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Toxic shock syndrome – the seven Rs of management and treatment

Amanda L. Wilkins [a], Andrew C. Steer [a,b,c,d], Pierre R. Smeesters [d,e,f], Nigel Curtis [a,b,c,*]

[a] *Infectious Diseases Unit, The Royal Children's Hospital Melbourne, Parkville, Australia*
[b] *Department of Paediatrics, The University of Melbourne, Parkville, Australia*
[c] *Infectious Diseases & Microbiology and Group A Streptococcal Research Groups, Murdoch Children's Research Institute, Parkville, Australia*
[d] *Centre for International Child Health, University of Melbourne, Melbourne, Australia*
[e] *Paediatric Department, Academic Children Hospital Queen Fabiola, Université Libre de Bruxelles, Brussels, Belgium*
[f] *Molecular Bacteriology Laboratory, Université Libre de Bruxelles, Brussels, Belgium*

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Summary Staphylococcal and streptococcal toxic shock syndrome (TSS) are associated with significant morbidity and mortality. There has been considerable progress in understanding the pathophysiology and delineating optimal management and treatment. This article reviews the management of TSS, outlining the 'Seven Rs of Managing and Treating TSS': **R**ecognition, **R**esuscitation, **R**emoval of source of infection, **R**ational choice of antibiotics, **R**ole of adjunctive treatment (clindamycin and intravenous immunoglobulin), **R**eview of progress and **R**educe risk of secondary cases in close contacts.

Introduction

Toxic shock syndrome (TSS) is a multi-system, life-threatening condition, caused predominantly by superantigen toxin-producing strains of *Staphylococcus aureus* and *Streptococcus pyogenes* (group A streptococcus [GAS]). Group C and group G streptococci also produce superantigens capable of causing TSS.[1] Rarely TSS can be associated with *Yersinia pseudotuberculosis*.[2] Staphylococcal TSS was first described by James Todd in 1978 in children[3] and streptococcal toxic shock-like syndrome was first reported in 1987.[4] While TSS is still associated with significant morbidity and mortality,

* Corresponding author. Department of Paediatrics, The University of Melbourne, The Royal Children's Hospital, 50 Flemington Rd, Parkville, 3052, Australia. Tel.: +61 3 9345 6366; fax: +61 3 9345 4751.
E-mail address: nigel.curtis@rch.org.au (N. Curtis).

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Table 1 Summary of the seven Rs of managing toxic shock syndrome

1. Recognition	• Early recognition • Recognition that not all TSS cases meet case definition
2. Resuscitation	• Aggressive fluid support • Respiratory and inotrope support
3. Removal of source of infection	• Surgical debridement of wounds, drainage of abscesses • Removal of tampons in staphylococcal TSS
4. Rational choice of antibiotics	• Appropriate empiric antibiotic choice • Consider need for MRSA cover
5. Role of adjunctive treatment	• Clindamycin • Intravenous immunoglobulin
6. Review progress	• Continued search for focus requiring surgical intervention • Rationalise antibiotic choice and duration
7. Reduce risk of secondary cases in close contacts	• Heightened index of suspicion • Consider chemoprophylaxis in close contacts of streptococcal TSS

there has been considerable progress made in understanding the pathophysiology and delineating optimal management and treatment.

There are a large and increasing number of both staphylococcal and streptococcal superantigens that can cause TSS and a revised nomenclature and categorisation of the strepotococcal pyogenic exotoxins has been proposed.[5] The superantigen toxins produced by these bacteria initiate a cytokine storm resulting in the characteristic clinical features of TSS, including fever and rash, followed by hypotension and multi-organ failure secondary to capillary leak. Formal diagnostic criteria have been devised for both streptococcal and staphylococcal TSS (Table 2).

This article reviews the management of TSS, starting from early recognition, to antimicrobial and adjunctive treatment, and prevention of secondary cases in close contacts. The following outlines the 'Seven Rs of Managing TSS' (Table 1).

1. Recognition

Early recognition of TSS is critical to ensure that appropriate treatment is implemented promptly. The high rate of morbidity and mortality that is still seen with TSS may be attributable to delayed recognition and treatment. The case definitions established by the Centers for Disease Control and Prevention (CDC) for both staphylococcal and streptococcal TSS are useful tools for research and surveillance, but have important limitations in clinical diagnosis. The definitions were designed to be highly specific for research purposes, rather than aiming to maximise detection and diagnosis of cases (i.e. high sensitivity) (Table 2).[6,7] Furthermore, in industrialised countries where there is now routine immunisation against other bacteria that have historically been important causes of sepsis in children (meningococcus and pneumococcus), the likelihood of TSS as a cause of sepsis is higher today than when the diagnostic criteria were first developed.

There are two specific issues for the clinician: first, some of the criteria can only be fulfilled in retrospect; and second, many cases do not fulfil these diagnostic criteria at presentation and indeed may not meet the criteria at any stage of the illness. Therefore, it is important to have a high index of suspicion for TSS in patients presenting with sepsis syndromes, especially where the patient presents with other features compatible with TSS (such as erythematous rash, conjunctivitis or early signs of other system involvement including abnormal liver function tests or abnormal clotting) or where there is a soft tissue focus of infection.

2. Resuscitation

The rapid progression from onset to multi-organ system failure in TSS necessitates immediate action with aggressive fluid resuscitation and concomitant respiratory and often inotropic support. If such intensive care support is not available, medical transfer to a tertiary referral hospital should be organised rapidly.

3. Removal of source of infection

Deep-seated soft tissue infections, including necrotising fasciitis, myositis and cellulitis, are commonly the source of infection (particularly in streptococcal TSS) and responsible for perpetuating the illness. Control of the source of infection by surgical debridement of wounds and drainage of abscesses are a priority in initial and ongoing management. Accordingly, initial assessment should involve meticulous examination to locate an infective source. This may require urgent CT or MR imaging.

Menstrual-related TSS should always be considered in any case of staphylococcal TSS. The rise in the number of such cases in the 1980s was related to a particular brand of tampon.[8] Although these hyper-absorbable tampons are no longer manufactured, the number of women with vaginal colonisation with toxin-producing strain of *S. aureus*

Table 2 The clinical case definitions of staphylococcal and streptococcal toxic shock syndrome.

Staphylococcal toxic shock syndrome clinical case definition[6]

1. Fever ≥38.9°C
2. Hypotension – Less than the 5th centile for age in children
3. Rash – diffuse macular erythroderma
4. Desquamation – 1 to 2 weeks after onset of illness
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 at least twice the upper limit of normal
   c. Mucous membranes – vaginal, oropharyngeal, conjunctival hyperaemia
   d. Renal – blood urea nitrogen or creatinine at least twice the upper limit of normal for age
   e. Hepatic – total bilirubin, alanine aminotransferase enzyme or asparate aminotransferase enzyme levels at least twice the upper limit of normal
   f. Haematological – platelets ≤100 × 10^9/L
   g. Central nervous system – disorientation or alterations in consciousness without focal neurological signs
6. Laboratory criteria: 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 which meets the laboratory criteria and four of the five clinical findings
Confirmed: case which meets the laboratory criteria and all six of the clinical findings

Streptococcal toxic shock syndrome clinical case definition[7]

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 – Less than the 5th centile for age in children
   b. Two or more of the following signs
      i. Renal impairment – creatinine greater than or equal to twice the upper limit of normal for age
      ii. Coagulopathy – platelets ≤100 × 10^9/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 – 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)

Note that criteria 4 and 6 in the case definition for staphylococcal TSS and criterion 1 for streptococcal TSS are not possible to fulfil at the time of presentation when treatment needs to be instigated. This highlights that a provisional diagnosis can and should be made without the need to fulfil these case definitions.

remains relatively unchanged, and cases therefore still occur.[9] Removal of the tampon is of critical importance and potentially life saving in the initial management of cases.

4. Rational choice of antibiotics

Broad-spectrum antibiotics should be administered as soon as possible in all suspected cases of TSS, preferably following collection of blood and other samples for culture. At our institution, current recommendations for empiric antibiotic treatment of suspected sepsis advocate the use of flucloxacillin and a third generation cephalosporin. In settings where the rate of methicillin-resistant *S. aureus* (MRSA) is high, initial cover should include vancomycin. Once an organism is identified, antibiotics should be rationalised: for GAS the treatment of choice is penicillin and for MSSA it is flucloxacillin or an equivalent beta lactamase-resistant penicillin.

5. Role of adjunctive treatment

Clindamycin

Clindamycin has multiple activities that make it potentially useful as an adjunctive treatment in TSS. These include the ability to overcome the 'Eagle effect', inhibition of superantigen toxin production, better tissue penetration and longer post-antibiotic effect than penicillins, and the

potentiation of phagocytosis. The Eagle effect refers to the phenomenon by which high numbers of streptococci in the stationary growth phase have decreased expression of penicillin-binding protein rendering penicillin less effective in killing the bacteria, regardless of dose.[10] Clindamycin can also reduce bacterial superantigen toxin production through the inhibition of transcription of exoprotein genes, thereby potentially interrupting any ongoing stimulation of the inflammatory cascade.[11] Improved outcomes have been reported with the combined use of a beta-lactam antibiotic and clindamycin.[12] Clindamycin should not be used alone because it is only bacteriostatic rather than bacteriocidal and because of reports of rising resistance.[13,14]

Intravenous immunoglobulin

The adjunctive use of intravenous immunoglobulin (IVIg) in TSS is supported on a theoretical basis by its anti-inflammatory and immunomodulatory properties, as well as evidence from observational studies and one historically controlled trial.[15] IVIg is prepared from a pool of many thousands of healthy blood donations. It contains mainly monomeric purified polyspecific immunoglobulin G (IgG) and a smaller fraction comprising other immunoglobulin isotypes and additional immunological components.[16] The cost of IVIg, its limited supply and the potential risks associated with the use of any blood product should be considered when deciding to use IVIg and weighed up against potential benefits. The beneficial anti-inflammatory and immunomodulatory activities of IVIg when used in TSS are thought to include the facilitation of antigen recognition, activation of the innate immune system, and the counteraction of superantigen toxin activity by neutralising antibody.

There is a lack of definitive evidence from randomised controlled trials for the efficacy of IVIg as an adjunctive treatment in TSS. However, observational studies support this, reporting lower mortality rates compared with the use of empiric antibiotics alone with or without clindamycin.[17–21] However, the majority of these studies focus on streptococcal TSS and few include children. The optimal dosing and timing of administration of IVIg in TSS is uncertain. Extrapolation from the literature from RCTs in Kawasaki disease suggests early treatment with a high dose (2 g/kg) is appropriate.[22] However, definitive trials are still required.

Two recent retrospective reviews from the UK and Australia describe the incidence of TSS and outcomes related to aetiology and adjunctive therapies. The study by the British Paediatric Surveillance Unit (BPSU) reported an overall incidence of 0.38 per 100,000 children.[21] This low incidence of TSS may be related to the difficulty in fulfilling the formal diagnostic criteria. The study showed an overall mortality rate of 16% with all fatal cases occurring in the streptococcal TSS group (8/29; 28%). Concerns have been raised over the low use of adjunctive therapies in this study population (only 20% received IVIg) despite the high proportion of severely unwell cases – 77% of patients required intensive care unit admission.[23] Notably, of the 8 cases of streptococcal TSS who died, none had received IVIg. The retrospective review of 62 Australian children with TSS showed a similar incidence of 0.40 per 100,000 children with a higher proportion of staphylococcal TSS cases (43/62; 69%) than streptococcal cases (19/62; 31%).[24] The patients with streptococcal TSS tended to be younger, more unwell and more likely to have sequelae. In contrast to the BPSU study, there was a 100% survival rate and a higher rate of adjunctive therapy use; IVIg or clindamycin was used in 58 children (94%) (clindamycin in 56 children, 90%, and IVIg in 30 children, 48%). There was a higher residual morbidity associated with streptococcal TSS than staphylococcal TSS (12/19, 63% vs 8/43, 19%, p=0.001). The overall lower mortality may have been related to the higher use of adjunctive therapy, although the higher rate of extracorporeal membrane oxygenation (ECMO) use may also have contributed.

6. Review progress

Ongoing management should include a continued search for any focus of infection that may require surgical intervention. Antibiotics should be rationalised based on culture results. Positive blood culture results are rare in staphylococcal TSS with less than 5% positive,[25,26] compared with 60–80% in streptococcal TSS.[27–30] A recent systematic review of the literature on duration of antibiotics for *S. aureus* bacteraemia recommends a minimum of 7 to 14 days total intravenous antibiotics with no switch to oral therapy.[31]

7. Reduce risk of secondary cases in close contacts

An increased risk of invasive GAS disease in close contacts of index cases has been well described.[32] A review of four large surveillance studies in industrialised countries reports a risk of invasive GAS disease in household contacts that is 151 times (95% CI 79–264) greater than that in the general population.[33] The risk is highest in the first 30 days after onset of illness in the index case, with most secondary cases occurring in the first week. There remains controversy as to whether close contacts should routinely receive antibiotic prophylaxis as there have been no randomised trials specifically investigating whether contact prophylaxis reduces the risk.

A study of streptococcal nasopharyngeal carriage was done in 105 close contacts of a fatal case of GAS necrotising fasciitis in a 7 year old child.[34] Close contacts in this report were defined as household or family contacts exposed to the index case for greater than 24 hours per week as previously defined based on carriage studies.[35] The same GAS clone identified as the causative organism in the index case was also present in the throat of 36% of close contacts using this definition. In contrast, the clone was present in only 2% of those not considered 'close' contacts using the study definition. The contacts carrying GAS received 10 days of oral amoxicillin and follow up at 2 months showed no additional cases of invasive GAS disease. This study highlights that targeted antibiotic treatment may be an effective approach to contact chemoprophylaxis. Support for contact prophylaxis is also provided by studies of symptomatic GAS pharyngitis cases which show an 80–95% reduction in nasopharyngeal carriage with antibiotic administration.[36–39]

Guidelines for chemoprophylaxis for contacts of patients with invasive GAS disease and streptococcal TSS cases differ around the world. Consistent across all guidelines is the

recommendation for a heightened index of suspicion and treatment for close contacts with symptoms suggestive of localised GAS infection. The US CDC recommends prophylaxis only for contacts with any additional risk factors for disease;[40] the UK Health Protection Agency recommends prophylaxis for mother-baby pairs where one has developed disease;[41] and the Public Health Agency of Canada recommends prophylaxis for all contacts.[42] The optimal antibiotic regimen is uncertain but suggested regimens include treatment with penicillin V 250 mg (<10 years old) or 500 mg (>10 years old) twice daily for 10 days plus rifampicin 10 mg/kg twice daily for 4 days.[43] An alternative regimen is cephalexin 250 mg four times daily for 10 days.[44]

A number of factors argue for offering antibiotic prophylaxis to close contacts. These include a significantly increased risk of disease in close contacts compared with the general population and minimal financial burden to the health care system given the small number of index cases each year. Additionally, a parallel can be drawn with invasive meningococcal disease, where there is evidence that contact chemoprophylaxis prevents secondary cases (risk reduced by approximately 84%, CI 36–96%, p=0.0008).[45] In contrast, concerns have been raised over the potential false reassurance prophylactic antibiotics may provide (and therefore possible delay in presentation), the risk of adverse drug reactions, and, on a population level, the contribution of the overuse of antibiotics to the rise in antibiotic resistance, although it must be noted that the number of people treated with antibiotics as contacts of patients with TSS would be low.

In conclusion, the early recognition and prompt appropriate management of TSS has the potential to reduce mortality and sequelae. Strategies to better define individuals at risk, to optimise diagnosis and therapy and to identify ways to achieve primary prevention are needed.

Conflict of interest

None

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