TOXIC SHOCK SYNDROME IN BURNS: DIAGNOSIS AND MANAGEMENT

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Arch Dis Child Educ Pract Ed 2007;**92**:ep97–ep100. doi: 10.1136/adc.2006.101030

Toxic shock syndrome (TSS), a toxin-mediated disease, is the most common cause of unexpected mortality in children with small burns. It is a diagnosis that is often missed because of non-specific signs and an ability to mimic other childhood illnesses. Any child with a pyrexia greater than 38.9℃, a rash, or a sudden change in clinical condition within a few days of a burn injury should be monitored closely for TSS. If there is co-incident hyponatraemia or lymphopaenia, or if there is any deterioration in clinical condition, the child should be managed with anti-staphylococcal and streptococcal antibiotics and passive immunity for toxins provided by fresh frozen plasma (FFP) or intravenous immunoglobulin (IVIG). It is essential that all paediatric and emergency departments accepting children with burns are aware of the symptoms, signs and early management of TSS.

INTRODUCTION

Toxic shock syndrome is a severe systemic illness characterised by shock, pyrexia, an erythematous rash, gastrointestinal disturbance and central nervous system signs including lethargy or irritability. It is mediated by toxins produced by some strains of bacteria, most commonly *Staphylococcus aureus* or Group A Streptococcus. It has a high associated mortality of up to 50% if untreated.[1–3] Children under 4 years of age with skin loss are particularly at risk, having not developed antibodies to the toxins produced by the bacteria.

Recent years have seen doctors found guilty of manslaughter for missing a diagnosis of TSS that resulted in the death of an adult patient, and their hospital heavily fined for lack of adequate supervision.[4] With the high mortality associated with full-blown TSS in children with burns, it is essential that all doctors involved in the care of these children are aware of how to diagnose and manage TSS.[5 6]

HISTORY

Toxic shock syndrome first appeared in the medical press in 1978.[1] The authors described a scarlet fever-like illness with high fever, erythroderma, confusion, diarrhoea and shock resulting in multiple organ failure in children aged 8–17 years with localised staphylococcal infections. It was postulated that an exotoxin was involved in causing the degeneration in the patients' condition and it was initially termed ''staphylococcal scarlet fever''. This was changed shortly thereafter to toxic shock syndrome.

Within two years there was a significant increase in the number of cases reported, with many involving young menstruating women using tampons.[7 8] Public interest was generated due to the high mortality in previously fit young women. Cases seemed to be particularly associated with the higher-absorbency tampons and the incidence of menstrual TSS decreased after these were removed from the market.[9 10]

In 1981 purification of an exotoxin from *Staphylococcus aureus*, considered to be responsible for TSS was achieved—enterotoxin F.[11] In the mid-1980s a specific exotoxin named staphylococcal toxic shock syndrome toxin 1 (TSST-1) was reported and found to be present in most (but not all) of the TSS cases seen.[12] It was assumed to be one of the major toxins responsible for the clinical effects of the disease. An exotoxin is a toxin that is excreted by a microorganism and if it has a specific effect on the gastrointestinal tract it can be referred to as an enterotoxin. Endotoxins are present in the actual cell wall of bacteria and not excreted.

In 1985, TSS was first reported in children with burns. The authors described a series of seven children admitted to a burns service, who deteriorated clinically with presumed TSS after relatively small burn injuries.[13] Three of the children died. A further retrospective study in 2003 described 13 children of mean age 20 months and a mean burn size of 12.5% body surface area, who also developed presumed staphylococcal TSS.[14] Seven of these children required admission to paediatric intensive care (PICU) and one child died. All Centers for Disease Control and Prevention (CDC) criteria (see box 1) for TSS were noted in six children and the majority in the other seven.[15 16] *Staphylococcus aureus* was grown from the wounds of all children. Since then, a number of other

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bacteria have been implicated including Group A Streptococcus, Pseudomonas and Klebsiella strains as well as other staphylococcal enterotoxins, so that TSS can now be seen as a global immune response to a number of different triggers.[17] In streptococcal TSS, streptococcal pyrogenic exotoxins A, B and C are thought to be responsible for the symptoms developed.[18]

Non-menstrual cases of TSS now outnumber menstrual TSS and the most common cause of TSS in the UK at the current time is a small burn in a child.

SUPERANTIGENS AND THE IMMUNE CASCADE IN TOXIC SHOCK SYNDROME

Toxic shock syndrome toxin-1 and the streptococcal enterotoxins involved in TSS are classed as superantigens.[9] These are proteins that are able to over-activate the immune system by bypassing the usual steps in the antigen-mediated immune response sequence. By this mechanism they are able to cause massive T-cell stimulation and an overwhelming immune cascade that is destructive to all end organs. This is why such a global response to these toxins is exhibited, with every major organ affected in full-blown disease.

The normal route by which T-cells are activated by antigens is for the antigen to be processed first by a molecule called the major histocompatability complex (MHC). The MHC then presents the processed antigen to the inner groove of the T-cell receptor and in this way about 1 in 10 000 of the T-cell population will be activated.[9 18 19]

In contrast, superantigens are able to bind to the outer groove of the MHC without requiring processing, and this then binds to the beta chain on the T-cell receptor. In this way up to 30% of the T-cell population can be stimulated.[9]

The end result is the production of huge quantities of cytokines such as tumour necrosis factor, interleukins and gamma interferon which are responsible for the overwhelming cell destruction and systemic disorder seen in TSS.[8 9]

Approximately 20% of species of *Staphylococcus aureus* are capable of producing TSST-1 given favourable conditions. It has also been shown that these bacterial exotoxins can be further potentiated by endotoxins produced from gram negative bacteria.[20] Thus the specific mix of bacteria in any given wound will be important in the pathogenesis of the disease.

WHY DO BURNED CHILDREN GET TOXIC SHOCK SYNDROME?

Patients with burns are at risk of developing TSS for the following reasons:

1. The protective skin barrier is destroyed.
2. There is impaired immunity due to diminished cell-mediated immunity, and decreased serum immunoglobulin and complement levels.
3. Ideal environmental conditions for toxin production exist in a burn wound after colonisation: aerobic environment, neutral pH and slightly elevated CO_2.[21]
4. Higher temperatures, which occur as a natural physiological response to a burn, also favour toxin production.
5. Serum in the interstitial space allows an ideal production medium for toxins.
6. *Staphylococcus aureus* is both the most common colonising bacteria in burn wounds and is also responsible for most TSS.

Development of TSS is dependent on factors including genetic predisposition, previous immunity, focus of infection and the correct environment for an organism to produce infections.[17] Burns are initially sterile. Colonisation of burn wounds with bacteria known to produce toxins (*Staphylococcus aureus* and Streptococcus) occurs after 1–2 days.[17 19] Antibody protection against TSST-1 increases with age;[3 22 23] of adults in their fourth decade, 90–95% have antibodies compared with 70% in early adulthood, and less than 30% in those under 5 years of age.[19 23] At birth passive immunity, lasting for 3–6 months, is conferred by the mother. Antibodies are also present in breast milk, so infants are partially protected.[19] This was illustrated in a study of 53 children presenting consecutively with burns. Of those aged 0.4–4 years (n = 38) with burns, 50% had anti-TSST-1 levels less than 0.2 on ELISA testing on admission, implying lowered antibody protection against TSST-1.[19] However, of the 12 infants, only 25% had anti-TSST-1 less than 0.2. Jacobson and colleagues also showed that the prevalence of protective antibodies was high in newborns, declined until 2 years and then gradually increased with age.[2] Unfortunately, most children presenting with burns are between 1 and 3 years of age.

Additional factors must also be important however, as some children with low antibody titres against TSST-1 with burns colonised with Staphylococcus did not develop TSS.[3 24–26]

It has been postulated that occlusive dressings such as Biobrane (Smith and Nephew, Biotech Pharmaceuticals, Morgantown, West Virginia, USA), vacuum assisted closure devices and other wound dressings may predispose to TSS.[21 27–30] In our experience, having used Biobrane as a routine part of the management of scalds in children, a comparison of the incidence of TSS for two years before and two years after the change to Biobrane showed a non-significant decrease in the incidence of TSS (unpublished data).

Toxic shock syndrome is more common in children with burns of relatively low body surface area.[2 6 14 22 31] This is considered to relate to the specific management of larger burns, which often involves surgical debridement and wound closure (removal of the site of bacterial contamination) and the use of blood products (provision of passive immunity against staphylococcal toxins).

INCIDENCE AND MORTALITY

Because of the difficulty in diagnosis, the true incidence of TSS is unknown. Incidence quoted in the literature ranges from 2.5–14% of in-patient burn populations.[14 17] The incidence of TSS seems to be remaining static over time despite different management techniques.[14 17 32]

Mortality can be as high as 15–50% when TSS is unrecognised and consequently untreated.[1 2 5 13 14 17]

PRESENTATION AND DIAGNOSIS OF TOXIC SHOCK SYNDROME IN CHILDREN

Toxic shock syndrome can be almost indistinguishable in its initial stages from other childhood illnesses (see box 3). The diagnosis of TSS is clinical.[3] The first published criteria for diagnosing TSS are the CDC criteria (see box 1).[15 29]

The CDC criteria are not fully applicable to children with TSS because of difficulties in communicating with toddlers, the fact that children may have a less pronounced prodromal period and the requirement to include desquamation in the diagnosis which occurs up to two weeks later and only if the disease is allowed to progress.[3 9] In 1990, Cole and Shakespeare brought

Box 1 Centers for Disease Control and Prevention criteria[15 16]

Major criteria (need all):
- Temperature >38.9°C
- Rash: diffuse macular erythroderma
- Desquamation: 1–2 weeks later
- Hypotension and poor peripheral perfusion

Involvement of three or more of:
- GI: vomiting or diarrhoea
- Muscular: severe myalgia or CPK twice upper limit of normal
- Mucous membranes: hyperaemia
- Renal: raised urea or creatinine >2× normal
- Hepatic: raised bilirubin, ALT, AST
- Haematological: platelets <100× 109/l
- CNS: disorientation or altered consciousness

out revised, abbreviated criteria for diagnosis, specifically for use in children (see box 2).[33]

Lymphopaenia has been found to be a useful way of confirming the diagnosis.[22 32 34] A prospective audit of all cases of TSS over three years at the South West Paediatric Burn Service found both lymphopaenia and hyponatraemia (prior to intravenous fluid administration) to be helpful markers of TSS. Of 13 consecutive children with presumed TSS, 77% were hyponatraemic and 70% lymphopaenic at the time of diagnosis. All presented with pyrexia (>39°C) and signs of shock (tachycardia and prolonged capillary refill time).[32] A rash developed in 85% of children and 85% showed signs of central nervous system disturbance such as irritability or drowsiness. The study found that the average age that a child with burns developed TSS was two years, with an average burn size of 9% and time of onset after burn injury of two days. Toxicology for TSST-1 is rarely useful in the acute situation as results usually take a number of weeks to return.[14] Parsonnet and colleagues suggest adding three laboratory criteria to the CDC criteria: the presence of *Staphylococcus aureus*, the toxigenicity of the Staphylococcus strain and the serological status of the patient with respect to the toxin.[35]

The typical presentation therefore, of a child with TSS, is a toddler with a small clean burn, two days post-burn injury with a sudden deterioration in clinical condition. This will include a temperature greater than 38.9°C, hypoperfusion, tachycardia, tachypnoea, lethargy/irritability and a non-specific rash. There is diarrhoea and/or vomiting in approximately half of the cases. Laboratory tests done before any treatment will show hyponatraemia and lymphopaenia (despite an often normal total white cell count). If left untreated other haematological changes including a coagulopathy and thrombocytopaenia may occur.[2 14 32]

Box 2 Abbreviated criteria[33]

- Pyrexia ⩾39°C
- Rash
- Diarrhoea +/− vomiting
- Irritability
- Lymphopaenia

Box 3 Differential diagnoses[9 21]

- Scarlet fever: high WBC, skin biopsy
- Rocky Mountain fever: distal petechial rash, headache
- Leptospirosis
- Kawasaki disease
- Meningococcaemia: petechial rash
- Toxic epidermolysis necrosis: extensive blistering
- Stevens–Johnson syndrome: involvement of mucous membranes
- Staphylococcal scalded skin syndrome: blistering

Management of toxic shock syndrome

Treatment of TSS should follow four main routes:

1. Resuscitation and stabilisation in a high-dependency area
2. Inspection and cleaning of the burn wound
3. Treatment with anti-staphylococcal (and streptococcal) antibiotics
4. Provision of passive immunity against TSST-1 with FFP or IVIG.

The administration of specific antibiotics is to lessen bacterial load and to inhibit further staphylococcal colonisation. Antibiotic therapy should aim to provide treatment for staphylococcal and streptococcal infections. However, as TSS is a toxin-mediated disease, it is vital that the toxins are neutralised to prevent further damage occurring.[19 23] The single most important measure in the management of TSS, is to provide passive immunity via the administration of preformed anti-TSST 1 antibodies either as IVIG or FFP.[17] Pooled adult FFP has approximately a 75% chance of containing specific anti-toxin immunoglobulins and will arrest the escalating process very quickly.[19] There is the risk of giving a blood product, but this must be weighed against the improvement in clinical condition which usually occurs within a couple of hours of administration of FFP, with almost all children fully recovered within 24 h, compared with a prolonged clinical course if not given.

Intravenous immunoglobulin is also effective. In a study in patients with streptococcal TSS, 21 patients who received IVIG were compared to 32 retrospective controls who did not. Those who received IVIG had a significantly better 30-day survival (67% vs 34%, $p = 0.02$). IVIG was found to enhance the ability of patient plasma to reduce T-cell production of IL-6 and TNF-α.[36] In another study, stopped prematurely, in 21 patients with streptococcal TSS, there was a 3.6 times higher mortality at 28 days in those not receiving IVIG.[37]

In our experience, protocol-driven management of TSS is vital. It will increase awareness of this uncommon complication of burns, allow early diagnosis and standardise management. The protocol used at our institution over the last five years (see box 4) has decreased both PICU admissions and mortality secondary to TSS to zero. We ascribe this to early detection and standardised management within a paediatric burns high-dependency service.

THE FUTURE

Children are still dying from a treatable complication of minor burn injuries. In a survey of TSS in 22 UK burns services in 1999, 82% of units had no defined criteria for diagnosis.[5 38] It is essential that national and regional protocols for TSS are developed and disseminated at the earliest possible opportunity.[6]

Box 4 Toxic shock syndrome management protocol

1. Intravenous access
2. Blood and microbiology samples
   - Full blood count, urea and electrolytes, clotting screen
   - Group and hold
   - Blood cultures
   - Wound swabs.
3. Treat hypoperfusion (capillary refill time >2 seconds)
   - Use non-glucose containing crystalloid in the first instance with boluses of 10 ml/kg and reassess. The child may require 40–60 ml/kg.
4. Start intravenous antibiotics
   - Flucloxacillin and penicillin in the first instance (consider MRSA if poor response).
5. Provide passive immunity
   - FFP 10 ml/kg (repeat if necessary) or immunoglobulin.
6. Clean burn wound
   - Remove dressings.
7. Consider catheterisation for fluid balance.
8. Manage in paediatric HDU.
9. Review hourly until improving.

These guidelines should become standard teaching at APLS/EMSB-type courses for all doctors likely to come across paediatric admissions after burn injury. It is also essential that parents of children with burns of any size are provided with discharge leaflets describing the symptoms and signs of TSS and what to do if these develop.

Prevention of TSS is proving difficult. Further research into antibacterial dressings or dressings which inhibit the production of bacterial toxins in burn wounds should be undertaken.[30 39] Prophylactic antibiotics also do not seem to be the answer, although we do believe that there should be formalised multicentre randomised controlled trials to compare the efficacy (or not) of prophylactic antibiotics in the prevention of TSS in children after burn injury.[3 22 40]

CONCLUSIONS

Toxic shock syndrome is an uncommon complication of burn injury. If missed, the mortality can be as high as 50%. Death from TSS is entirely preventable if simple diagnostic criteria and management guidelines are followed. It is absolutely vital that any doctor managing children with burns in a primary, secondary or tertiary care setting is fully conversant with these. TSS is a toxin-medicated disease *not* a septicaemia, and confidence in management can only be achieved by the use of passive immunity as well as antibiotics.

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The tragic death of Ahil Islam led to the commissioning of this paper.

Competing interests: None declared.

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