Gram-positive toxic shock syndromes

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Toxic shock syndrome (TSS) is an acute, multi-system, toxin-mediated illness, often resulting in multi-organ failure. It represents the most fulminant expression of a spectrum of diseases caused by toxin-producing strains of *Staphylococcus aureus* and *Streptococcus pyogenes* (group A streptococcus). The importance of Gram-positive organisms as pathogens is increasing, and TSS is likely to be underdiagnosed in patients with staphylococcal or group A streptococcal infection who present with shock. TSS results from the ability of bacterial toxins to act as superantigens, stimulating immune-cell expansion and rampant cytokine expression in a manner that bypasses normal MHC-restricted antigen processing. A repetitive cycle of cell stimulation and cytokine release results in a cytokine avalanche that causes tissue damage, disseminated intravascular coagulation, and organ dysfunction. Specific therapy focuses on early identification of the illness, source control, and administration on antimicrobial agents including drugs capable of suppressing toxin production (eg, clindamycin, linezolid). Intravenous immunoglobulin has the potential to neutralise superantigen and to mitigate subsequent tissue damage.

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Introduction

Gram-positive infections are responsible for approximately 50% of sepsis cases in the USA.[1] In addition to classic sepsis syndromes, several Gram-positive species are also capable of producing disease through toxin production. Toxic shock syndrome (TSS) is an acute, multi-system, toxin-mediated illness, typically resulting in shock and multi-organ failure early in its clinical course. It represents the most fulminant expression of a spectrum of diseases caused by toxin-producing strains of *Staphylococcus aureus* and *Streptococcus pyogenes* (group A streptococcus [GAS]).

Despite a mortality rate higher than that of meningococcal septicaemia, TSS has not achieved the same level of awareness among health-care professionals, who will generally encounter very few recognised cases during their careers. TSS may present anywhere within the health-care system, from occupational health departments to specialist hospital units, and may progress with a rapidity that, once seen, is never forgotten. It is therefore essential that all health-care practitioners have a sound appreciation of the epidemiology, pathophysiology, clinical features, and management of TSS.

Epidemiology

Staphylococcal toxic shock syndrome

Staphylococcal TSS was first reported in 1978 and came to prominence in the early 1980s in the USA in association with the use of highly absorbent tampons among young healthy women, with high percentages of vaginal cultures yielding *S aureus*.[2] During this period, the peak incidence was reported to be between 6·2 and 12·3 cases per 100 000 inhabitants per year in active surveillance programmes.[3] With changes in tampon manufacture and usage advice, the incidence fell to around one case per 100 000 inhabitants per year in the USA.[4] Data from a surveillance programme in Minneapolis-St Paul for 2000–03 suggest local increases, with a rise from 0·9 to 3·4 cases per 100 000 inhabitants per year over the 4-year period.[5] Currently, 1–5% of healthy women have vaginal colonisation with a toxin-producing strain of *S aureus*. This is unchanged from 1980–81, although overall staphylococcal colonisation has increased.[6] A French surveillance study of 55 TSS cases over a 30-month period has suggested that non-menstrual staphylococcal TSS is more prevalent than menstrual TSS, accounting for 62% of the cases. There were no deaths in the menstrual TSS group compared with a mortality of 22% for non-menstrual cases.[7]

Non-menstrual TSS may result from any primary staphylococcal infection, or indeed from colonisation with a toxin-producing strain of *S aureus* (including meticillin-resistant *S aureus* [MRSA]). It can arise after disruption of the skin or mucous membranes, in association with abscesses or burns, and after surgical procedures, although commonly no source of infection is confirmed.[8] In light of this, TSS should be considered in patients with shock and infection with *S aureus*.

Streptococcal toxic shock syndrome

A second toxic-shock-like syndrome attributed to *S pyogenes* was reported in 1987.[9] Streptococcal TSS secondary to invasive GAS soft-tissue infections had a mortality of approximately 30% in some early series.[10] Studies from Australia, Denmark, and the USA cite the incidence of invasive GAS infection at between 1·5 and 5·2 cases per 100 000 inhabitants per year, higher rates being found at the extremes of age and among ethnic minorities.[11–13] 5–14·4% of cases developed streptococcal TSS with an attendant case fatality of 23–44%. Higher incidence was also observed in those with underlying chronic illness, after varicella infection, and with non-steroidal anti-inflammatory drug use. Recently, published data from 11 European countries (Strep-EURO) gave an incidence of streptococcal TSS of 13% in streptococcal infection from any source. This increased dramatically to 50% in patients with necrotising fasciitis. The 7-day mortality from streptococcal TSS was 44%.[14]

Pathophysiology

Superantigens trigger a cytokine avalanche

Bacterial toxins are pivotal to the pathogenesis of staphylococcal and streptococcal TSS. They act as superantigens, which are protein toxins that share the

ability to trigger excessive and non-conventional T-cell activation with consequent downstream activation of other cell types, and cytokine/chemokine release.[15] In addition to Gram-positive organisms, some Gram-negative bacteria, *Mycoplasma* spp, and certain viruses are known to produce these proteins, and so-called endogenous superantigens are found coded within the human genome (generally within endogenous retroviral sequences). The staphylococcal and streptococcal superantigens identified to date are single-chain proteins expressed as precursor molecules, which are then cleaved to release the functional extracellular toxin.[16] The structure and function of *S aureus* and *S pyogenes* superantigens are the best characterised.[17,18]

Superantigens bypass conventional mechanisms of MHC-limited antigen processing, whereby antigens are processed into peptide fragments within antigen-presenting cells such as monocytes. These fragments are then presented to the T cell via a specific peptide-binding groove of the MHC class II molecule. T cells will only respond if they recognise the class II molecule and the specific antigen fragment being presented. By contrast, superantigens bind simultaneously as unprocessed intact proteins directly to the MHC class II molecule and to the T-cell receptor (TCR).[18,19] They bind at sites distant to the conventional peptide-binding area, primarily to the variable Vβ region on the TCR, although a small number of superantigens bind to the TCR α chain.[20,21] The interaction of superantigen with specific TCR Vβ regions induces clonal expression of T cells possessing those specific Vβ TCR patterns. This allows identification of a characteristic Vβ signature for the superantigen concerned and may be diagnostically useful.[22–24]

Binding activates up to 20–30% of host T cells, whereas conventional antigen presentation activates only around 0·01% of the host T-cell population.[18,25,26] Interestingly, endogenous superantigen gene sequences seem to downregulate the expression of T cells with the Vβ TCR appropriate to that superantigen. This may prevent subsequent expansion of that T-cell population in response to exogenous superantigen challenge, offering a degree of protection to the host by limiting the inflammatory consequences of the exposure.[27]

When superantigen binds to TCR and MHC class II, there is a rapid increase in cytokine expression by T cells (primarily lymphotoxin α, interleukin 2, and interferon γ) and by antigen-presenting cells such as monocytes (primarily tumour necrosis factor [TNF], interleukin 1β, and interleukin 6), probably linked to activation of the transcription factor nuclear factor κB (NFκB).[28] NFκB has a central role in the generation and expansion of the inflammatory response, activation of coagulation, and the development of organ dysfunction (figure). The degree of NFκB activation also correlates with mortality risk.[29,30] Recently, antioxidant agents such

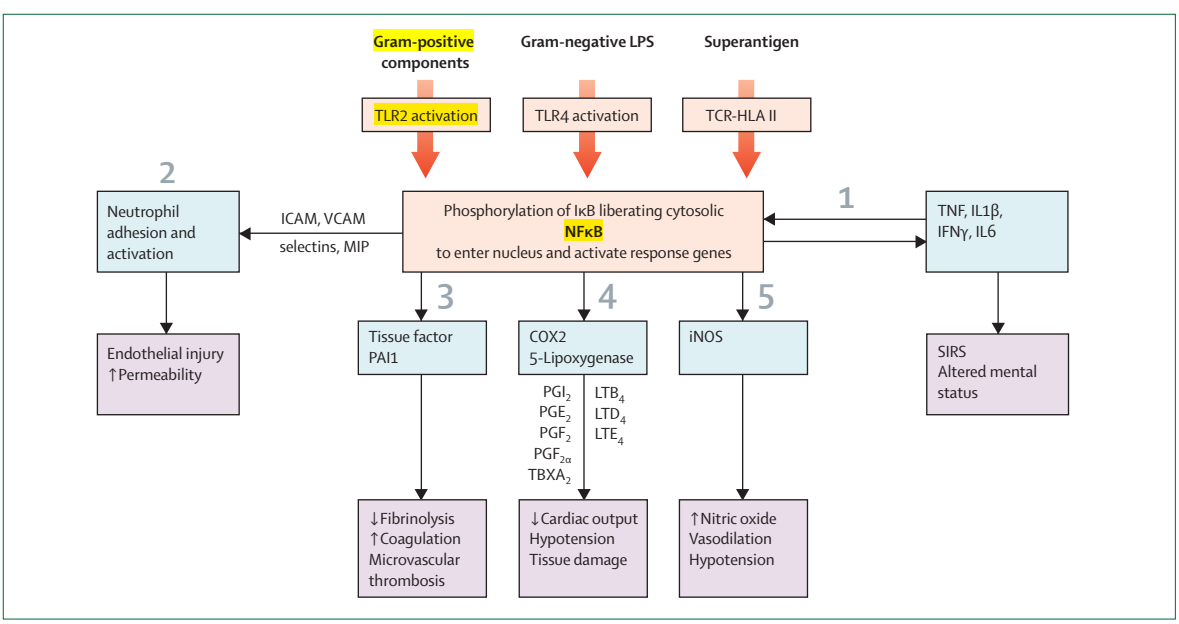

Figure: **Nuclear factor κB (NFκB) has a central role in the generation and propagation of the inflammatory response**
Activation of Toll-like receptor (TLR) 2 pathways by Gram-positive components, TLR4 pathways by Gram-negative products, and superantigenic stimulation, all bring about a sequence of events that allow free NFκB to pass into the nucleus and bind to DNA. These events lead to (1) expression of inflammatory mediators and amplification of the inflammatory cascade; (2) neutrophil adhesion and activation; (3) activation of tissue factor and plasminogen activator inhibitor 1 (PAI1) to reduce fibrinolysis and enhance coagulability; (4) induction of cyclo-oxygenase 2 (COX2) and 5-lipoxygenase systems elaborating pro-inflammatory prostanoids, leukotrienes, and thromboxane A2 (TBXA2); and (5) inducible nitric oxide synthase (iNOS) acceleration with consequent vasodilatation and hypotension. Adapted from Liu et al.[29] ICAM=intercellular adhesion molecule. IκB=inhibitor of NFκB. IFNγ=interferon γ. IL1β=interleukin 1β. IL6=interleukin 6. LPS=lipopolysaccharide. LTB4=leukotriene B4. LTD4=leukotriene D4. LTE4=leukotriene E4. MIP=macrophage inflammatory protein. PGE2=prostaglandin E2. PGF2α=prostaglandin F2α. PGI2=prostaglandin I2. SIRS=systemic inflammatory response syndrome. TCR=T-cell receptor. TNF=tumour necrosis factor. VCAM=vascular cell adhesion molecule.

as N-acetyl cysteine have been shown to reduce T-cell proliferation and cytokine expression through inhibition of NFκB in a superantigen-stimulated cell-line model, and other inhibitory approaches are under active investigation.[31,32]

T-cell activation leads to recruitment of further T and B cells to the site of infection. Clonal T-cell expansion continues, as does activation of antigen-presenting cells, further amplifying the release of pro-inflammatory mediators and contributing to increased procoagulant activity.[33] A complex interplay exists between the cytokines released during this pro-inflammatory avalanche, with interferon γ rapidly inducing TNF and interleukin-6 expression.

Superantigen structure–activity relations

Superantigens have been grouped into five distinct populations (I–V) based on their phylogenetic relations.[26] Superantigens take part in two key interactions, first with MHC class II and second with the TCR, using mechanisms that are thought to differ across the five superantigen groups.[34]

Superantigens interact with the MHC–peptide antigen complex in four main ways.

First, they bind to the MHC α subunit at a site that extends over the peptide surface and contacts the β subunit. This peptide-dependent interaction is exemplified by *S aureus* TSS toxin 1 (TSST1).

Second, they bind to the MHC α subunit without any interaction with the peptide. This peptide-independent interaction is seen with group II superantigens such as staphylococcal enterotoxin B (SEB) and enterotoxin C3.

Third, they bind to the MHC β subunit in a zinc-dependent manner and involving multiple sites of interaction with the peptide. This occurs at areas common to multiple peptides and is seen with group IV and V superantigens such as SpeC and staphylococcal enterotoxin K, respectively.

Finally, they bind by a combination of the first and second methods (eg, staphylococcal enterotoxin A).[35]

The structural conformation of superantigen interaction with TCR Vβ has also been studied.[34–36] Although all superantigens seem to bind to the second complement-determining region (CDR2), the Vβ region contains multiple hypervariable elements and superantigens vary in their binding specificity and cross-reactivity to these elements. Superantigens with low specificity, such as SEB and staphylococcal enterotoxin C3, require only a few of these elements to complete binding (eg, CDR2 and hypervariable region 4). As specificity increases (eg, SpeA), more and more of these hypervariable components are required, and hydrogen bonds form between the superantigen and TCR. With even greater specificity (eg, SpeC), the complete TCR hypervariable element series (ie, CDR1–3 and hypervariable region 4) is required. TSST1 shows the greatest degree of specificity, targeting a loop in the third framework region rather than relying on interaction with multiple hypervariable elements. TSST-1 also requires the presence of a particular residue in a particular location within the third framework region loop (Lys62) to activate T cells. The group V superantigen staphylococcal enterotoxin K possesses an extended α3–β8 loop with a specific residue that binds to Vβ 5.1, and third and fourth framework regions, and is critical for T-cell activation.

T-cell activation may vary between groups on the basis of the overall affinity and conformation of the MHC–superantigen–TCR complex. First, TSST1 (group I) acts as a bridge between TCR and MHC molecules, with no direct MHC–TCR contact. The affinity of the TSST1–TCR and TSST1–MHC interactions is similar to that of conventional MHC–TCR interactions and is an effective T-cell activator. Second, group II superantigens such as SEB act as a wedge between MHC and TCR, preventing contact between TCR and peptide antigen. However, there is direct MHC–TCR contact. The SEB–MHC and SEB–TCR interactions are not sufficient to achieve effective T-cell activation. However, the additional MHC–TCR interaction brings the total affinity to the point at which T-cell activation occurs. Third, group IV superantigens such as SpeC form a bridge between MHC and TCR and again allow no direct MHC–TCR contact, as with TSST1. However, the resulting conformational planes are different. The combined affinities of the zinc-dependent TCR interaction and the Vβ contact are sufficient for T-cell activation.

Specific superantigen–disease associations

In menstrual TSS, the superantigen–disease relation is clearly apparent, with staphylococcal TSST1 responsible for nearly all (95%) menstrual-related TSS cases.[37,38] The strong relation to menstrual-related TSS cases has traditionally been attributed to the ability of TSST1 to cross mucosal barriers, although SEB is also able to cross nasal, conjunctival, and vaginal mucosa.[39] Of note, TSST1 is also detectable in approximately 50% of non-menstrual TSS, the remaining cases being due primarily to SEB and less often to other members of the family, such as staphylococcal enterotoxins C, G, and I.[40] Reports of TSST1 in association with MRSA are becoming more frequent. Highly virulent clones of MRSA that harbour the TSST1 gene (*tst*) have been associated with TSS, a critical point for clinicians to remember when managing patients with MRSA and shock.[41]

There are multiple associations between streptococcal superantigens and invasive diseases. One of the most intriguing is soluble streptococcal M protein type M1. M1 streptococcal isolates are well known to be more virulent, and recent work suggests that soluble M1 proteins may also be superantigenic, preferentially activating T cells with Vβ2 and Vβ4 TCR. M proteins also activate T cells via Toll-like receptor 2 (TLR2).[42,43] The status of M protein as a superantigen remains contentious.

The expression of superantigen genes is also important. Four alleles of the streptococcal pyrogenic exotoxin A (*speA*) gene, designated *speA1–A4*, have been found in isolates from patients with severe invasive GAS disease.[44] Geographic distribution of genetic strains is wide, with organisms expressing SpeA2 and SpeA3 being responsible for the most (60–90%) streptococcal TSS episodes in Europe, North America, and Australia.[45] In the Danish data that contributed to the Strep-EURO study, either SpeA or SpeC was present in all cases of streptococcal TSS.[12]

Superantigen acts synergistically with endotoxin

Critically ill patients may be exposed to both endotoxin from Gram-negative organisms and superantigen from toxin-producing Gram-positive organisms, even if the organism is simply colonising the patient. In animals, co-administration of endotoxin and superantigen reduced the median lethal dose by up to 50 000 times compared with either toxin given alone.[46] Immune effector cells recognise so-called pathogen-associated molecular patterns such as lipopolysaccharide from Gram-negative organisms and lipoteichoic acid from Gram-positive organisms.[47] This recognition is intimately involved in the genesis of the endotoxin–superantigen double hit. Although there is a degree of overlap, the detection system for lipopolysaccharide mainly involves activation of a Toll-like receptor (TLR4) and the co-receptor MD2, and that for Gram-positive organisms mainly involves lipoteichoic acid or peptidoglycan activation of TLR2.[48,49] The detailed biology of these receptors has been well reviewed elsewhere.[50–52] Activation of each of these recognition systems results in pro-inflammatory mediator release and further inflammatory stimulation via NFκB. Superantigen–MHC binding up-regulates the TLR4/MD2 receptor system, priming monocytes for endotoxin exposure, amplifying the expression of TNF, interleukin 6, and interleukin 1β, and inducing vasodilatation through type I interferon over-stimulation of inducible nitric oxide synthetase.[53] In addition, streptococcal superantigens seem to up-regulate TLR2, which may become diagnostically useful in identifying streptococcal toxin-mediated disease in a manner analogous to Vβ expansion.[54]

***Panel 1:* Staphylococcal toxic shock syndrome clinical case definition**

1 Fever ≥38·9°C
2 Rash—diffuse macular erythroderma
3 Desquamation—1–2 weeks after onset of illness, especially of palms and soles
4 Hypotension—systolic blood pressure ≤90 mm Hg for adults
5 Multi-system involvement—3 or more of the following:
  a Gastrointestinal—vomiting or diarrhoea at the onset of illness
  b Muscular—severe myalgia or elevated creatine phosphokinase
  c Mucous membranes—vaginal, oropharyngeal, conjunctival hyperaemia
  d Renal—blood urea nitrogen or creatinine twice-upper limit of normal
  e Hepatic—total bilirubin twice-upper limit of normal
  f Haematological—platelets ≤100×10⁹/L
  g CNS—disorientation or alterations 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 classification

Probable: case with five of the six clinical findings described
Confirmed: case with all six of the clinical findings described

Mobility of superantigen genes across streptococcal strains

The genetic plasticity of the streptococcal genome results from the presence of bacteriophages within the genome (so-called prophages) and may contribute to the observed variability in virulence.[55] Prophage genetic material may account for up to 10% of the streptococcal genome.[56] Most GAS superantigen genes are found within these prophage sequences (also called pathogenicity islands or genomic islands), and these phages are capable of transferring superantigen genes between GAS strains, or indeed from GAS strains to group C and theoretically to group G streptococci.[57] In so doing, they can convert a non-virulent or less virulent strain into a highly virulent one. Incidence of invasive group C and G streptococcus also seems to be increasing, along with the presence of superantigen genes within these organisms.[58] An Australian study has recently identified superantigen genes in GAS isolates and correlated the superantigen with *emm* gene type (the gene encoding M protein).[59] 26 different superantigen profiles were present in 107 isolates, distributed among 22 different *emm* types. These results were similar to previous reports and support the hypothesis that conserved superantigen profiles result from surface M proteins influencing the entry of bacteriophages in a selective manner.

Host–pathogen interactions

Not all patients colonised or infected with a toxin-producing strain of *S aureus* or *S pyogenes* go on to develop TSS or streptococcal TSS, and secondary infection rates are low. The interaction between the host immune system and the pathogen may play a major part in response to the bacterial and toxic challenge.

Deficient antibody titres and TSS

The absence of antibodies to superantigens seems to be a major risk factor for the development of TSS.[25,60] More than 85% of women aged 13–40 years have TSST1 antibody at concentrations thought to be protective.[38] Low or negative concentrations have been found in 90·5% of patients with menstrual TSS and more than 50% of these patients failed to seroconvert within 2 months of their illness.[61] This finding may predispose these individuals to repeated episodes of streptococcal TSS and has been

linked to the ability of TSST1 to suppress the action of immunoglobulin-secreting cells.[25] The superantigen-mediated cytokine response is associated with minimum T-helper type 2 cell response, resulting in failure to support B-cell proliferation and differentiation. In addition, high concentrations of TSST1 induce B-cell apoptosis. Concentrations of antibody to streptococcal superantigens are lower in those with invasive disease than in healthy controls.

HLA haplotype variation and severity

The magnitude of the inflammatory response is closely linked to disease severity and may be governed by host genetic factors such as MHC class II haplotype.[62] The sites at which superantigens bind to HLA class II are polymorphic, and differences in binding are indicated by a varying T-cell and cytokine response. For example, the DRB1*15/DQB1*06 haplotype is associated with strong protection from streptococcal TSS and reduced cytokine concentrations during GAS infection, whereas the DRB1*14/DQB1*05 haplotype is associated with predisposition to TSS.[63,64]

Sex-dependent response to sepsis and superantigen shock

The relation between sex and susceptibility to sepsis is complex, with 17β oestradiol having variable effects on immune function (low concentrations augmenting and high concentrations inhibiting interleukin-6 and TNF release), and applicability of animal studies to the human setting is under debate.[65] Men are thought to have an increased risk of post-injury bacterial sepsis, bacteraemia, referral to intensive care, risk of septic shock, and mortality in conventional sepsis. Women have been shown to have a more pronounced and prolonged immune reaction to sepsis, whereas men seem more prone to develop variable degrees of immunoparesis after the initial immune response.[66] However, the female preponderance in superantigen-mediated shock extends to non-menstrual TSS.[3] Something different seems to be occurring in superantigen-mediated shock that alters the influence of sex away from that found in septic shock. The exact nature of this difference is unclear, but seems in part related to oestrogen. In a transgenic mouse model, females were (1) more susceptible to *S pyogenes* sepsis, (2) had a significantly more pronounced TNF response to superantigen (SEB) than males, (3) had lower concentrations of soluble TNF receptors I and II both at baseline and on superantigenic challenge, suggesting deficient TNF removal, and (4) had a greater degree of TNF-induced hepatic apoptosis and hence liver damage than males.[67] In addition, the investigators were able to show that pre-treatment with the oestrogen receptor modulator tamoxifen decreased both the early and late rise in TNF, reduced the level of hepatic apoptosis, and increased concentrations of soluble TNF receptors. This area requires cautious interpretation and further study.

***Panel 2:* Streptococcal toxic shock syndrome clinical case definition**

1 Isolation of group A β-haemolytic streptococci:
  - a From a normally sterile site—blood, CSF, peritoneal fluid, tissue biopsy
  - b From a non-sterile site—throat, vagina, sputum

2 Clinical signs of severity:
  - a Hypotension—systolic blood pressure ≤90 mm Hg in adults
  - b Two or more of the following signs:
    - i Renal impairment—creatinine >2 mg/dL (>177 μmol/L)
    - ii Coagulopathy—platelets ≤100×10⁹/L or disseminated intravascular coagulation
    - iii Hepatic involvement—alanine aminotransferase, aspartate aminotransferase, or total bilirubin twice the upper limit of normal
    - iv Adult respiratory distress syndrome
    - v Generalised, erythematous, macular rash that may desquamate
    - vi Soft-tissue necrosis, including necrotising fasciitis, myositis, or gangrene

Case classification

Probable: case fulfils 1b and 2 (a and b) if no other cause for the illness is found

Definite: case fulfils 1a and 2 (a and b)

Clinical features and diagnosis

TSS is characterised by an acute, progressive illness associated with fever, rapid-onset hypotension, and accelerated multi-system failure. Multi-system involvement is usually established by the time of presentation. Clinical case definitions for both syndromes have been proposed (panels 1 and 2).[68,69]

Staphylococcal toxic shock syndrome

Staphylococcal TSS presents abruptly with an influenza-like prodromal illness consisting of fever, gastrointestinal upset, and severe myalgia, followed commonly by confusion, lethargy, and agitation. Symptoms of hypovolaemia are common at presentation. If present, a focus of infection is more likely to be superficial, may complicate burns or a surgical wound, or may result from a foreign body. Desquamation is a characteristic late feature of staphylococcal TSS, occurring 10–21 days after disease onset. Of note, blood cultures are positive in fewer than 5% of cases of staphylococcal TSS.[8]

The clinical features of menstrual and non-menstrual TSS are identical in most cases. Up to 95% of patients diagnosed with menstrual TSS have an onset of illness during menstruation.[70] Patients with non-menstrual TSS are more likely to have acquired the condition nosocomially and to have had prior antibiotic treatment. Fever and rash are more prevalent in early illness, and non-menstrual TSS is more frequently associated with CNS manifestations and renal complications.[8] Non-staphylococcal enterotoxin A and non-TSST-1 superantigens seem to have greater neurotoxic potential.[7] Post-operative non-menstrual TSS usually occurs within 48 h of surgery, and in many cases evidence of clinically significant surgical site infection is lacking at the time of presentation. After the onset of symptoms, progression is rapid and multi-organ failure can be present in as little as 8–12 h. Recurrence of menstrual TSS has been well documented, but recurrence

	Option 1	Option 2 (β-lactam intolerant)	Option 3	Comments
Group A streptococcus	Penicillin G and clindamycin	Macrolide or fluoroquinolone, and clindamycin	Linezolid or daptomycin or tigecycline	Macrolide and fluoroquinolone resistance increasing
MLS-resistant group A streptococcus	Penicillin G, and vancomycin or teicoplanin	Vancomycin or teicoplanin	Linezolid or daptomycin or tigecycline	Macrolide resistance associated with clindamycin resistance
Meticillin-sensitive *S aureus*	Cloxacillin or nafcillin or cefazolin, and clindamycin	Clarithromycin and clindamycin	Rifampicin, and linezolid or daptomycin or tigecycline	..
Meticillin-resistant *S aureus*	Clindamycin or linezolid, and vancomycin or teicoplanin	NA	Rifampicin, and linezolid or daptomycin or tigecycline	..
Glycopeptide resistant or intermediate *S aureus*	Linezolid and clindamycin (if sensitive)	NA	Daptomycin or tigecycline	Incidence increasing. Geographical patterns highly variable

MLS=macrolide, lincosamide, and streptogramin B. NA=not applicable.

Table: **Antimicrobial options in toxic shock syndrome**

of non-menstrual TSS is rare. Non-menstrual TSS must be considered in the aetiology of shock states in patients with definite or suspected staphylococcal infection.

Streptococcal toxic shock syndrome

Streptococcal TSS more commonly arises from deep-seated invasive soft-tissue infections such as necrotising fasciitis, cellulitis, and myositis. Pain may be severe and relentless and is a common reason for seeking medical attention. An influenza-like illness is also common in the early stages with fever, sore throat, swollen lymph nodes, and gastrointestinal upset. Those patients with a defined entry site may have early and visible signs of inflammation. In the absence of a defined portal of entry, clinical evidence of a deep infection becomes more obvious as the illness progresses. The initiating injury may be blunt trauma, muscle strain, and haematoma or joint effusion and may seem trivial, so careful history taking is essential. Examination may reveal bruising, haemorrhagic bullae, skin sloughing, and oedema. Hypotension and organ dysfunction are rapidly progressive.

Most (60%) patients with streptococcal TSS have positive blood cultures.[71] Presence or absence of bacteraemia does not affect mortality. The diagnosis of streptococcal TSS is confirmed when GAS are cultured from normally sterile body fluids in patients with shock and multi-organ failure. The mortality associated with streptococcal TSS is much higher than with staphylococcal TSS, and has been quoted at up to 80% in association with myositis.[26] A murine model of the disease suggests that an early initial infection may be followed up to 3 weeks later by bacteraemia, at which point symptoms and signs of the disease appear; the same study also found that trivial injury such as bruising amplified the severity of the bacteraemia.[72]

Therapeutic strategies

Supportive management and source control

Immediate intervention and resuscitation are required. In the early stages of illness, the causative organism will be unknown and the same basic therapeutic strategy should be applied as to any case of septic shock with active fluid resuscitation, early use of vasopressors and inotropes, or both, and intubation and mechanical ventilation if required. An appropriate antimicrobial regimen should begin immediately after culture samples have been taken.

A thorough search for infective focus is essential. The presence of necrotising fasciitis or myositis mandates immediate aggressive surgical debridement and is a true surgical emergency. The underlying tissue infection may be much more extensive than initially appreciated, and the rate of spread may exceed the rate of debridement if a conservative approach is taken. Surgical wounds should be considered potential sources of infection, even in the absence of overt signs. Any infected wound should be reopened and widely debrided, and packs or infected devices removed. In women, a vaginal examination should be done and any tampon or foreign body removed.

Antimicrobial therapy to reduce toxin production and organism load

Inadequate initial antibiotic therapy increases mortality in intensive-care patients with severe sepsis and septic shock.[73–75] Clinical trial data comparing antibiotic regimens in TSS are scarce. Recommendations are based on in-vitro studies and theoretical principles, and include the use of a β-lactam agent and a lincosamide, pending culture results.[76] Therapy is focused on reducing both exotoxin production and organism load. In cases in which the causative organism is unknown, the antibiotic regimen should cover both *S aureus* (including MRSA if indicated) and *S pyogenes*. An increasing range of antimicrobial agents are active against Gram-positive organisms, and definitive therapy decisions require knowledge of local drug availability, clinical preferences, and sensitivity pattern. Potential therapeutic agents for various causative organisms and strains are shown in the table.

Therapeutic principles

GAS remain exquisitely sensitive to β-lactam agents, including penicillin G, an agent often considered as part of first-line therapy. This drug is usually given with clindamycin, which has inhibitory actions on protein synthesis including superantigen production. Although penicillin G is bactericidal, it has been shown to be less effective for higher organism loads. This is perhaps due to the reduced expression of penicillin-binding proteins by bacteria in the stationary phase of growth, which is reached more rapidly with large organism loads.[77] Streptococcal resistance to macrolides and fluoroquinolones seems to be increasing, particularly in Europe and Asia. In addition, macrolide resistance is

linked to lincosamide (clindamycin) resistance in so-called macrolide–lincosamide–streptogramin-B-resistant *S pyogenes*.[78,79] Therapy for MRSA has commonly included vancomycin; however, *S aureus* strains with intermediate sensitivity or resistance to glycopeptides are increasing.[80] The newer agents such as linezolid, daptomycin, and tigecycline are active against *S pyogenes*, MRSA, and intermediate strains, and represent effective (if expensive) agents to fall back on.

Rationale for clindamycin in initial therapy regimens

Clindamycin is a bacteriostatic lincosamide with efficacy unaffected by bacterial growth phase or inoculum size. In a murine model of *S pyogenes*-induced myositis, penicillin was ineffective if treatment was delayed by more than 2 h after onset of infection, whereas mice receiving clindamycin had improved survival even if treatment was delayed.[81] Clindamycin has been shown to inhibit toxin production by both *S aureus* and *S pyogenes*. In-vitro models comparing the effects of clindamycin, linezolid, and penicillin on SpeA release have shown a significant decrease in SpeA production in regimens containing clindamycin and linezolid as opposed to penicillin G alone, despite the theoretical ability of clindamycin to suppress synthesis of penicillin-binding proteins.[82] This antagonistic effect does not seem to be clinically relevant with adequate drug doses. Linezolid and clindamycin have both been shown to reduce TSST1 production, and clindamycin significantly reduces SpeA expression by *S pyogenes* compared with ampicillin.[83] Linezolid has been used successfully to treat staphylococcal TSS and has been shown to reduce TSST1 production.[84]

Effects and mechanism of intravenous immunoglobulin

Patients with a deficient antibody response against TSST1 are at increased risk of primary or recurrent TSS, and patients with invasive GAS infections have significantly lower concentrations of superantigen-neutralising antibodies.[60] Case reports published in the mid-1990s suggested improved outcomes for patients with streptococcal TSS treated with intravenous immunoglobulin.[85–87] Administration of intravenous immunoglobulin can block in-vitro T-cell activation by staphylococcal and streptococcal superantigens. Factors beyond the presence of neutralising antibodies may contribute to the efficacy of intravenous immunoglobulin, at least in vitro, because the suppressive effect of whole intravenous immunoglobulin on SEB-induced T-cell proliferation and cytokine production remains significant even after removal of specific anti-SEB antibody from the preparation.[88,89]

In a Canadian comparative observational study, 21 patients receiving intravenous immunoglobulin had a 30-day survival of 67% compared with 34% in the 32 control cases.[90] Patients treated with intravenous immunoglobulin were more likely to have had surgery and to have received clindamycin, and inclusion of historical controls may have introduced bias. Analysis of plasma from ten cases and ten controls showed a significant reduction in T-cell-triggered production of interleukin 6 and TNF after a single dose of intravenous immunoglobulin.

A subsequent multicentre, randomised, placebo-controlled trial studied the efficacy of intravenous immunoglobulin as adjunctive therapy in streptococcal TSS.[91] The trial was terminated due to slow patient recruitment after 21 patients were enrolled (ten received intravenous immunoglobulin and 11 received placebo). The primary endpoint was 28-day mortality, but despite a 3·6 times higher mortality in the placebo group (36% *vs* 10% in treatment group), significance was not reached. There was a greater improvement in sepsis-related organ failure assessment score on days 2 and 3 of the study in the treatment group, and intravenous immunoglobulin produced 87–100% inhibition of GAS strains on in-vitro testing.

S aureus was isolated from blood culture in one patient in this trial and was found to be inhibited to a lesser degree by intravenous immunoglobulin. This finding prompted a comparison study to investigate differential effects of intravenous immunoglobulin on staphylococcal and streptococcal superantigen production.[92] Culture supernatants of *S pyogenes* were consistently inhibited to a greater degree than those of *S aureus*. The investigators concluded that higher doses of immunoglobulin might be required to provide protective titres and clinical efficacy in the treatment of staphylococcal TSS. In the original trial, the dose used was 1 g/kg bodyweight on day 1 followed by subsequent doses of 0·5 g/kg on days 2 and 3, but a superior dose regimen for staphylococcal disease has not been confirmed. Different preparations may vary in their neutralising capacity, probably due to differences (perhaps geographical) in organism exposure in the donor population.[93]

The mortality risk and rapidity of decline in staphylococcal and streptococcal TSS are such that delays in effective therapy have significant potential to worsen outcome. On this basis, we argue that immunoglobulin therapy should not be unreasonably delayed in such cases. However, no clear information exists on what constitutes a safe delay. The UK Department of Health has issued guidance on the use of immunoglobulin.[94] For the management of invasive streptococcal disease (presumably not just streptococcal TSS), they advise that intravenous immunoglobulin "may be added to adequate toxin-neutralising antimicrobials, source control, and sepsis management when these approaches have failed to elicit a response."[94] In the absence of a recommendation relating to time delay, we advise that the same approach to timing be taken for streptococcal TSS as is recommended for staphylococcal TSS. In this setting, the guidance states that intravenous immunoglobulin "may be used for TSS resulting from an infection refractory to several

Search strategy and selection criteria

Data for this Review were identified by a Medline search restricted to English-language articles. The search terms used were "toxic shock", "staphylococcal sepsis", "streptococcal sepsis", "superantigen", "nuclear factor kappa B", "toll-like receptor", "immunity", "enterotoxin", "exotoxin", "T-cell receptor", "septic shock", and "immunoglobulin". Further articles were identified through review of the references in selected papers. No limit was set on publication dates or types.

hours of aggressive therapy, in the presence of an undrainable focus, or when there is persistent oliguria with pulmonary oedema".[94] Our approach is to consider use of intravenous immunoglobulin in patients in whom there has been no clinical response within the first 6 h of aggressive supportive therapy.

Conclusions

TSS is a global disease entity caused by pathogens with the ability to evolve in terms of superantigen generation and avoidance of the human immune defence. Despite intense research efforts, we do not yet have new clinically available therapies capable of neutralising superantigen-mediated T-cell activation. Further research is required to address timing and components of therapy. In the clinical arena, a sound understanding of the pathophysiology, a high index of suspicion, early diagnosis, and immediate intervention are the best ways to combat the significant mortality and morbidity of TSS. Given the supportive background research and the severity of this syndrome, we recommend a therapeutic approach in both staphylococcal and streptococcal TSS that incorporates prompt use of toxin-neutralising antimicrobials such as clindamycin or linezolid, along with early intravenous immunoglobulin therapy in cases in which there is failure to improve with aggressive support and source control.

Conflicts of interest

We declare that we have no conflict of interest.

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