are outlined in the guidelines of the Surviving Sepsis Campaign [38••]. This incorporates the concept of "early goal-directed therapy" based on a study of the protocol-guided management of septic shock patients in the emergency department [39]. The approach is outlined in Fig. 1, and includes basic measures (eg, administration of supplemental oxygen

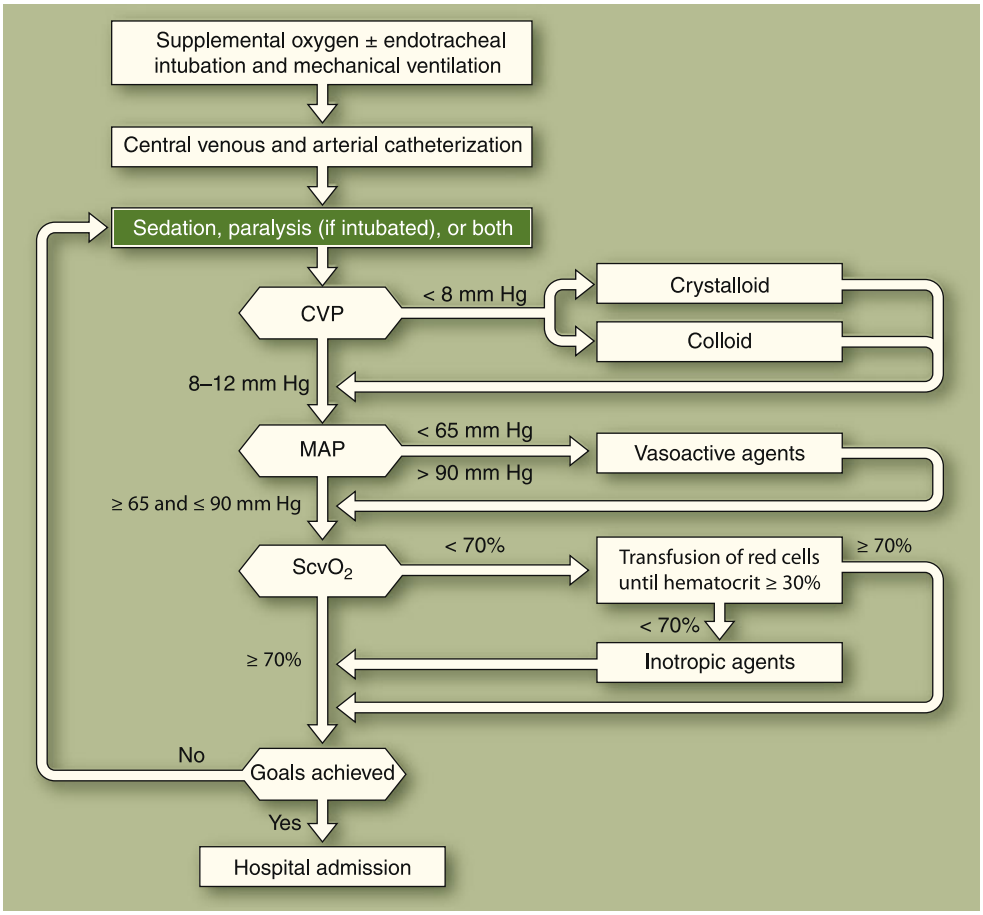

Fig. 1 Early goal-directed therapy in severe sepsis and septic shock. CVP—central venous pressure; MAP—mean arterial pressure; $ScvO_2$—oxygen saturation in the superior vena cava measured from central venous catheter. (*From* Rivers et al. [39], with permission. Copyright © 2001, Massachusetts Medical Society. All rights reserved)

therapy) and fluid resuscitation with isotonic crystalloids or colloids targeted to a mean arterial pressure of 65 mm Hg and urine output of 0.5 mL kg^{-1} $hour^{-1}$, which can be commenced on a general ward or in the emergency department. More advanced resuscitation targets include a central venous pressure (CVP) of greater than 8 mm Hg and superior vena caval oxygen saturation ($ScvO_2$) ≥70%, although normalization of serum lactate is an equally valid resuscitation endpoint [40•]. Failure to achieve a satisfactory mean arterial pressure despite adequate fluid loading is an indication for vasopressor therapy, generally with norepinephrine or dopamine. Many units prefer norepinephrine because of its side-effect profile [41]. Failure to achieve adequate oxygen delivery, as evidenced by low $ScvO_2$ or ongoing elevation of lactate, should lead to further fluid challenges, transfusion of packed red cells if the hematocrit is less than 30%, or addition of a dobutamine infusion, especially if significant ventricular dysfunction is present.

Patients with TSS frequently require endotracheal intubation and mechanical ventilation to improve oxygenation, particularly in the context of acute lung injury, and a lung-protective ventilatory strategy (tidal volumes of 6 mL kg^{-1} predicted body weight, plateau pressure ≤30 cm H_2O, use of positive end-expiratory pressure, 40° head-up position, permissive hypercapnia if necessary) should be used. Other supportive measures may include hydrocortisone (in doses <300 mg/d) and/or vasopressin (0.03 units/min) for catecholamine-resistant shock, glycemic control (goal glucose 150 mg/dL), blood products, enteral (preferred) or parenteral nutrition, venous thrombosis and stress ulcer prophylaxis, and renal replacement therapy.

Bacterial source control—whether removal of a tampon, debridement of an infected wound, or drainage of a focal collection—must be undertaken at an early stage. Appropriate antibiotic therapy should be initiated within an hour of the diagnosis, with blood cultures taken prior to this. Although not specifically studied in TSS, delay is strongly associated with increased mortality in severe sepsis.

Because therapy is often commenced before the diagnosis of TSS is clear, initial antimicrobial regimens must be sufficiently broad to cover all likely pathogens based on the available information. Inadequate initial antimicrobial therapy worsens outcome in severe sepsis. Many potential regimens are available for cases in which a diagnosis of TSS has been made. The β-lactam agents nafcillin, cloxacillin, and flucloxacillin are widely used as therapy for MSSA strains (with or without an aminoglycoside). However, in vitro studies suggest that use of these bactericidal drugs increases expression and release of toxins such as TSST-1. Vancomycin, commonly used as a first-line agent for MRSA, has a similar mechanism of action to β-lactams, although no specific effect on TSST-1 concentrations has been reported. In addition, vancomycin resistance is on the increase in many areas. Clindamycin, a bacteriostatic lincosamide, was demonstrated to reduce TSST-1 production by up to 90% in vitro and is a useful agent to include along with a bactericidal agent, at least initially. Clindamycin is unsuitable for monotherapy because of high constitutive and inducible resistance rates, particularly among methicillin-resistant strains [42, 43]. In light of the recent data on TLR2-related immunomodulation by *S. aureus*, it was postulated that perhaps bacteriostatic agents such as clindamycin maintain the presence of TLR2-stimulating bacterial cell wall components, and in so doing indirectly lead to down-regulation of the T-cell response [24••]. It is also useful to note that linezolid and tigecycline were shown to have inhibitory effects on toxin production [44, 45] and may be useful alternatives, particularly in the context of MRSA. Several other agents have potent antistaphylococcal activity, either alone or in combination with another drug. Quinupristin/dalfopristin was shown to be particularly effective against intracellular *S. aureus* [46] and rifampicin and fusidic acid may have a role as supplementary agents. Potential antimicrobial options are summarized in Table 2, although it must be emphasized that no in vivo data exist to support any particular regimen, and local practices and resistance patterns should be taken into account. Similarly, no experimental data exist to support an

Table 2 Antimicrobial options in staphylococcal toxic shock syndrome

Organism	Option A	Option B (β-lactam intolerant)	Option C
Methicillin-sensitive *Staphylococcus aureus*	Nafcillin or cloxacillin or flucloxacillin, and clindamycin	Clarithromycin +/− gentamicin, and clindamycin	Linezolid or daptomycin or tigecycline, +/− rifampicin
Methicillin-resistant *S. aureus*	Vancomycin or teicoplanin, and clindamycin	N/A	Linezolid or daptomycin or tigecycline, +/− rifampicin
Glycopeptide-resistant or glycopeptide-intermediate sensitivity *S. aureus*	Linezolid +/− clindamycin, or daptomycin	N/A	Tigecycline

N/A not applicable

extended duration of therapy beyond that indicated for the source infection and guided by clinical and laboratory response.

On the basis that patients lacking an effective antibody response to TSST-1 and other superantigens are at increased risk for TSS, intravenous immunoglobulin has been used as adjunctive therapy. Several case reports and one small randomized trial suggested clinical improvement following its use in streptococcal TSS, although large-scale trials are lacking [47, 48]. In vitro suppression of T-cell proliferation and cytokine release in response to staphylococcal enterotoxin B was demonstrated even in the absence of specific antibodies, suggestive of an immunosuppressive effect beyond antibody-mediated toxin neutralization [49]. Little data exist on the use of immunoglobulin in staphylococcal TSS, although immunoglobulin was shown to inhibit leukocyte proliferation in response to staphylococcal superantigens in vitro [50]. Of note in this study, however, was the finding that the immunoglobulin dose required to inhibit the response to staphylococcal superantigen activity was significantly higher than that required to inhibit the response to streptococcal superantigens, and the concentration varied with the immunoglobulin preparation used, presumably reflecting varying antibody activity among donors. In summary, adjuvant therapy with human immunoglobulin may be of benefit and should be considered in patients unresponsive to conventional therapy after several hours, although the optimal dose and duration of therapy are unknown.

Activated protein C (drotrecogin alfa) was used successfully in staphylococcal TSS, although criteria are unclear for its use in this setting. Current guidelines for septic shock recommend consideration of activated protein C in patients without contraindications who are considered to be at high risk of death, typically with multiple organ dysfunction and Acute Physiology and Chronic Health Evaluation (APACHE) 2 scores greater than 25 [38••].

Current areas of research into therapy for staphylococcal TSS include the development of a neutralizing monoclonal antibody to TSST-1 and other superantigens, the use of TLR2 ligands to induce immunomodulation, and the use of fixed antibodies in high-affinity columns to extract toxin from plasma.

Outcomes

TSS has a mortality rate of 4% to 22%. Mortality is significantly higher in nonmenstrual than in menstrual cases, reflective of the wider age range, frequent delayed diagnosis, and increased comorbidities in this group. Although rare, recurrence of staphylococcal TSS was reported in both menstrual and nonmenstrual cases.

Conclusions

Staphylococcal TSS is an uncommon but important condition resulting from an overwhelming superantigen-mediated T-cell activation resulting in rapidly progressive shock and multiple organ dysfunction, often in young and previously healthy patients, and usually requiring intensive care. A high index of suspicion is critical to making the diagnosis because the clinical picture is frequently indistinguishable from classical septic shock, and sources of staphylococcal infection or colonization must be actively sought. Antistaphylococcal treatment should include antimicrobials that have been shown to reduce the rate of toxin release (eg, clindamycin, linezolid, or tigecycline) and an antistaphylococcal bactericidal agent (eg, nafcillin or vancomycin). Human immunoglobulin and activated protein C may be considered as adjunctive therapy in the most severely ill patients who are poorly responsive to conventional therapy. Despite the aggressive nature of the disease, the likelihood of a good outcome can be improved with prompt recognition, targeted resuscitation, aggressive antimicrobial therapy, and organ support in an intensive care unit.

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- •• Of major importance

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