

Staphylococcal Toxic Shock Syndrome: A Superantigen-Mediated Disease

Case presentation: A 37 year-old woman with fever, rash and hypotension

L.F. is a 37 year-old woman without significant past medical history who presented to an outside hospital with fever, rash and malaise. Two days prior to admission, the patient awoke with nausea followed by profuse bilious vomiting and loose stools. Concomitantly, she noted a new red rash in the folds of her groin. The rash subsequently progressed to involve her trunk and extremities and was later associated with sore throat and fever.

The patient presented to an outside emergency department, where she was found to have a temperature of 104.5, blood pressure of 80/58 and tachycardia to the 130s. On exam, she was ill-appearing but alert and oriented. Her skin exam was remarkable for a diffuse blanching erythematous rash most prominent in the groin and lower abdomen. HEENT exam revealed conjunctival injection as well as erythema of the posterior oropharynx. Her neck was supple, and there was no lymphadenopathy. Cardiac and chest exams were within normal limits, with the exception of tachycardia. Abdomen was nontender without organomegaly. Gynecologic exam revealed vaginal hyperemia but no discharge or cervical motion tenderness.

Laboratory studies were remarkable for a hematocrit of 32, white blood cell count of 3.10 with 58% bandemia, and a platelet count of 120. Chemistries were remarkable for renal insufficiency (BUN 29, creatinine 1.5) with pyuria (25 wbc/hpf) and LFT abnormalities (AST 131, ALT 209, total bilirubin 2.5). PTT and INR were prolonged without evidence of DIC. A rapid strep test and monospot were negative. Cultures of blood, throat, urine and cervix were obtained.

The patient had an allergy to penicillin (rash), no recent travel and no known insect bites. On further questioning, she reported that five days prior to admission she had noted the onset of her first menses since the delivery of her daughter 9 months previously, and that she had been using super-strength tampons through the day of admission.

The diagnosis of toxic shock syndrome was suspected, and the patient was transferred to the intensive care unit at Brigham and Women's Hospital. Her course was remarkable for massive fluid resuscitation with approximately 15L of crystalloid. She was treated with 10 days of vancomycin and clindamycin and had steady clinical improvement. A cervical culture was positive for 4+ *S. aureus*; this isolate was subsequently determined to be a TSST-1 producing strain. Serum antibodies to TSST-1 were absent on presentation.

In convalescence, the patient reported significant desquamation, especially of her palms and soles, as well as prolonged malaise and fatigue. Convalescent serologies are pending.

Historic and Epidemiologic Features of Staphylococcal Toxic Shock Syndrome:

Staphylococcal toxic shock syndrome was first described by James Todd and colleagues in 1978. In this case series, the authors described seven children between the ages of 8 and 17 who presented with high fever, headache, confusion, conjunctival hyperemia, scarlatiniform rash, subcutaneous edema, vomiting, diarrhea, refractory hypotension, oliguria and acute renal failure (1). Five of these patients were studied prospectively and found to have *S. aureus* infection related to phage-group I on mucosal or abscess sites. One patient died, and each of the survivors had desquamation of the hands and feet during convalescence. Streptococcal infection, leptospirosis, Rocky Mountain Spotted Fever and other viral exanthems were excluded, and the phrase "toxic shock syndrome" (TSS) was coined to describe this newly-recognized disease process.

In retrospect, cases of TSS may have been described in the literature as far back as 1927 when Stevens presented two older children with erythroderma, moderate toxicity and mild desquamation associated with local staphylococcal infections (2). Twelve additional cases of "staphylococcal scarlet fever" are reported in the literature between 1927 and 1973 (3).

Menstrual-associated staphylococcal TSS was first noted when seven menstruating women with clinical signs and symptoms similar to those described by Todd were hospitalized in Madison, Wisconsin between July 1979 and January 1980. A letter describing the clinical features of the syndrome and its apparent epidemiologic

link to menses was sent to physicians in Wisconsin in January 1980 and led to the development of a statewide surveillance system. 38 cases were subsequently detected via the surveillance system, and a case control study of these cases was reported in the *New England Journal of Medicine* in December 1980 (4). 35 of these described cases occurred during menses, and tampon use was significantly correlated with risk of disease (OR 7.5). 74% of women who had vaginal or cervical cultures obtained were positive for *S. aureus*.

In 1981, Bergdoll and Schlievert independently described an exotoxin from isolates of TSS-associated *S. aureus* (5,6). The toxin has since been called toxic shock syndrome toxin 1 (TSST-1) and is generally considered to be the major cause of TSS. TSST-1 is produced by more than 95% of *S. aureus* strains associated with menstrual TSS; this is in contrast to typical clinical isolates in which TSST-1 is produced in only 5-25% of strains (4,7). Seroepidemiologic studies in TSS patients indicate that TSST-1 specific antibodies are often low or absent during acute illness and that seroconversion can be documented during convalescence (8). Age-matched healthy controls typically have high levels of anti-TSST-1 antibody.

A number of hypotheses have been generated to explain the association between tampon use and menstrual-associated TSS. In general, tampons may increase local levels of oxygen or bind magnesium, both of which are factors favoring toxin production (9). The presence of a foreign body may also alter the normal vaginal flora, favoring the overgrowth of *S. aureus*. Particular degradation products of the carboxymethylcellulose element of Rely, a brand of highly-absorbent tampons, were noted to support the growth of the TSS strain of *S. aureus*. Menstrual-associated TSS reached epidemic proportions in 1980-81 in association with the marketing of super-absorbent tampons. The Rely brand was removed from the market in 1985 with a subsequent dramatic decline in menstrual-associated cases. The incidence rate decreased from 6-12 cases/100,000 women ages 12-49 in 1980 to 1 case/100,000 women ages 15-44 in 1986 (10).

Since the change in tampon production, recent epidemiologic studies indicate that non-menstrual TSS represents an increasing proportion of cases, accounting for up to one-half of reported cases in some series (10). Non-menstrual TSS has been associated with a variety of clinical situations including surgical and postpartum wound infections, mastitis, septorhinoplasty, sinusitis, osteomyelitis, burns and influenza infection. Non-menstrual TSS is more commonly hospital-acquired and may be associated with a higher rate of severe complications. Interestingly, only 60-75% of *S. aureus* strains associated with nonmenstrual TSS are TSST-1 producing (7). Other staphylococcal toxins, particularly enterotoxins B and C, have been implicated in nonmenstrual TSS. Notably, pyrogenic exotoxins of group A streptococci are also capable of causing an identical syndrome to staphylococcal TSS. Trauma, injury and surgical procedures are commonly associated with streptococcal TSS, and the case fatality rate ranges from 30-70% as compared to 5% with staphylococcal TSS.

Table 1: Case definition of TSS

Clinical Finding	Description
Fever	Temperature > 102F
Rash	Diffuse macular erythroderma
Desquamation	1-2 wks after onset of illness, especially palms/soles
Hypotension	
Multisystem involvement (3 or more systems)	GI: vomiting or diarrhea Muscular: myalgia, CK at least 2 x normal Mucous membrane hyperemia Renal: elevated BUN/Cr at least 2 x normal, pyuria (>5 wbc/hpf) Hepatic: elevated total bilirubin, transaminases at least 2 x normal Hematologic: platelet count <100,000
Laboratory criteria	CNS: disorientation Negative results on the following tests, if performed: blood, throat, CSF cultures (blood culture may be positive for <i>s. aureus</i>) Rocky Mountain spotted fever, leptospirosis, measles

The case definition established by the CDC in 1981 continues to constitute the criteria for diagnosis and is outlined in table 1. A confirmed case is one in which all six of the clinical findings are present; a probable case is one in which five of the six findings are present. Additional laboratory findings which are pathognomonic for TSS but are not currently included in the case definition include: isolation of *S. aureus* from a mucosal or normally sterile body site, production of TSST-1 by an incriminated staphylococcal isolate, serologic susceptibility at the time of acute illness, and development of antibody to the toxin during convalescence.

A number of distinctive laboratory changes occur in TSS, as outlined in table 2. Leukocytosis with a marked increase in circulating immature granulocytes is common, occurring in more than one-third of cases. Profound hypoproteinemia and hypoalbuminemia are suggestive of leakage of fluid high in protein from the vasculature. Hypophosphatemia is often present; the mechanism, although unclear, is particularly intriguing in the presence of acute renal failure. Hypocalcemia may be related to hypoproteinemia, but also has been associated with high circulating levels of immunoreactive calcitonin.

Table 2: Distinctive laboratory findings in TSS

Immature and mature neutrophils >90% of white blood cell differential
Hypoproteinemia/hypoalbuminemia
Pyuria
Hypocalcemia
Hypophosphatemia
Hypoferrinemia
Azotemia
Intrahepatic cholestasis
Increased liver enzymes
Increased creatine phosphokinase
Coagulopathy

Chesney P. Rev Infect Dis. 1989;S1-S7.

Although complete recovery is the norm, chronic neurologic sequelae are sometimes encountered after an episode of TSS. Rosene and colleagues studied 12 women with a recent history of menstrual-associated TSS using a battery of neuropsychological tests. Clinical sequelae including memory deficits, impaired concentration and nonspecific EEG abnormalities were noted in 6/12 women (11). In Chesney's original description of the clinical features of TSS, 22 of 22 patients reported prolonged weakness and fatigue up to several months' duration (12).

Patients with TSS, especially menstrual-associated TSS, can develop recurrent episodes of disease. Ten of the 35 women with menstrual-associated TSS described in the first report in the *NEJM* had recurrent illness: five women had two episodes, and five women had three or more episodes (4). Typically, each episode was progressively less intense.

Antimicrobial treatment of TSS:

Systemic antistaphylococcal antibiotics have been considered part of the standard therapy for TSS since Davis and colleagues demonstrated that the rate of recurrence was significantly lower (less than 10%) in menstrual-associated TSS patients who received cephalosporins or penicillinase-resistant penicillins (4).

The effect of topical antimicrobial agents on TSS-associated *S. aureus* strains has also been studied. Concerned for the existence of TSS in burn patients, Edwards-Jones studied the effect of various sublethal concentrations of topical antimicrobial agents on the production of TSST-1 by *S. aureus* strains isolated from hospitalized patients (13). Silver sulfadiazine cream, which is used routinely for the treatment of burns, notably caused an increase of at least four-fold in the production of TSST-1 in 45% of the strains, whereas mupirocin ointment caused a marked decrease in toxin production in 47% of strains and did not cause an increase in toxin production in any of the strains. The authors postulated that this differential effect on toxin production may have been related to the mechanism of action of silver sulfadiazine, leading to increased TSST-1 synthesis or improved transport across the cell membrane.

Clindamycin inhibits protein synthesis after binding to the 50S subunit of bacterial ribosomes and has been noted to suppress expression of certain bacterial exotoxins, such as exfoliative toxin and streptolysin O

and S, by unclear mechanisms. In a small study, Schlievert and Kelly described the effect of clindamycin on growth and toxin production of six TSS-associated *S. aureus* isolates, including one “high-toxin producer” MN8 (14). The authors found that clindamycin significantly inhibited toxin production at concentrations which did not substantially affect bacterial growth.

TSST-1: A Prototypic Superantigen:

TSST-1 is a chromosomally-encoded toxin that is produced by more than 95% of *S. aureus* strains associated with menstrual TSS and by 60-75% of strains associated with nonmenstrual TSS (4,7). TSST-1 was one of the first bacterial toxins associated with human disease to be recognized as a superantigen. Superantigens are protein products of microorganisms and plants which are capable of inducing extensive T-cell activation via a mechanism that is distinct from that of conventional antigens.

A conventional antigen is initially taken up by an antigen presenting cell (APC), such as a macrophage, B cell or dendritic cell, and then processed into peptides by proteases. These antigenic peptides bind in a groove formed by the interaction of the alpha and beta chains of the class II MHC. The peptide – MHC complex is expressed on the surface of the APC, and the T-cell then interacts with that complex via the antigen specific T-cell receptor.

Unlike conventional antigens, superantigens do not require processing by APCs, but rather form a direct cross-link between different allelic forms of the MHC class II molecule and the V β chain of the T-cell receptor, which lies outside the hypervariable antigen-detecting region. As a result, superantigens bypass the mechanism of antigen specificity and are capable of stimulating *all* T-cells possessing a specific V β sequence on the T-cell receptor.

Whereas <1 cell per 10,000 lymphocytes responds to a conventional antigen, a superantigen is capable of stimulating as many as 20% of circulating lymphocytes. Each superantigen recognizes between one and five V β s, and each superantigen has its own signature profile of V β stimulation. Hallmarks of the immune response induced by a superantigen include: (1) extensive proinflammatory cytokine production (2) changes in the number of circulating V β -restricted T-cells (3) polyclonal B cell activation (4) apoptosis of clonally activated T-cells after initial stimulation.

All of these characteristics are observed in TSST-1 mediated TSS. *In vitro*, TSST-1 is a powerful but selective stimulator of V β 2+ human T-cells. Choi and colleagues used quantitative PCR to study the T-cell repertoire of 8 patients with TSS (15). Five patients were found to have amplification of V β 2+ T-cells. In these patients V β 2+ cells comprised 30-70% of circulating T-lymphocytes, compared with 10% in the the control group. Serial evaluation of two patients revealed that the V β 2+ T cell percentage had returned nearly to normal by 45-60 days after the acute episode.

In vitro and mouse studies demonstrate rises in cytokine levels in response to stimulation with TSST-1. TNF α and TNF β are produced, followed sequentially by IL-2, IL-6, IL-1 and IFN γ . TNF α is thought to be an important mediator of many of the clinical features of TSS.

Table 3: Organisms Producing Putative Superantigens

Species	Organism
Bacterial	Staphylococcus aureus
	Streptococcus pyogenes
	Mycoplasma arthritidis
	Yersinia enterocolitica
	Yersinia pseudotuberculosis
	Mycobacterium tuberculosis
	Clostridium perfringens
Viral	Mouse mammary tumor virus
	Rabies virus
	Herpesviruses: EBV, H. saimiri
	HIV
Parasitic	Toxoplasma gondi
	Plasmodia

Many bacterial, viral and protozoal organisms have been found to produce superantigens, as outlined in table 3. Perhaps the most well-characterized superantigens are the pyrogenic toxins made by *S. aureus* and group A streptococci. There are several stretches of homology that are shared among the toxins produced by these two organisms, and these stretches may localize to site of class II MHC binding (16).

The widespread production of superantigens by such different microorganisms likely reflects convergent evolution driven by advantageous elements of the host's immune reaction. The exuberant cytokine and immune response induced by superantigens is followed by deletion and anergy of activated T-cells; this may ultimately impair the host immune response to the superantigen-producing pathogen. Alternatively, the extensive local inflammation induced by a superantigen may facilitate bacterial invasion.

Superantigens in Human Disease:

Although the supporting data is strongest for TSS, superantigens have been implicated in a number of other human diseases. In each of these illnesses, an abnormal state of immunologic activity is observed, and many of the hallmark effects of superantigens are evident. In particular, V β skewing of the T-cell repertoire is present, and a toxin-secreting microbe has been isolated. Fever and a variety of skin rashes are common clinical features of these syndromes and are likely related to extensive cytokine activity. Superantigens also may be especially associated with skin disorders due to upregulation of cutaneous lymphocyte-associated antigen. Treatment of peripheral blood mononuclear cells with staphylococcal enterotoxin B, TSST-1, and streptococcal pyrogenic exotoxins A and C significantly upregulates the expression of this antigen, which is involved in the migration of T-cells to the skin (17). In the skin, these T-cells may mediate damage via local secretion of cytokines or via cytotoxicity directed toward cells expressing autoantigens.

Table 4 enumerates the human diseases that have been associated with microbial superantigens. Factors including dose of toxin, route of exposure and host susceptibility may affect the particular manifestation of a particular superantigen-mediated disease. This discussion will focus briefly on the examples of Kawasaki syndrome and guttate psoriasis.

Table 4: Human Diseases Associated with Superantigens

Human Disease	Associated Superantigen	V β skewing
Acute syndromes		
Toxic shock	TSST-1	+
	Staphylococcal enterotoxin B,C	
	Streptococcal pyrogenic exotoxins A,C,G,H	+
	Streptococcal superantigen	
Food poisoning	Staphylococcal enterotoxins A-G,H,I	
Kawasaki's	?TSST-1	+
Scarlet fever	Streptococcal pyrogenic exotoxins	
Autoimmune diseases		
Guttate psoriasis	Streptococcal pyrogenic exotoxin C	+
Rheumatoid arthritis		+
Dermatomyositis		+
Type I DM		+

Kawasaki Syndrome:

Kawasaki syndrome (KS), also called mucocutaneous lymph node syndrome, was first described in Japan in 1967. It is an acute febrile illness that occurs primarily in infants and young children and is characterized by conjunctival injection, oropharyngeal changes, erythroderma and a nonsuppurative cervical lymphadenopathy. A polymorphous rash is an important clinical feature of KS, and similar to TSS, the convalescent phase may be characterized by sheet-like desquamation that begins in the periungual regions of the hands and feet. Up to 25% of children with KS will develop coronary artery aneurysms if left untreated. KS is now considered one of the major causes of acquired heart disease in children, surpassing rheumatic fever in many parts of the world.

An etiologic agent has yet to be consistently isolated from children, but several aspects of the disease suggest an infectious process. For instance, outbreaks of KS are geographically clustered, often with

seasonal predominance. Nationwide epidemics of KS occurred in Japan in 1979, 1982 and again in 1985 (18). The increased prevalence of KS in children of Japanese and Korean origin, including those living in the United States, suggests that a genetic predisposition may also exist.

In contrast to the difficulty isolating an infectious agent, studies of the immune status of children with KS consistently reveal a profound degree of immunoregulatory abnormalities that are not characteristic of most other febrile exanthems of childhood. In particular, cytokine production is increased and autoantibodies are noted. There is polyclonal B cell activation and increased numbers of activated macrophages and CD4+ T cells (19). At least five laboratories have reported TCR V β (predominantly V β 2 but also V β 8) skewing in patients with KS. Leung and colleagues have demonstrated the selective expansion of V β 2+ T cells in the myocardium and coronary artery aneurysm of a child who died 3 weeks after the onset of KS (20). Superantigen-producing bacteria were isolated from throat, axilla, groin or rectal cultures in 13 of 16 consecutive Kawasaki patients and only 1 of 15 control patients with a febrile illness at one institution (21). 11/13 superantigen-positive cultures from these patients contained TSST-1 secreting *S. aureus* and 2/13 contained streptococci producing SPEB or SPEC.

Of note, not all investigators have been able to identify V β skewing in KS patients. This may result from the fact that the change induced by superantigens in the T-cell repertoire is a dynamic process. Skewing is most consistently detected during the second week of illness, with T-cell distribution subsequently beginning to normalize, likely due to the migration of activated T cells migrate into inflamed tissue.

Guttate Psoriasis:

Some investigators have postulated a role for superantigens in the development and perpetuation of autoimmune diseases, such as psoriasis and rheumatoid arthritis. Due to their ability to stimulate polyclonal activation of T-cells, superantigens have the capacity to trigger potentially autoreactive T-cells that have escaped the processes of tolerance; they thus may be insidiously involved in the development of autoimmune disease. Animal models support this hypothesis, as superantigens are frequently arthritogenic in animals, and V β skewing can be detected in joint fluid.

Psoriasis is a common inflammatory autoimmune skin disorder characterized by the eruption of reddish, silvery-scaled maculopapules, usually on the trunk, knees, elbows and scalp. Immunosuppressive drugs that inhibit T-cell activation and cytokine release, such as anti-CD3, corticosteroids and cyclosporin A, are effective treatments for psoriasis, which strongly implicates T-cell activation in the pathogenesis of the disease.

Guttate psoriasis is a well-defined form of psoriasis which is characterized by the abrupt appearance of multiple small psoriatic lesions, primarily on the trunk; 70% of patients with guttate psoriasis eventually develop chronic plaque psoriasis. The acute eruption of guttate psoriasis is frequently associated with a preceding streptococcal throat infection or a rise in serum antistreptococcal titers. Streptococcal isolates from these patients consistently produce streptococcal pyrogenic exotoxin C, a known superantigen (22). In a study of 10 patients with acute guttate psoriasis, Leung and colleagues demonstrated a selective expansion and accumulation of V β 2+ T cells in the psoriatic lesions as well as in perilesional skin (23). No such skewing was evident in the peripheral blood of these patients. Group A streptococci were isolated from seven of the study patients, and all seven isolates produced streptococcal pyrogenic exotoxin C.

Coupled with the observation that superantigens upregulate the expression of CLA on T-cells, these findings support the idea that following an episode of pharyngitis, a streptococcal superantigen (in particular SPEC) selectively drives the expansion and cutaneous localization of V β 2+ T cells. These populations may remain persistently activated due to abnormal recognition of skin autoantigens which have determinants that are cross reactive with bacterial antigens. Notably, autoantibodies recognizing antigens present in keratinocytes have been demonstrated in psoriatic patients but not in healthy controls (24).

Immunologic Therapies for TSS and Other Superantigen-associated Diseases:

Given that superantigens induce disease by triggering an excessive cellular immune response, immunomodulating therapies should offer promise in the treatment of these often life-threatening conditions. In fact, a number of such treatment options have already been explored for TSS and the other superantigen-mediated human diseases.

In 1984, Todd and colleagues performed a case-control evaluation of 45 patients with staphylococcal TSS to evaluate the effect of corticosteroid therapy on clinical outcome (25). 25 case patients received an average of 38 mg/kg total dose of a prednisone equivalent over an average of 3.4 days. Compared with 20

patients who did not received corticosteroids, case patients had a shorter duration of fever and a more rapid return to a stable clinical condition if corticosteroids were administered within the first two to three days of TSS.

In vitro, IVIG can block T-cell activation by staphylococcal and streptococcal superantigens; in vivo, it has proven useful in treating several superantigen-mediated diseases (26). The Ontario Streptococcal Study Group conducted an observational study of the effect of a single dose of 2g/kg of IVIG on 30-day survival in 21 patients with streptococcal TSS (27). IVIG-treated patients were more likely than historical controls to survive for both 7 days (90% vs. 50%) and 30 days (67% vs. 34%). The use of historical controls in this study posed some difficulties in the interpretation of results, as significantly less control patients received clindamycin or surgical debridement. However, in a multivariate model including antibiotic treatment and use of surgery, APACHE II score and IVIG therapy were the only two variables of importance in predicting mortality. The odds ratio for survival of patients treated with IVIG was 8.1 (95% CI 6-45). Immunologic analyses were also performed on 10 patients treated with IVIG. Compared to plasma obtained from these patients at baseline, plasma obtained after IVIG treatment was able to inhibit the mitogenicity of the culture supernatant from the patient's own streptococcal isolate. Cytokine production by peripheral blood mononuclear cells was also decreased following IVIG administration. These findings support the conclusion that IVIG can effectively neutralize bacterial exotoxins in vivo. Additionally, IVIG non-specifically inhibits cytokine synthesis and immune activation.

IVIG is standard therapy for the treatment of KS. In a randomized trial of 168 patients published in 1984, a dose of 400 mg/kg/day on four consecutive days was given along with high dose aspirin through the 14th day of illness (28). At 2 (8 vs 23%) and 7 weeks (4 vs. 18%) after enrollment, coronary artery abnormalities were significantly less in the group treated with IVIG. For KS, IVIG is currently given in a single dose of 2g/kg based on follow-up studies which showed a more rapid resolution of fever and decreased duration of hospitalization with this dose. In patients who fail to defervesce after the initial dose of IVIG, retreatment is sometimes considered.

Arad and colleagues recently described a synthetic peptide antagonist derived from a domain of staphylococcal enterotoxin B (SEB) that in vitro is capable of preventing cytokine production induced by TSST-1, staphylococcal enterotoxins A and B and streptococcal pyrogenic exotoxin A in human peripheral blood mononuclear cells (29). This peptide encompasses a highly but not absolutely conserved region of the superantigen family located outside the known binding domains for the MHC class II complex and the T-cell receptor; it may function by blocking the interaction of costimulatory molecules. In mouse models, this peptide is also capable of blocking lethality of TSST-1 and SEB and serves as a potent adjuvant in inducing cross-immunity to challenge with superantigens aside from SEB. These results are preliminary but may represent an exciting novel mechanism for protecting against superantigen-mediated disease.

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