Toxic shock syndrome: causes in people with burn wounds

Toxic shock syndrome (TSS) is a rare complication of colonisation or infection by toxin-producing strains of *Staphylococcus aureus* and has often been associated with tampon use, although menstrual-associated TSS has declined over recent years. Non-menstrual-associated TSS can occur in a variety of conditions including small percentage burns in children. Adults with burns are not normally at risk, but there have been a few reported cases. This article will discuss what factors are involved in the development of TSS in people with burn wounds.

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KEY WORDS
Toxic shock syndrome
Staphylococcus aureus
Burn wounds

Toxic shock syndrome (TSS) is a rare complication resulting from colonisation or infection with a toxin-producing strain of *Staphylococcus aureus*. It was first described in 1978 by Todd et al who saw seven cases of TSS in young children with similar symptoms (fever, vomiting, diarrhoea, rash) that progressed to disseminated intravascular coagulation, shock and multi-organ failure. It was soon confirmed in five of the seven cases, that the syndrome was a result of infection associated with *S. aureus* of phage group 1 (Todd et al, 1978). It was shown that toxic shock syndrome toxin-1 (TSST-1) was involved in the pathogenesis of the syndrome (Bergdoll et al, 1981; Schlievert et al, 1981; Bergdoll and Schlievert, 1984) and since then there have been reported cases associated with other staphylococcal exotoxins, namely enterotoxin A, B and C (SEA–C) (Yaqoob et al, 1990).

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In 1980, after a strict definition of TSS was devised by the Centers for Disease Control and Prevention in Atlanta, USA (Chesney et al, 1981), there were hundreds of notified TSS cases in young women associated with menstruation. Epidemiological studies in the US showed that this sudden increase was due to the introduction of a highly absorbent tampon containing carboxymethylcellulose, Rely™, produced by Proctor and Gamble (Schlievert et al, 1984). Subsequently these were shown to increase production of TSST-1 by *S. aureus* in vitro (Lee et al, 1987) and were recalled and discontinued in 1980 which led to a subsequent decrease in the incidence of menstrual-related TSS (MTSS) (Schuchat and Broome, 1991) (*Figure 1*). In addition, details of TSS and symptoms were included in all packs of tampons, raising awareness of the risks with users. Tampons are now predominantly made of cotton and rayon (Schuchat and Broome, 1991).

Since carboxymethylcellulose was removed from tampons, the incidence of MTSS has equalled that of non-menstrual TSS (NMTSS) (Marples and Wieneke, 1994). NMTSS occurs in men, women and children and is associated with a plethora of localised focal infections involving *S. aureus*. Foci include surgical

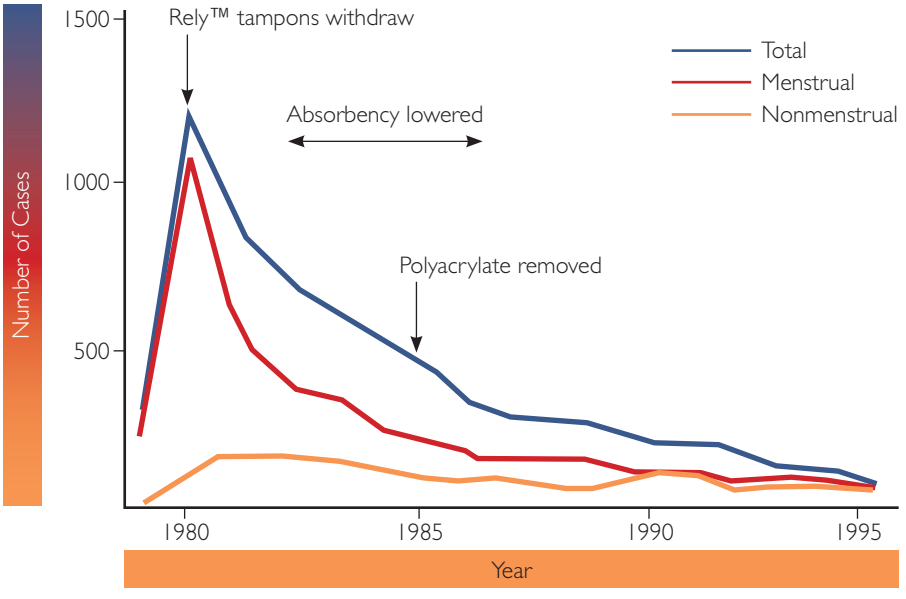

Figure 1. The incidence of TSS per year in the USA 1979–1996 (adapted from Hajjeh et al, 1999).

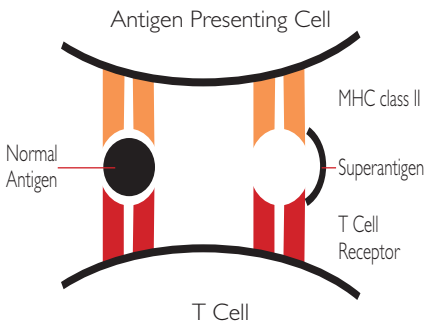

Figure 2. A schematic diagram of the interaction of a normal antigen (left) and superantigen (right) with the T cell and MHC II on an antigen presenting cell. A normal antigen lies within the groove formed within the MHC II after antigen processing. Superantigens bind to the outer part of the MHC II without any processing.

wounds, pregnancy termination, deep abscesses, lacerations, furuncles (an infection of a hair follicle) (Reingold et al, 1982), pyomyositis (Gahrn-Hansen et al, 1989), rhinoplasty (Allen et al, 1990) and burns (Frame et al, 1985). Cases of TSS associated with wounds are nearly all following injury, primarily small percentage burns (Frame et al, 1985; Egan and Clark, 1988; McAllister et al, 1993). However, there has been one reported case of TSS associated with a foot ulcer in a male patient with diabetes (Arnold et al, 2001).

The symptoms of TSS (*Table 1*) are predominantly due to the action of TSST-1, whose molecular shape makes it a powerful superantigen (SAg) which causes an over-stimulation of T-cells in the immune system (Marrack and Kappler, 1990; Fleischer, 1994). Antigen processing happens when proteins that have been endocytosed are degraded inside the cell by enzymes (usually acid-dependent proteases) and presented via the MHC II complex on the outside surface so they can be recognised by T cells, allowing activation of the immune system. Without any antigen processing, the SAgs cross-link the variable region on the T-cell receptor (TcR) of T cells with the outer groove of the major histocompatibility complex (MHC) II molecules on the host cells. In normal antigen processing, the antigen is presented via the inner groove of the MHC II molecule to T cells. Between 5–30% of the T cells can be activated by an SAg whereas conventional antigen presentation will only stimulate one in 10,000 cells (Marrack and Kappler, 1990) (*Figure 2*). This causes an overproduction of an array of cytokines, such as tumour necrosis factor (TNF), interleukin-1 (IL-1), IL-2, IL-6 and interferon. It appears to be the over activation of the immune system by these cytokines that produce some of the clinical symptoms seen in TSS (Kotzin et al, 1993; Drake and Kotzin, 1992; Kotb, 1995).

Studies have implicated staphylococcal SAgs in other syndromes such as neonatal toxic shock syndrome-like exanthematous disease (NTED) characterised by skin eruption caused by TSST-1 producing strains of *S. aureus* (Iwatsuki et al, 2006), atopic disease (Michie and Davis, 1996; Baker 2006), nasal polyposis caused by the effect of the SAg on the local nasal mucosa (Tripathi et al, 2005), and sudden infant death (Newbould et al, 1989; Gordon et al, 2002). Atopic disease is a common sequela of TSS and in one study 16 out of 68 patients recovering from TSS caused by TSST-1-producing strains of *S. aureus* developed chronic dermatitis compared with no patients in the group who had septic shock caused by Gram-negative bacteria (Michie and Davis, 1996). Antibodies to TSST-1 are protective and they work by preventing the activation of T cells by the superantigenic TSST-1 and overproduction of cytokines (Takei et al. 1993). This is a major factor for the prevention of TSS and work is currently progressing toward developing vaccines against some of the virulence factors.

Streptococcal pyogenic toxins (SPE) A–C produced by *Streptococcus pyogenes* can cause a condition very similar to TSS and is called toxic shock-like syndrome (TSLS) (Martin and Green, 2006). Typically from day four of the streptococcal infection, shock and fasciitis are also seen (Roggiani and Schlievert, 1994).

TSS as a complication of a small percentage burn

Frame et al (1985) described the first case of TSS in children with burn wounds. Several cases followed (Farmer et al, 1985; Egan and Clark, 1988; McAllister et al, 1993; Johnson and Pathirana, 2002). Some of these cases (usually <10%) resulted in death where an uneventful recovery would have been expected (McAllister et al, 1993). In a typical case of TSS in a patient with burns, the patient will present with severe pyrexia (40°C), tachycardia (200 beats/min), and tachypnoea (51 breaths/min) quite soon after admission (mean 2.2 days). This progresses rapidly to vomiting, diarrhoea, rash, and oliguria. Some may also show neurological disturbances and if intervention is not implemented at this stage the patient will develop multi-organ failure (McAllister et al, 1993). Specific treatment against the toxin involves the use of passive antibodies present in intravenous human immunoglobulin, fresh frozen plasma or whole blood as 75% of these fluids have been shown to contain antibodies for TSST-1 (Childs et al, 1994). These antibodies act by protecting the patient against the effects of the toxin. Flucloxacillin is administered to destroy the *S. aureus* and prevent any further release of toxin. The effects of hypovolaemic shock are clinically supported with blood or plasma expanders (McAllister et al, 1993).

Table 1.
Classic criteria for clinical diagnosis of TSS

- Fever above 38.9°C
- Hypotension or orthostatic dizziness
- Diffuse or palmar erythroderma
- Desquamation of hands and feet
- Hyperaemia of conjunctivae and of the mucous membranes of the oropharynx or vagina
- Multisystem dysfunction which must include at least four of the following:
  - Diarrhoea and vomiting
  - Alterations in consciousness
  - Impaired renal function
  - Impaired hepatic function
  - Thrombocytopenia
  - Elevated muscle creatinine phosphokinase
  - Cardiopulmonary dysfunction
  - Decreased serum calcium and phosphate

(Davis et al, 1980; Chesney et al, 1981)

Why does TSS develop?

Why TSS develops is not clearly understood but it appears to be

dependent on several factors (Edwards-Jones and Shawcross, 1997):

- The person has to be infected or colonised by a toxin-producing strain of *S. aureus*
- The correct environmental conditions must be present to stimulate production of TSST-1 (or an equivalent superantigenic toxin)
- The person must not have protective antibodies to TSST-1 and other staphylococcal enterotoxins (Takei et al, 1993) from a previous exposure (typically during transient nasal colonisation)
- The person must be genetically susceptible to the superantigenic effects of the toxin.

Each of these factors will now be discussed in relation to patients with burns.

Colonisation/infection of the burn wound

Immediately following injury the wound is sterile but within a few hours it rapidly becomes colonised by a variety of bacteria, usually derived from the host, or in some cases from an external source. *S. aureus* is the most frequently isolated pathogen found in a burn wound and the colonisation rate can be as high as 30% (Lawrence, 1992) with 11% of patients becoming colonised within one day of injury (Childs et al, 1994). It has been shown that 55% of *S. aureus* isolated from patients with burn wounds can produce one or more toxins and the incidence of TSST-1 and SEA–D toxin from these isolates were 16.6%, 13%, 12%, 23% and 3.6% respectively (Edwards-Jones et al, 1996). This shows that not all isolates of *S. aureus* produce the toxins equally. In the same study, 20.7% of patients carried more than one strain of *S. aureus*.

The extent of the burn (total body surface area [TBSA]), the depth of the burn or evidence of infection will effect the subsequent management of the patient in terms of administration of antibiotics, dressing protocol and intravenous fluids. Patients with more than 10% TBSA burns are usually infused with intravenous fluids or plasma expanders to replace fluid losses (Muir and Barclay, 1962), whereas patients with less than 10% TBSA burns generally do not receive fluids unless it is clinically indicated. Their treatment focuses primarily on wound management. TSS associated with burns is more common in people with less than 10% TBSA burns (Edwards-Jones and Shawcross, 1997; Johnson and Pathirana, 2002), and it is postulated that this group do not receive the passive immunity that is effected via blood products. Childs et al (1994) discussed this and showed that 75% of infused whole blood or fresh-frozen plasma contained antibodies to TSST-1.

Wound management procedures for the patient with burns differ between burns units; but the majority use ointments and/or impregnated dressings in an attempt to prevent infection (Edwards-Jones et al, 2000). Antibiotic prophylaxis is not part of the normal management of burns, but some units now administer prophylactic antibiotics to reduce the risk of a patient developing TSS (Johnson and Pathirana, 2002; Rashid et al, 2005) although there is no consensus among burn centres (Papini et al, 1995; Edwards-Jones et al, 2000).

Environmental factors influencing toxin production

Several physical factors in the burn wound, such as the oxygen availability, the pH of surrounding fluid and the availability of trace metal ions create a favourable environment for toxin production that normally occurs at the end of the exponential growth phase of bacteria. Several of these factors have been shown to increase TSST-1 toxin production in vitro (Kass et al, 1987; Sarafian and Morse, 1987; Reeves, 1989; Wong et al, 1990). The presence of both blood and protein is also known to increase the amount of TSST-1 produced by *S. aureus* (Todd et al, 1987). Topical antimicrobial agents (Edwards-Jones and Foster, 1994; 2002), wound dressings (Buck et al, 2000) and the mixed population of bacteria found growing together in a wound can affect the levels of extra-cellular enzymes and TSST-1 produced by *S. aureus* in vitro (Sergent and Edwards-Jones, 1996). In a study by Holland et al (1998), supernatant fluid of *S. epidermidis* was shown to reduce TSST-1 production. It is not known if the same effects occur at wound sites; but it merits further investigation. New technologies (microarrays) are now available to allow this to be investigated more comprehensively.

In a number of case reports, dressing components have been implicated as possible environmental factors that stimulate toxin production (Egan and Clark, 1988; Weinzweig et al, 1994). It is possible that some dressings provide conditions that are favourable for toxin production, perhaps through chelation of magnesium or other metal ions. Some highly absorbent burn dressings contain carboxymethylcellulose (British National Formulary, 1994) which was a component of the tampons that were implicated in menstrual-related TSS. Sub-lethal levels of silver sulphadiazine have been shown to increase TSST-1 production in vitro in 45% of strains of *S. aureus* although the precise mechanism has not yet been determined (Edwards-Jones and Foster, 1994).

A commonly-used silver dressing has also been shown to increase TSST-1 production in vitro in a liquid culture medium as well as in a semi-solid model system (Buck et al, 2002). Sub-lethal levels of silver sulphadiazine and the silver dressing were also shown to inhibit staphylococcal metalloprotease and other virulence factors such as haemolysins (Edwards-Jones and Foster, 2002; Buck et al, 2002). Although these in vitro data indicate a risk of developing TSS with the use of these ointments and dressings, large numbers of cases of TSS have not been reported associated with their use (Edwards-Jones et al, 2000).

Protective antibodies

Antibodies to TSST-1 are usually absent from the sera of patients with TSS, in contrast to age-matched control subjects (Bonventre et al, 1984) and patients who suffer recurrent TSS do not produce antibodies to either TSST-1 and other enterotoxins (Crass and Bergdoll, 1986). TSST-1 antibodies are protective and can prevent the development of TSS in animal models when given passive immunisation with TSST-1 monoclonal antibodies (Best et al, 1988). A study undertaken in 1983 showed that TSST-1 antibodies develop with age and that

47%, 58%, 70%, 88%, 96% and 99% of the population have antibodies at the ages of one, five, 10, 20, 30, and 50 years respectively (Vergeront et al, 1983). This was confirmed in children admitted to a paediatric burns unit in Manchester where 49% of children possessed antibodies to TSST-1 (Childs et al, 1994; 1999). This implies that the children under five years are at greater risk of developing TSS because of the lack of protective antibodies to TSST-1.

The occurrence of antibodies to other enterotoxins, such as SEA–E, varies within the population (Notermans et al, 1983). The risk of developing TSS for a person aged over 50 years is extremely rare (1%), but not totally unknown. Two cases of TSS have been described in adult patients with burns. The first case, in 1999, was a 38-year-old woman with 25% flame burns who was colonised by an *S. aureus*-producing enterotoxin B (Withey et al, 1999) and the second was a 64-year-old man with 15% scald in whom the focus of infection was not determined (Masaki et al, 2004). These two cases confirm that the development of TSS does not depend upon one single factor. Studies by Jacobson et al (1989) showed that patients infected with a TSST-1-producing strain of *S. aureus* who also lacked the antibodies to TSST-1 did not develop TSS. This was later substantiated by Childs et al (1994) in a prospective study undertaken on children with burns.

Genetic susceptibility

S. aureus can cause local infections as well as toxin-mediated disease and can be lethal in the case of sepsis and associated shock (Astiz and Rackhow, 1998). Genetic predisposition to this has been increasingly recognised (Holmes et al, 2003). Inherent genetic susceptibility to the superantigenic effects of the toxins may be a contributory factor in the development of TSS and has been investigated (Llewelyn et al, 2006) but there is still much information to be determined before a full understanding is forthcoming. Staphylococcal enterotoxins A and B (both SAgs) have been shown to stimulate expression of intracellular adhesion molecule (ICAM) and human leucocyte antigen (HLA)-DR in normal human keratinocytes (Morishita et al, 1999), and very recent studies have shown that there are differences in binding and presentation of the staphylococcal SAg staphylococcal enterotoxin A by different HLA-DR alleles (Llewelyn et al, 2006). If this is the case then this subtle difference could account for the severity of disease in different patient groups. It may be that binding of the different SAgs with different HLA-DR allelic types can ultimately affect levels of expression of cytokines.

The increase in knowledge is leading to improvements in diagnosing TSS, which has always been difficult because the early stages resemble many common infectious diseases and TSS is not often confirmed until the latter stages when the patient has gone into multi-organ failure and shock. Recent studies have shown that the expansion of T-cell V2 families in peripheral blood can be used as a rapid diagnostic test for TSS using a flow cytometer (Matsuda et al, 2003).

Future research

TSS is a complex disease and in order to unravel how it develops in the susceptible host, a full understanding of the interaction of the bacteria and the host has to fully elucidated.

We know that it is not a single toxin-producing strain of *S. aureus* causing TSS in patients with burns. This is slightly different to that seen in menstrual TSS where Musser et al (1990) showed that it was predominantly a single clone causing TSS in this group of patients. Non-menstrual TSS is caused by a number of staphylococcal SAgs (TSST-1, SEA, SEB, SEC) and all of these have been described in burn-associated TSS. Expression of these SAgs and a variety of enzymes are coordinated and controlled by complex multi-level regulatory systems within the genome of the staphylococcus (Arvidson and Tegmark, 2001). Small molecules identified as octapeptides in staphylococcal species and N acyl-homoserine lactone molecules in Gram-negative bacteria (Williams et al, 2000) can be secreted into the surrounding environment by one strain and have an effect on gene expression by another bacterial strain (Balaban et al, 1995; Ji et al, 1995). When the concentration reaches an optimal level, an array of virulence factors/secondary metabolites (including toxins and enzymes) are produced (Novick et al, 1993). This phenomenon is termed quorum sensing and is dependent on the concentration of organisms. The cells signal to each other and communicate using these molecules. Furthermore it has become more apparent that bacteria grow in communities as biofilms therefore requiring a very sophisticated system of communication (Lyon and Novick, 2004).

In vitro studies have shown that biofilm formation has been inhibited by ribonucleic-acid-III-inhibiting peptide (RIP) that enhances the effects of antibiotics and cationic peptides. RIP is part of the regulatory system and has been extracted and purified. This compound thus has potential as a new molecule that may have a use in prevention or treatment of colonistion/infection and ultimately toxin expression (Lyon and Novick, 2004). This may result in suppression of virulence factors and may have an impact on wound healing as well as the development of TSS. This complex sequence of events can be confounded by alteration of the wound environment and subsequent gene expression by topical antimicrobial agents and dressings. Now with new technologies and the ability to examine gene expression at the molecular level using microarrays we may eventually unravel some of these complex interactive events. In addition, further information on host susceptibility to TSS and the role of the HLA type warrants further investigation. Understanding exactly how a disease is caused may allow the use of some of the molecules as potential new treatments.

Questions that need answering include:

- What happens at a local level (i.e. to the wound healing process) when superantigenic toxins produced by *S. aureus* are released into the local wound environment?
- Do they cause an overstimulation of the inflammatory process in the wound bed?
- Could superantigens be used at

appropriate doses as possible modulators of the inflammatory process?
- Could they have a role to play in chronic wounds?

Conclusion

How bacteria either in isolation or in mixed culture cause the over-stimulation of the immune system via cytokines and genetic predisposition leading to TSS needs to be determined. New technologies are becoming available to unravel some of these events at a molecular level and with detailed clinical studies we may be able to identify susceptible patients more rapidly. With appropriate vaccination or prophylactic treatment it may be possible to eradicate this rare complication of burn wounds in the future. WUK

Key Points

- Toxic shock syndrome is a rare complication of minor burns in children.
- The superantigenic toxins of *Staphylococcus aureus* are responsible for the development of the syndrome.
- Topical antiseptics and dressings have been implicated as possible risk factors.
- Antibodies to the toxins are protective.

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