Toxic Shock Syndromes

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25.1 Introduction

Staphylococcal toxic shock syndrome (TSS) was first described in seven children aged 8 – 17 years by Todd et al. in 1978 [1]. It shortly thereafter became well known as an illness of menstruating women who used tampons [2, 3]. The syndrome is characterized by rapid onset of fever, hypotension, and multisystem failure with desquamating rash occurring in convalescence [4]. The majority of early cases reported were menstrually associated (MTSS) but this has been changing with an increasing proportion of cases non-menstrually associated (NMTSS) [5].

In the late 1980s, cases of severe invasive group A streptococcal (GAS) infections associated with a similar clinical presentation to staphylococcal TSS began to appear in the literature [6 – 8]. This streptococcal toxic shock-like or streptococcal toxic shock syndrome (STSS) shares in common features of fever, shock, and multisystem organ failure with staphylococcal TSS [4, 9]. In contrast, STSS has no menstrual association, is more common at extremes of age and is a much more lethal condition compared to TSS with case fatality rates of approximately 50 % as compared to 5 – 10 % respectively [5, 10 – 14]. STSS is occasionally associated with the severe soft tissue infection necrotizing fasciitis, which has been popularly called "flesh eating disease" by the media [15].

25.2 Epidemiology

25.2.1 Staphylococcal Toxic Shock Syndrome

There have been significant changes in the rates of TSS since its first description nearly three decades ago. In the early 1980s the incidence peaked and there was much public awareness [14]. Case-control studies identified white race, young women (under 20 years), barrier contraceptives, and use of tampons, particularly the superabsorbent variety Rely brand, as risk factors for acquiring TSS [2, 16 – 18]. The Rely brand tampon was withdrawn from the market in 1980 and there was a temporally associated decrease in TSS incidence from rates of approximately 10 per 100,000 young women in 1980 to 1 per 100,000 in 1986 [2, 14, 19 – 21].

Following the initial identification of MTSS cases, there were increasing numbers of NMTSS cases reported. The majority of NMTSS cases are nosocomially acquired and the sources of infection may be either genital, such as with postpartum or contraceptive diaphragm associated illness, or non-genital such as with postoperative wound infection, burns, cellulitis, and rarely necrotizing fasciitis [5, 22, 23]. Since the mid 1980s rates of NMTSS have been similar to those for MTSS. The overall incidence of TSS has been less well documented since the late 1980s but rates did not evidently increase for years after until just recently when an increase in cases was noted in the Minneapolis-St. Paul (Twin Cities) area in the United States [24, 25]. The case fatality rate for TSS is lowest for vaginally associated disease in young females under 15 years old (2 %) and highest in men (17 %) and non-vaginally associated cases in women (13 %) over 45 years old [26].

25.2.2 Streptococcal Toxic Shock Syndrome

Invasive GAS infections, defined as the isolation of *Streptococcus pyogenes* from normally sterile sites such as blood or cerebrospinal, pleural, or deep tissue aspirate fluid, have re-emerged in recent decades as significant causes of severe infections. These infections were common until the middle of the twentieth century but then decreased in incidence for poorly defined reasons. The global burden of invasive GAS disease is estimated at more than 600,000 cases yearly with rates dramatically higher in less developed countries [27]. Population-based studies have shown that invasive GAS disease in Europe and North America occurs at an incidence of 2 – 5 per 100,000 [10, 13, 28, 29]. Among cases of invasive GAS infection, STSS occurs in approximately 5 – 15 % (incidence of 0.2 – 0.7 per 100,000 population) and necrotizing fasciitis in 3 – 6 % [12, 13, 29, 30].

Although early studies suggested that STSS was more common among healthy young individuals, pro-

spective population based studies have demonstrated that this is not the case [8, 10, 11, 13]. The risk for development of STSS is highest in the elderly and those with chronic underlying illnesses [10, 13]. Important risk factors for development of invasive GAS infection and STSS determined by population-based studies include extremes of age, black as compared to white race, and coexistent HIV infection, malignancy, heart disease, diabetes, lung disease, and alcohol abuse [10, 12, 28]. Skin trauma or breakdown is observed as a preceding event to invasive GAS disease in approximately one-third of cases but the relative risk associated with this is unknown. In children, varicella is the most important documented risk factor for acquisition of invasive GAS disease and necrotizing fasciitis [10, 12, 13].

Approximately one-half of patients with necrotizing fasciitis have concomitant STSS, although only one-quarter of cases of STSS have necrotizing fasciitis [10, 12, 15]. The most common foci of infection associated with STSS include soft tissue infection, pneumonia, bacteremia with no focus, and septic arthritis [10]. The case fatality rate of invasive GAS infection is markedly increased when associated with STSS, with rates of 45 – 81 % identified in population based studies [10, 12, 28, 29]. Necrotizing fasciitis in the absence of criteria for STSS does not increase the case fatality rate above that for invasive GAS infections alone.

25.3 Etiology and Pathogenesis

25.3.1 Staphylococcal Toxic Shock Syndrome

TSS is caused by toxigenic strains of *Staphylococcus aureus*. The evidence supporting a toxic pathogenesis in TSS includes the clinical findings of multisystem involvement in the absence of systemic infection (positive blood cultures in less than 10 % of cases) and the ability to reproduce a TSS-like illness in rabbits using purified *S. aureus* toxins [5, 31, 32]. There is strong evidence implicating toxic shock syndrome toxin-1 (TSST-1) and the staphylococcal enterotoxins as the etiologic agents of TSS [33]. TSST-1 was identified independently by Bergdoll et al. and Schlievert et al. in 1981 and its role in TSS is widely accepted [34, 35]. This protein is produced by over 90 % of MTSS isolates and the majority of NMTSS isolates [33, 35]. The staphylococcal enterotoxins are commonly co-produced with TSST-1 and are likely responsible for the syndrome in non-TSST-1 producing isolates from TSS cases [33, 36]. Staphylococcal enterotoxin B is produced by the majority of NMTSS isolates in which TSST-1 is not produced and is likely the cause of the disease in these cases [5, 36 – 38]. TSST-1 negative TSS has a higher case-fatality rate which may reflect the higher rate of co-morbid medical conditions typical of NMTSS patients or the different toxins mediating the illness [33].

It is not clear why TSS emerged as a "new" complication of *S. aureus* infections in the late 1970s. Retrospective studies have identified that *S. aureus* has had the ability to produce TSST-1 since at least the 1950s [39]. The onset of MTSS in the 1980s appears to be closely related to the use of superabsorbent tampons, as these products probably increase the risk of MTSS by altering the vaginal milieu to encourage *S. aureus* colonization and promote toxin production. In vitro studies of TSST-1 expression by *S. aureus* have identified that production is highly variable according to the environment and that an aerobic, pH neutral, low magnesium environment optimizes toxin production [40]. Tampons may increase the risk of TSS by promoting these conditions. A recent study conducted in North America found that colonization by TSST-1 producing *S. aureus* strains was common in young women and that most had neutralizing titers of antibodies [41]. It is less clear which factors have been involved in the development of NMTSS. It is possible that this condition has been present at a low baseline rate for many years but not widely identified until surveillance for MTSS brought it to attention. MTSS and NMTSS appear to be distinct microbiologically as one clone appears to be responsible for the majority of cases of MTSS whereas isolates from NMTSS are heterogeneous [42].

TSST-1 and the staphylococcal enterotoxins are superantigens which induce widespread immune activation and subsequent shock [43 – 45]. In the usual cell mediated immune response, T cells recognize antigen presented by the major histocompatibility complex II positive antigen presenting cells with high specificity. The population of T cells that respond are selected based on the specificity of their T cell receptor, which is determined by the combination of the variable gene segments Vα, Vβ, Jα, Jβ, and Dβ [43]. However, superantigens bypass the usual antigen presenting process and activate T cells based on Vβ specificity alone [43, 46]. This leads to a relatively non-specific activation of large populations of T cells. For instance, TSST-1 is Vβ2 restricted and may stimulate up to 50 % of all T cells [47]. The result of this activation is the release of potent mediators of inflammation including interleukins 1 and 6 and tumor necrosis factor, which ultimately lead to the clinical manifestations of TSS.

25.3.2 Streptococcal Toxic Shock Syndrome

The pathogenesis of STSS is less well defined than TSS and it appears to be related to both the invasiveness of the organism as well as to the systemic toxins it produces. Identification of virulence determinants is further complicated by the fact that the same strains that

cause severe invasive disease are commonly non-disease associated, and that there is considerable heterogeneity among isolates from different cases of STSS [48]. Unlike in TSS where systemic effects are observed typically in association with a localized infection, STSS is characterized by severe bacteremic infection typically in with a rapidly progressive local focus of disease. No single factor has been identified that enables *S. pyogenes* to aggressively invade tissue but potential virulence determinants include M proteins and enzymes such as streptokinase, hyaluronidase, deoxyribonucleases, and proteinases [49]. Although there is a broad range of M protein types observed with severe GAS disease, M1 and M3 have been observed to occur at higher rates with invasive infection [28, 50]. However, the association of M-type with severe disease is modest and these proteins may be markers for other yet identified invasive factors.

There are a number of exotoxins that may potentially mediate STSS although a single one has not been identified as the cause. The streptococcal pyrogenic exotoxins (SPE) function as superantigens and are structurally related to the staphylococcal enterotoxins [43–45]. Strains of GAS producing SPE A in North America and SPE B and SPE C in Europe have been associated with STSS [51, 52]. Mitogenic factor and streptococcal superantigen have been identified from STSS isolates but their role is unclear [53, 54]. Watanabe-Ohnishi et al. showed that characteristic Vβ restricted T cell population changes occurred in cases of STSS that were not related to SPE and suggested that an unidentified superantigen may be involved [55].

25.4 Diagnosis

The diagnosis of TSS or STSS is based on identifying a syndrome of shock, fever, and multisystem failure with the fulfillment of criteria for one of these conditions. The Centers for Disease Control and Prevention case definition for TSS is shown in Table 25.1 and the criteria for STSS as defined by the Working Group on Severe Streptococcal Infections are shown in Table 25.2 [4, 9]. The diagnosis of TSS requires a high index of suspicion because it is a clinical diagnosis having no single diagnostic test and the infection source is often mild or clinically not readily evident. The diagnosis of TSS does not necessarily require isolation of *S. aureus* although most cases will have evidence of this infection. STSS is usually easier to diagnose than TSS because of the usually fulminant illness and high rate of blood culture positivity (>90%) in this condition [10]. However, the early presentation of patients who later develop STSS is often non-specific and delays in diagnosis and treatment are not uncommon. Unlike in TSS where the causative agent

Table 25.1. Staphylococcal toxic shock syndrome: case definition[4]

All of:
1. Fever: temperature ≥38.9°C
2. Rash: diffuse macular erythroderma
3. Desquamation: 1–2 weeks after onset of illness, particularly of palms, soles, fingers, and toes
4. Hypotension: systolic blood pressure <90 mmHg for adults or <5th percentile by age for children or orthostatic syncope

And

Involvement of three or more of the following organ systems:
- A. Gastrointestinal: vomiting or diarrhea at onset of illness
- B. Muscular: severe myalgia or creatinine phosphokinase level greater than twice the upper limit of normal
- C. Mucous membranes: vaginal, oropharyngeal, or conjunctival hyperemia
- D. Renal: BUN or serum creatinine greater than twice the upper limit of normal; or ≥5 white blood cells per high power field in the absence of a urinary tract infection
- E. Hepatic: total bilirubin, or transaminase greater than twice the upper limit of normal
- F. Hematology: platelets <100,000/mm^3
- G. Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

And

Negative results on the following tests if obtained:
- A. Blood, throat or cerebrospinal fluid cultures; blood cultures may be positive for *S. aureus*
- B. Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles

Table 25.2. Streptococcal toxic shock, case definition [9]

I. Isolation of group A streptococcus (*S. pyogenes*)
- A. From a normally sterile site (e.g., blood, CSF, pleural or peritoneal fluid, tissue biopsy, surgical wound)
- B. From a non-sterile site (e.g., throat, sputum, vagina, superficial skin lesion)

II. Clinical signs of severity
- A. Hypotension: systolic blood pressure ≤90 mmHg in adults or <5th percentile for age in children

And
- B. ≥2 of the following:
  1. Renal impairment (creatinine >177 μmol/l for adults or twice upper limit of normal for age or baseline level in chronic renal insufficiency)
  2. Coagulopathy (platelets ≤100,000 or disseminated intravascular coagulation)
  3. Liver involvement (transaminases or bilirubin ≥ twice upper limit normal or baseline in pre-existing liver impairment)
  4. Adult respiratory distress syndrome (pulmonary infiltrates and hypoxemia without heart failure) or evidence of diffuse capillary leak (generalized edema or pleural or peritoneal effusions with hypoalbuminemia)
  5. Generalized erythematous macular rash that may desquamate
  6. Soft tissue necrosis (necrotizing fasciitis, myositis, or gangrene)

Illness with:
IA and II (A and B) – definite case
IB and II (A and B) – probable case, if no other etiology defined for illness

does not need to be isolated, the definition of STSS requires the isolation of GAS from the patient [4, 9].

TSS and STSS share many clinical features in common which may be the result of the shock state or more specifically related to individual toxin effects. In these syndromes, shock is multi-factorial and may be due to vasodilatation, non-hydrostatic protein leakage with subsequent intravascular volume depletion, hypovolemia from diarrhea, vomiting, and fever, and myocardial depression [56–58]. The myocardial dysfunction when it occurs demonstrates the picture of a reversible toxic cardiomyopathy or myocarditis. The shock state commonly leads to renal impairment from pre-renal failure or acute tubular necrosis [59]. Electrolyte abnormalities are non-specific and may include low serum calcium, magnesium, sodium, potassium, and phosphate. The elevated transaminase and bilirubin levels commonly observed are most likely related to shock liver. Adult respiratory distress syndrome (ARDS) is more common in STSS but may also occur in TSS. Pleural effusions are common in severe cases of toxic shock and may be complicated by empyema [60].

Toxin manifestations that may be independent of the shock state occur commonly especially in TSS. In TSS the rash is typically a diffuse macular erythroderma with desquamation most pronounced in the hands and soles at approximately 1–3 weeks after illness onset. The rash in STSS is similar but desquamation occurs less commonly. TSS may be associated with mental status changes ranging from headache to encephalopathy, which may lead to persistent cognitive impairment [61]. Vomiting and inflammatory diarrhea are common in TSS, as is sterile pyuria, and may be a result of severe illness or secondary to toxin(s).

Necrotizing fasciitis occurs commonly in association with STSS and is diagnosed if histopathological examination reveals necrosis of fascia with edema and polymorphonuclear infiltrate [15]. This diagnosis may also be made if tissue necrosis is evident clinically or at surgical exploration. Necrotizing fasciitis is a rapidly progressive infection that is often difficult to diagnose clinically. In the early stages there may be necrosis of the underlying fascia despite normal overlying skin. Clues to the diagnosis include pain out of proportion to physical findings, edema, and/or erythema in the setting of symptoms and signs of infection including fever, arthralgias, and myalgias [62]. Rapid changes in clinical findings are particularly worrisome for this diagnosis. Creatine kinase levels are often elevated but this test is both insensitive and non-specific and therefore inadequate to rule out necrotizing fasciitis. Soft tissue radiograms rarely show air in tissue in necrotizing fasciitis due to GAS and are unhelpful to exclude this diagnosis. Magnetic resonance imaging has been proposed as a test to diagnose necrotizing fasciitis but performance of this test should not delay definitive diagnosis by surgical exploration and biopsy which is the standard of care [62]. Since no symptom, sign, or non-invasive investigation reliably rules out a diagnosis of potentially limb or life-threatening necrotizing fasciitis, surgical exploration should be performed in all cases for which the diagnosis is entertained. The procedure has minimal morbidity but a missed or delayed diagnosis of necrotizing fasciitis has very serious and often lethal consequences.

In both TSS and STSS the differential diagnosis includes a broad range of inflammatory conditions. Rocky Mountain spotted fever caused by *Rickettsia rikkettsii*, typhus, meningococcemia, Lyme disease, and leptospirosis are all infections associated with rash that may mimic TSS. Toxic epidermal necrolysis, erythema multiforme, and Stevens-Johnson syndrome all present with rash and fever. Septic shock due to other bacterial organisms may also be difficult to differentiate from toxic shock. Kawasaki disease is an acute illness of children characterized by fever, rash, lymphadenopathy, oral involvement and peripheral extremity changes that must be differentiated from TSS because this condition is complicated by coronary artery aneurysms in approximately 25 % of untreated cases [63].

25.5 Treatment

The general principles of treatment of TSS and STSS are similar to other causes of severe sepsis and septic shock and may involve supportive care, anti-microbials, source investigation and control, and adjunctive therapies [64]. There have been no large randomized trials in the specific treatment of TSS or STSS and management is based primarily on expert opinion and from experience in related conditions. The spectrum of TSS ranges from relatively mild to severe disease whereas STSS is nearly always severe. For example, in one prospective study, 80 % of cases of STSS required ICU care, 60 % needed mechanical ventilation and 52 % vasopressor support [12]. In all cases of STSS and TSS, if ICU care is not initially deemed to be necessary, close monitoring on the hospital ward is required with a low threshold to transfer to ICU care in the event of clinical deterioration.

The general principles of supportive care for patients with TSS and STSS are shared in common with other etiologies of severe sepsis and septic shock and should reflect current widely accepted guidelines [64]. These may include, but are not limited to, early recognition and prompt and aggressive hemodynamic support [65], endotracheal intubation and mechanical ventilation using a lung protective low tidal volume strategy [66], appropriate use of sedative medications and paralytic agents [67], renal replacement therapy

[68], aggressive glucose and electrolyte management [69], activated protein C infusion in severe cases [70, 71], and low-dose adrenocorticoid replacement therapy [72].

Antibiotic therapy is essential in the treatment of TSS and STSS. Antibiotics for TSS are most important for preventing relapse in MTSS but are usually also needed to treat the local infection in NMTSS [73]. Prompt use of antibiotics in STSS is critical because this is nearly always a systemic infection. *S. aureus* is usually resistant to penicillin and in some regions it is commonly methicillin resistant. *S. pyogenes* is universally susceptible to penicillin. However, even if in vitro susceptible, in TSS and STSS beta-lactam antibiotics may be limited in treatment because of the "inoculum effect" [74]. This occurs when the bacteria are present in high concentrations and are in stationary phase with the subsequent reduced production of penicillin binding proteins, the target of beta-lactam antibiotics. Clindamycin is a protein synthesis inhibitor antibiotic that has in vitro activity against both *S. aureus* and *S. pyogenes*. It is not affected by the inoculum effect and also may treat toxic shock by inhibiting toxin production [75]. Clindamycin has been shown to be more effective than penicillin in mouse models of GAS myositis and in case-control studies in humans with STSS [76]. Our recommendations are that high doses of clindamycin should be used with a penicillinase resistant penicillin in TSS, and with penicillin in STSS unless susceptibility testing demonstrates resistance. Since in many cases it is difficult to differentiate among TSS, STSS, and Gram-negative septic shock in the initial presentation, clindamycin should be used with a broad spectrum, β-lactamase resistant agent until microbiologic diagnosis is achieved. In regions where MRSA is a concern, vancomycin or linezolid should be added to this empiric regimen.

Source control is commonly required in TSS and STSS. Any localized infection source requires intervention such as removal of tampons or wound packing, or surgical drainage of infected wounds, abscesses, or empyemas. Necrotizing fasciitis must be investigated and treated surgically without delay because this condition is typically fulminant. Adequate drainage and excision of necrotic tissue is mandatory and repeated surgical procedures or repeated exploration are needed in the treatment of this condition. Wounds should generally be packed open until the infection has been cured, at which time closure or grafting may be performed as appropriate.

There are many proponents of intravenous immunoglobulin (IVIG) therapy as an adjunctive treatment for TSS and STSS and in many regions it is viewed as a standard of care [77, 78]. Intravenous immunoglobulin contains neutralizing antibodies to staphylococcal and streptococcal superantigens and has anti-cytokine activity [15, 79, 80]. Although there is rationale for IVIG use in these syndromes based in theory, several lines of laboratory investigation, and retrospective clinical series, no definitive clinical trial has been conducted and there remains clinical equipoise as to whether IVIG should be used in the treatment of TSS and STSS [81]. One prospective, randomized control comparing IVIG and placebo in the treatment of STSS has been reported [82]. However, this study was ended prematurely after enrolling only 21 patients and as a result was underpowered to detect any significant mortality difference. We recommend the use of IVIG as an adjunctive therapy for STSS and TSS where the disease presentation is particularly severe or rapidly progressive despite prompt institution of other recommended therapies. In children with TSS or STSS it is important to exclude Kawasaki disease as this condition shares many features with toxic shock and may be diagnosed simultaneously [63]. If there are clinical criteria for Kawasaki disease or evidence of coronary involvement then IVIG is clearly indicated based on its proven efficacy in reducing the risk of developing coronary aneurysms from 23% to 2% [83]. Echocardiography is the screening procedure of choice to detect coronary aneurysms and it is our recommendation that this test is performed on all children with TSS or STSS.

Preventive measures may play a role in the management of TSS and STSS. In MTSS it is prudent to recommend against the use of superabsorbent tampons. If these products are used then the absorbency and amount of time they are left in place may best be minimized [25]. Risks for NMTSS may be reduced by careful wound care and prompt treatment of infection in surgical cases. Recurrence is common in TSS and there may be a role for eliminating *S. aureus* asymptomatic carriage in the nares using topical mupirocin [2, 84]. Invasive GAS disease has an estimated household contact transmission risk of 3 per 1,000 that is comparable to rates observed for meningococcal disease [10]. Antibiotic prophylaxis for close contacts of patients with STSS may be beneficial but the best way to approach this issue remains to be defined [85, 86]. In children, 16% of all cases of invasive GAS disease are complications of varicella infection and it has been estimated that 10% of all invasive GAS in children would be prevented by routine vaccination for varicella at 1 year of age [13].

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