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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 which 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.

Introduction

Staphylococcal toxic shock syndrome (TSS) is a rare complication of infection with Staphylococcus aureus, specifically toxin-producing strains. While the precipitating infection may appear to be minor, toxins, the most commonly implicated of which is toxic shock syndrome 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 both hospital and community acquired methicillin resistant Staphylococcus aureus (MRSA) infection.

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

Epidemiology

Toxic shock syndrome was first described in 1978 [1] and there were subsequent reports 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 6-12 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 notified to the CDC per year in the United States in the last 5 years [3]. In one active surveillance area in Minneapolis-St Paul, 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 programme suggest an incidence of 2.1 per 100,000.

Colonisation 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 colonisation in just under 10% [6]. Overall only a small proportion, under 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 1-3% of the adult female population [8]. The events that culminate in the shift of S. aureus from colonisation 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 has been reported in Europe and Japan [9,10], although the status of these strains in the United States is unclear. While the existence of TSST-1-producing MRSA strains is of concern, there is conflicting evidence as to a possible association between methicillin resistance and superantigen production [7, 11-13].

Due to non-specific 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, and available figures may well underestimate the true incidence.

Pathophysiology

S. aureus produces a range of protein exotoxins which 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 as their emetic potential remains unproven) [14**]. All are virulence factors acting as superantigens to trigger excessive and non-conventional T-cell activation with potentially catastrophic over-amplification 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 II molecule on the antigen presenting cell (APC). This conventional process allows T cell responses only when both the class II molecule and specific antigen fragment are recognised. Superantigens directly stimulate T cells by binding as unprocessed, intact proteins directly to the T cell receptor (TCR) and MHC class II 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 has shown that although each Vβ signature analysed 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 over 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 toxic shock syndrome. Experimentally, cytokine release is biphasic, with an initial rise in interleukin-2 (IL-2), tumour 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 kappa-B (NFκB), which plays a key role in the expansion of the inflammatory response [20]. In vitro it has been demonstrated that it is the early cytokine burst that is responsible for lethality and is mediated via TNF-α, rather than the underlying Th1 response [19].

Recently it has been shown that superantigens have the ability to up-regulate monocytic toll-like receptor 2 (TLR2) expression through MHC class II signalling [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 has been 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 signalling, especially in critical illness. Toll-like receptor signalling is considered pro-inflammatory as their activation co-ordinates 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 has recently been hypothesised that staphylococcal cell wall peptidoglycans that bind TLR2 can actually downregulate superantigen induced T cell activation via IL-10 (generated by antigen-presenting cells) and cause apoptosis of monocytes and macrophages [23*]. The authors, interestingly, suggest that S. aureus may use TLR2 signalling to dampen the exotoxin-induced host immune response, , and so enhance its chances of survival. In addition to benefitting 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; 50-80% 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 looking at over 250 S. aureus samples from hospital inpatients has shown that MRSA isolates harboured 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 has been implicated in over 95% of cases, presumed to be due to the toxin's ability to traverse mucosal barriers. Staphylococcal cytolysin α-toxin induces a strong pro-

inflammatory 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 has also been associated with non-menstrual TSS in around 50% of cases, the remainder being primarily due to 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 with one early study demonstrating 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 sero-conversion remained low [26]. This failure to acquire immunity may result from a lack of Th2 response and also the ability of TSST-1 to induce T-cell dependant 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 has recently been observed that SEA binding to HLA-DR4 and HLA-DR15 is markedly greater than 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 II 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 multi-organ failure over the course of several hours, often without a very obvious septic focus. While 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. Post-operative 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 has recently been identified in a significant proportion of patients with chronic rhinosinusitis [29], and a recent review of 76 cases of paediatric TSS found evidence of acute rhinosinusitis without other sources of infection in 17 (21%), suggesting that this may be a common and under-recognised source of toxigenic S. aureus [30].

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

At the time of presentation, patients are often profoundly unwell with high fever, tachycardia, vasodilatation, tachypnoea, 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, although this is usually not diagnostically useful at presentation since it often occurs 1-2 weeks after disease onset.

Progression to multiple organ failure is usual over the course of 6-12 hours, with fluid-unresponsive hypotension due to vasodilatation and massive capillary leak, acute kidney injury, disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS) 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 as well as opportunity for therapeutic intervention to reduce bacterial and toxin load.

Making a clinical diagnosis of TSS is often difficult, particularly in patients with co-morbidities 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 post-

partum 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 (SIRS) out of proportion to a minor skin or soft tissue infection. Vaginal examination should be carried out 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, for example in non-Caucasian patients. Differential diagnoses (in addition to conventional septic shock) include streptococcal toxic shock, meningococcal septicaemia, 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.

Haematological investigations will commonly reveal a neutrophilic leucocytosis and evidence of DIC (elevated prothrombin and activated partial thromboplastin times and decreased platelet count). A transient leucopenia has occasionally been observed, which has been 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, hypoalbuminaemia and abnormal electrolyte concentrations. Cultures and gram staining of any likely sites of infection are mandatory, with vaginal swabs positive for Staphylococcus aureus in over 90% of menstrual-related cases even in the absence of overt vaginal infection. In contrast to streptococcal toxic shock syndrome, blood cultures may be positive for S. aureus in less than 5% of cases. Chest X-ray findings are likely to be those of acute respiratory distress syndrome, although a staphylococcal pneumonia or empyema may be the infective source. Other radiological investigations (including CT and MRI) may be indicated to exclude alternative diagnoses or occult infective foci.

While 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 centres. Polymerase chain reaction-based detection of staphylococcal superantigen genes [33] may provide prompt support for the diagnosis. 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 utilising this test to complement clinical criteria has been shown to reduce the time taken for 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 toxic shock syndrome comprises supportive measures, targeted antibiotic therapy, and adjunctive immunomodulatory therapy. In addition, a number of potentially useful therapies are under development.

The majority of patients will 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 toxic shock syndrome 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 Figure 1 and includes basic measures such as

administration of supplemental oxygen therapy, and fluid resuscitation with isotonic crystalloids or colloids targeted to a mean arterial pressure of 65 mmHg and urine output of 0.5 ml kg^{-1} $hour^{-1}$, which can be commenced on a general ward or the emergency department. More advanced resuscitation targets include a central venous pressure (CVP) of greater than 8 mmHg and superior vena caval oxygen saturation ($ScvO_2$) greater than or equal to 70%, although normalisation 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 due to 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 haematocrit 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 PEEP, 40° head up position, permissive hypercapnia if necessary) should be utilised. Other supportive measures may include hydrocortisone (in doses < 300mg/day) and/or vasopressin (0.03 units/minute) for catecholamine-resistant shock, glycaemic 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 this has not been specifically studied in toxic shock syndrome, delay is strongly associated with increased mortality in severe sepsis.

As therapy will often be commenced before the diagnosis of TSS is clear, initial antimicrobial regimes must be sufficiently broad to cover all likely pathogens based on the available information. Inadequate initial antimicrobial therapy worsens outcome in severe sepsis. There are many potential regimens for cases where a diagnosis of TSS has been made. The β-lactam agents nafcillin, cloxacillin, and flucloxacillin are widely used as therapy for methicillin-sensitive Staphylococcus aureus 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, has been 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 due to 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 has been 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 have been shown to have inhibitory effects on toxin production [44,45] and may be useful alternatives, particularly in the context of MRSA. There are of course several other agents with potent anti-staphylococcal activity, either alone or in combination with another drug. Quinupristin/dalfopristin has been 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 summarised in Table 2, although it must be emphasised that there is no in vivo data to support any particular regime, and local practices and resistance patterns should be taken into account. Similarly, no experimental data exists to support an 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 toxic shock syndrome, intravenous immunoglobulin has been used as adjunctive therapy. Several case reports and one small randomised trial suggested clinical improvement following its use in streptococcal toxic shock syndrome although large-scale trials are lacking [47,48]. In vitro suppression of T-cell proliferation and cytokine release in response to staphylococcal enterotoxin B has been demonstrated even in the absence of specific antibodies, suggestive of an immunosuppressive effect beyond antibody-mediated toxin neutralisation [49]. Little data exists on the use of immunoglobulin in staphylococcal TSS, although immunoglobulin has been shown to inhibit leucocyte 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 is unknown.

Activated protein C (Drotrecogin alfa) has been used successfully in staphylococcal toxic shock syndrome, although criteria for its use in this setting are unclear. 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) II scores greater than 25 in patients [38**].

Current areas of research into therapy for staphylococcal toxic shock syndrome include the development of a neutralising 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 4-22%. Mortality is significantly higher in non-menstrual than menstrual cases, reflective of the wider age range, frequent delayed diagnosis, and increased co-morbidities in this group. Although rare, recurrence of staphylococcal toxic shock syndrome has been reported in both menstrual and non-menstrual cases.

Conclusions

Staphylococcal toxic shock syndrome 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 as the clinical picture is frequently indistinguishable from classical septic shock and sources of staphylococcal infection or colonisation must be actively sought. Anti-staphylococcal treatment should include antimicrobials which have been shown to reduce the rate of toxin release such as clindamycin, linezolid or tigecycline, as well as an antistaphylococcal bactericidal agent such as nafcillin or vancomycin. Human immunoglobulin and activated protein C may be considered as adjunctive therapy in the most severely ill patients 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 within an intensive care unit.

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Table 1. Staphylococcal Toxic Shock Syndrome Case Definition - adapted from [31]:

1. Fever ≥ 38.9°C
2. Rash – diffuse, macular erythrodermic
3. Desquamation, especially of palms and soles, 1-2 weeks after onset of illness
4. Hypotension – Systolic blood pressure < 90 mmHg in adults
5. Multi-system involvement – 3 or more of the following:
   a) Gastrointestinal – vomiting or diarrhoea at onset of illness
   b) Muscular – severe myalgia or elevated creatine phosphokinase
   c) Mucous membranes – vaginal, oropharyngeal or conjunctival hyperaemia
   d) Renal – blood urea nitrogen or creatinine twice upper limit of normal
   e) Hepatic – serum bilirubin twice upper limit of normal
   f) Haematological – platelet count < 100×10^9 L^{-1}
   g) CNS – disorientation or alteration in consciousness without focal neurological signs
6. Negative results on the following tests:
   a) Blood, throat or cerebrospinal fluid culture (blood culture may be positive for S. aureus)
   b) Rise in titre to Rocky mountain spotted fever, leptospirosis, or measles

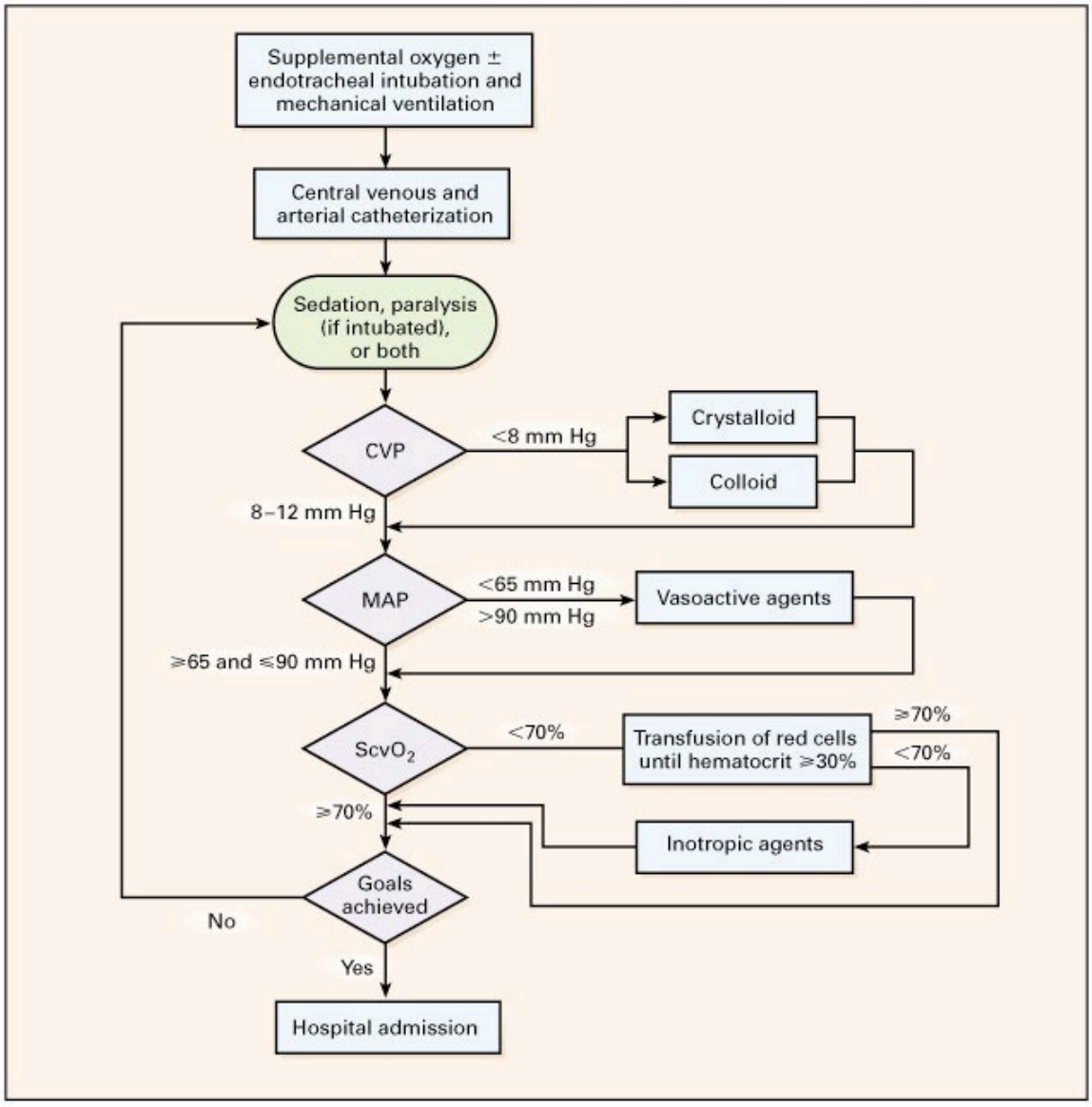
Case definition:

Probable – case with 5 of 6 clinical criteria present

Confirmed – case with all 6 clinical criteria present

Table 2. Antimicrobial options in Staphylococcal toxic shock syndrome			
Organism	Option A	Option B (b-lactam intolerant)	Option C
Methicillin-sensitive S. 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		linezolid or daptomycin or tigecycline, +/- rifampicin
Glycopeptide-resistant or intermediate sensitivity S. aureus (GRSA/GISA)	linezolid +/- clindamycin, or daptomycin		tigecycline

Figure 1: Early Goal-Directed Therapy in Severe Sepsis and Septic Shock [39]



$ScvO_2$: oxygen saturation in the superior vena cava measured from central venous catheter. MAP: mean arterial pressure. CVP: central venous pressure.