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Toxic Shock Syndrome in Children

Epidemiology, Pathogenesis, and Management

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Contents

Abstract

Toxic shock syndrome (TSS) is an acute, toxin-mediated illness, like endotoxic shock, and is characterized by fever, rash, hypotension, multiorgan involvement, and desquamation. TSS reflects the most severe form of the disease caused by *Staphylococcus aureus* and *Streptococcus pyogenes*. A case definition for staphylococcal TSS was well established in the early 1980s and helped in defining the epidemiology. Since the late 1980s, a resurgence of highly invasive streptococcal infections, including a toxic shock-like syndrome, was noted worldwide and a consensus case definition for streptococcal TSS was subsequently proposed in 1993. Both TSS and the toxic shock-like syndrome occur at a lower incidence in children than in adults.

Changes in the manufacturing and use of tampons led to a decline in staphylococcal TSS over the past decade, while the incidence of nonmenstrual staphylococcal TSS increased. Nonmenstrual TSS and menstrual TSS are now reported with almost equal frequency. The incidence of streptococcal TSS remains constant after its resurgence, but varies with geographic location. Streptococcal TSS occurs most commonly following varicella or during the use of NSAIDs. Sites of infection in streptococcal TSS are much deeper than in staphylococcal TSS, such as infection caused by blunt trauma, and necrotizing fasciitis. Bacteremia is more common in streptococcal TSS than in staphylococcal TSS. Mortality associated with streptococcal TSS is 5–10% in children, much lower than in adults (30–80%), and is 3–5% for staphylococcal TSS in children.

TSS is thought to be a superantigen-mediated disease. Toxins produced by staphylococci and streptococci act as superantigens that can activate the immune system by bypassing the usual antigen-mediated immune-response

sequence. The host-pathogen interaction, virulence factors, and the absence or presence of host immunity determines the epidemiology, clinical syndrome, and outcome.

Early recognition of this disease is important, because the clinical course is fulminant and the outcome depends on the prompt institution of therapy. Management of a child with TSS includes hemodynamic stabilization and appropriate antimicrobial therapy to eradicate the bacteria. Supportive therapy, aggressive fluid resuscitation, and vasopressors remain the main elements. An adjuvant therapeutic strategy may include agents that can block superantigens, such as intravenous immunoglobulin that contains superantigen neutralizing antibodies.

1. Background

Toxic shock syndrome (TSS) is an acute illness characterized by fever, rash, hypotension, multiorgan system dysfunction, and desquamation. TSS is mainly caused by toxin-producing strains of *Staphylococcus aureus* and *Streptococcus pyogenes*. It was originally described in 1978 with *S. aureus* infection in children,[1] and in 1980 an epidemic occurred with tampon use. In 1987, a disease similar in appearance to TSS, but caused by invasive streptococci, was reported and was subsequently known as streptococcal TSS,[2,3] which shared many common clinical features of staphylococcal TSS. Numerous population-based and hospital-based reports were published describing the epidemiology and clinical spectrum of both staphylococcal TSS and streptococcal TSS in adults. There are relatively few reports on the pediatric population. Both of these entities are reviewed in this article.

1.1 Search Strategy and Selection Criteria

To ensure that all the cases of toxic shock were included, we conducted a MEDLINE search using the search terms 'toxic shock syndrome' and 'child'. Only those published in English and from which pediatric data can be extracted are included in this article. For staphylococcal TSS, 27 reports were retrieved from 1982 to May 2003, mostly extracted from case reports. For streptococcal TSS, larger series were retrieved and 30 reports were selected in this review article from 1991 to May 2003, using The Working Group on Severe Streptococcal Infections case definition. Tables I and II summarize the frequency of both TSSs in children.

2. Epidemiology

2.1 Staphylococcal Toxic Shock Syndrome (TSS)

Staphylococcal TSS was first reported in 1978 in previously healthy children with *S. aureus* infection.[1] An epidemic soon followed in 1979–80 and 90% of cases were associated with tampon use in healthy, young menstruating women.[64] In 1986, active surveillance in the US found a substantial decrease in the incidence of menstrual TSS. Incidence rates decreased from 6 to 12 per 100 000 population among women aged 12–49 years in 1980 to 1 per 100 000 population among women aged 15–44 years in 1986.[65] The cumulative incidence in 1996 was 0.5 per 100 000 population.[66] Factors contributing to the decline in menstrual TSS included changes in tampon composition, decrease in tampon absorbency, changes in usage pattern, standardized labeling, and greater awareness among women and physicians.[65,66]

Passive surveillance data from 1979 through 1996 also showed the declining trend of menstrual TSS and the increase in the proportion of nonmenstrual cases.[66] Both menstrual and nonmenstrual TSS cases occurred primarily in Caucasian women. Menstrual TSS declined from 91% of all TSS cases during 1979–80 to 59% during 1987–96. Nonmenstrual TSS accounted for 54% by active surveillance in 1986[65] and 41% (range: 30–55%) by passive surveillance in 1996.[66] Nonmenstrual TSS and menstrual TSS cases are now reported with almost equal frequency. Of the nonmenstrual cases of TSS, 18.3% were reported after surgical procedures, 11.5% were postpartum or postabortion, and 23% were associated with nonsurgical cutaneous lesions. The nonmenstrual cases reported after surgical procedures increased from 14% during 1979–86 to 27% during 1987–96. During the 17-year period, 50 cases of TSS in children aged ≤5 years were reported; more than half of these occurred in children aged ≤2 years, and 61.7% were associated with nonsurgical cutaneous lesions. The overall case-fatality ratio in children was 4%.[66] The mortality rates were 3% for menstrual and 5% for nonmenstrual cases.[66]

In the UK, it was estimated that 3–13% of children admitted to the burns unit develop TSS.[67,68] The number of TSS reported in children aged <10 years is quite low, despite children having a low antibody titer to TSS toxin-1 (TSST-1) and the increased prevalence of nasal colonization (10%) with TSST-1 positive strains.[6,69]

The incidence of postoperative cases of TSS following all types of surgery was estimated to be 3 per 100 000 population, but it was higher following ear, nose, and throat surgery (16.5 per 100 000 population).[70]

Risk factors for nonmenstrual TSS include colonization of a toxin-producing strain of *S. aureus*, absence of protective antitoxin

Table I. Summary of literature reports of staphylococcal toxic shock syndrome (STSS) in children from 1982 to 2003

Study location (year)	Age range (years)	No. of pts	Bacteremia (no. of pts)	Mortality for STSS [no. (%)]	Sites of isolation	Predisposing event	Remarks	Reference
Colorado, New York (1978)	8–17	7	0	1 (14.3)	Nasopharyngeal, vaginal, tracheal or empyema, abscess	NA	Exotoxin	1
Atlanta (1982)	0–10	4	NA	NA	NA	NA	STSS not associated with menstruation 1980–1	4
(1983)	2	1	0	0 (0)	Tracheal aspirates	None		5
Colorado (1984)	5–10	7	1	1 (14.3)	Pleural effusion 1/7, wound 1/7, throat 1/7	None	Sterile cultures of all sites 3/7	6
Ontario (1984)	2	1	0	0 (0)	Tracheal aspirates	None		7
Michigan (1984)	13	1	0	0 (0)	Nasal packing	None		8
(1985)	13	1	0	0 (0)	Tracheal aspirates	None		9
Billericay (1985)	NA	7	0	4 (57)	NA	Burn	Cases from 1982 to 1984	10
London (1985)	0–10	6	2	0 (0)	Blood 2/6, wound 2/6	Burn		11
Lille (1986)	8	1	0	0 (0)	Tracheal aspirates	None		12
Minnesota (1986)	15–16	2	0	1 (50)	Respiratory secretions	Influenza B	Virus culture	13
Oregon (1987)	13	1	0	0 (0)	Tracheal aspirates	Influenza A	Seroconversion	14
Roanoke (1987)	18	1	0	1 (100)	Sputum and lung tissue	Influenza B	Influenza-like illness during outbreak	15
Minnesota (1987)	5–16	5	0	4 (80)	Respiratory tract secretions	Influenza B	Seroconversion 1/2 Virus culture 1/2	16
Nashville (1988)	7	1	0	0 (0)	Throat, peritoneal fluid, and ileum	Enterocolitis		17
St. Louis (1988)	16	1	0	0 (0)	Pus from thigh	HIV infection and hemophilia	Recurrent STSS	18
Arizona (1988)	6	1	0	0 (0)	Ear lobe	Ear piercing		19
Vancouver (1989)	4–7	2	1	2 (100)	Ascites, mesenteric lymph node, blood	Neuroblastoma 1/2	Atypical STSS (without rash and rash after shock)	20
Connecticut (1989)	13	1	1	0 (0)	Subperiosteal pus	None	Clavicle osteomyelitis	21
Edinburgh (1990)	2	1	0	0 (0)	Wound	Burn	TSST-1	22
Denver (1990)	8–14	3	0	0 (0)	Sinus aspirates	Varicella 1/3		23
Wiltshire (1990)	NA	12	0	5 (42)	Wound	Burn		24
Bronx (1991)	12	1	1	0 (0)	Tracheal aspirates	Influenza A	Seroconversion	25
Missouri (1993)	8	1	0	0 (0)	Nostril	Influenza A	Virus culture	26
Illinois (1994)	2	1	0	0 (0)	Wound	Burn	TSST-1	27
New York (1996)	6	1	0	0 (0)	Sinus aspirate	HIV infection	Recurrent STSS	28
London (1996)	2	1	0	0 (0)	Tracheal aspirates	None		29
Alberta (1996)	13	1	0	0 (0)	Nasal mucosa	None	Concomitant Kawasaki disease	30
Leuven (1997)	1	1	0	0 (0)	Inguinal lymph node aspirate	None	STSS without rash TSST-1	31
Cardiff (1999)	9	1	NA	0 (0)	Dental abscess	None	TSST-1	32
Wiltshire (2002)	1	1	0	0 (0)	Wound	Burn	TSST-1	33

NA = not available; **pts** = patients; **TSST-1** = toxic shock syndrome toxin-1.

Table II. Summary of literature reports of frequency of streptococcal toxic shock syndrome (STSS) in children from 1991 to 2003

Study location (year)	Age range (years)	No. of pts	Bacteremia (no. of pts)	STSS [no. (%)]	Mortality for STSS (no.)	Overall mortality [no. (%)]	Remarks	Reference
Denver (1991)	0–19	33	33	NA	NA	2 (6.1)	GAS bacteremia from 1980 to 1990	34
Winston-Salem (1991)	0–16	22	16	1 (4.5)	0	0 (0)	GAS sterile site isolates from 1983 to 1990	35
Kansas City (1991)	3–11	29	29	5 (17)	0	0 (0)	GAS bacteremia from 1971 to 1990	36
Minnesota (1991)	0–14	6	4	2 (33)	0	0 (0)	Serious GAS infections from 1985 to 1988	37
Umea (1992)	0–20	14	3	0 (0)	0	0 (0)	GAS bacteremia from 1988 to 1999	38
London (1992)	0–10	4	4	4 (100)	0	0 (0)	GAS bacteremia and hypotension	39
Minnesota (1992)	0–16	22	2	1 (4.5)	1	1 (4.5)	GAS bacteremia from 1984 to 1990	40
Lyon (1992)	6–10	2	2	2 (100)	1	1 (50)	STSS	41
Ontario (1993)	0–16	6	5	NA	NA	2 (33)	GAS sterile site isolates from 1987 to 1990	42
Dallas (1994)	1–5	6	1	3 (50)	0	0 (0)	GAS sterile site isolates complicating varicella, 1993	43
Toronto (1994)	0–17	24	19	1 (4.2)	0	0 (0)	GAS sterile site isolates from 1985 to 1991	44
Boston (1995)	0–6	62	62	4 (6.5)	1	2 (3.2)	GAS bacteremia from 1977 to 1992	45
Seattle (1995)	0–10	14	2	5 (35.7)	0	0 (0)	GAS necrotizing fasciitis complicating varicella from 1993 to 1995	46
Jerusalem (1995)	0–11	29	29	1 (3.4)	0	1 (3.4)	GAS bacteremia from 1987 to 1994	47
Nashville (1995)	2–8	15	7	7 (46.7)	1	1 ((6.7)	GAS necrotizing fasciitis complicating varicella from 1973 to 1993	48
Berkeley (1996)	0–8	24	10	5 (20.8)	0	4 (16.7)	GAS sterile site isolates complicating varicella, 1994	49
Ontario (1996)	0–9	64	NA	4 (6.3)	NA	NA	GAS sterile site isolates from 1992 to 1993	50
Beer-Sheva (1997)	0–15	43	37	3 (6)	0	0 (0)	GAS sterile site isolates from 1980 to 1994	51
North Carolina (1997)	0–20	38	NA	5 (13.2)	0	0 (0)	GAS sterile site isolates from 1987 to 1995	52
Atlanta (1998)	0–9	41	9	3 (7.3)	NA	2 (4.9)	GAS sterile site isolates from 1994 to 1995	53
Washington (1999)	0–10	19	5	5 (26)	0	0 (0)	GAS necrotizing fasciitis complicating varicella from 1993 to 1995	54
Mexico (2000)	1–14	3	1	1 (33)	0	0 (0)	GAS necrotizing fasciitis complicating varicella from 1998 to 2000	55
Ontario (2000)	0–17	243	158	16 (7)	9	10 (4.1)	GAS sterile site isolates from 1992 to 1996	56
Sweden (2000)	0–19	43	NA	10 (23.3)	6	6 (14)	GAS sterile site isolates from 1994 to 1995	57
Taiwan (2001)	4–8	3	2	3 (100)	1	1 (33)	STSS	58
Taiwan (2001)	0–20	12	12	6 (50)	4	4 (33)	GAS bacteremia from 1995 to 2000	59
Israel (2002)	0–15	195	37	5 (2.6)	NA	1 (0.5)	GAS sterile site isolates from 1997 to 1998	60
USA (2002)	0–10	226	NA	6 (2.7)	NA	NA	GAS sterile site isolates from 1995 to 1999	61
Nottingham (2002)	0–5	3	3	3 (100)	0	0 (0)	GAS myositis	62
Tel Aviv (2002)	0–18	17	10	1 (5.9)	0	0 (0)	GAS sterile site isolates from 1995 to 1997	63

GAS = group A streptococci; **NA** = not available; **pts** = patients.

antibodies, and an infected site. Staphylococcal TSS has been reported in association with any primary staphylococcal infection, after surgery, with any disruption of the skin or mucous membrane, or placement of a foreign body, and sometimes, no obvious site of infection.[71]

2.2 Streptococcal TSS

The incidence of streptococcal TSS corresponds to the incidence of invasive group A streptococcal (GAS) disease, which varies according to geographic location. In the late 1980s, reports suggested the emergence of a toxic shock-like syndrome,[2] and a consensus case definition was subsequently established in 1993.[3] Population-based studies were then conducted to assess the incidence of invasive GAS disease, as well as streptococcal TSS.

An active surveillance in 1995–9 conducted in five US states showed that the annual incidence of invasive GAS infections was 3.5 cases (from 2.5 to 4.3) per 100 000 population and was stable during this period.[61] This rate was comparable to those reported from Arizona (4.3 per 100 000)[2] and from Georgia (5.2 per 100 000),[53] but was much higher than that reported from Ontario, Canada (1.5 per 100 000).[50] The incidence was highest among those aged ≥65 years, followed by those aged <2 years. Infection was 1.6-fold more common among non-Caucasian individuals. The rate of streptococcal TSS among the invasive GAS infections was 6%, and was lower in children aged <10 years (2.7%) than in those aged >10 years (6.4%).[61] This rate was much lower compared with those from other studies (4.2–6.3%).[44,50]

The annual incidence of invasive GAS infection in Israel was 3.7 cases per 100 000 population[60] and was similar to the recent report in the US.[61] However, the incidence in the Jerusalem cohort was 3-fold higher (11 per 100 000) than that in the national cohort, which was ascribed to the higher reporting accuracy. The actual incidence in Israel was believed to be closer to that of the Jerusalem cohort. The incidence of GAS infection in children aged ≤5 years in a Jerusalem cohort was higher than previously reported (19 per 100 000). In this cohort, large families and crowded living conditions facilitated the spread of streptococci. The annual incidence of streptococcal TSS in Israel was 0.25 per 100 000,[60] similar to that reported from Ontario, Canada (0.2 per 100 000),[50] and less than that reported from Atlanta, Georgia (0.71 per 100 000).[53] The incidence of streptococcal TSS was highest in adults aged >45 years (0.57 per 100 000), followed by children aged <5 years (0.36 per 100 000), and was lowest in persons aged 16–45 years (0.16 per 100 000).[60]

Children aged <10 years are less likely to develop streptococcal TSS and have a lower mortality rate than adults.[44,50,61] Studies that reported both pediatric and adult streptococcal TSS were few. In the series reviewed by Davies et al.,[44] only 4% of 51 children with invasive GAS infection had features of streptococcal TSS compared with 43% of 209 adults. The overall mortality rate of invasive and streptococcal TSS in these series was only 7.8% in the 51 children and 43% in the 209 adults. In Ontario, Canada, 5% of 73 invasive cases in children aged ≤14 years and 29% of 59 elderly persons aged ≥75 years developed streptococcal TSS. The mortality rate was also lower in children (8.3%) than in adults (29%).[50] A follow-up surveillance report by the Ontario Group A Streptococcal Study Group demonstrated that the annual incidence of invasive GAS disease in children was 1.9 per 100 000 population, and the rate of streptococcal TSS was 7%, resulting in an annual incidence of streptococcal TSS in children being 0.13 per 100 000 population, and a case-fatality rate of 56% (or 27.3% if limited only to cases fulfilling consensus criteria for streptococcal TSS).[56]

The overall mortality rate published in a pediatric series was 5–10% and 30–80% in adults.[72] In Atlanta, Georgia, no significant age-specific differences in incidence and mortality rate of streptococcal TSS were noted (12% for <10 years and 16% for >65 years, mortality rate 48% in total, for all age groups).[53] In Taiwan, a hospital-based study[59] reported an extremely high incidence of streptococcal TSS in children with GAS bacteremia, 50% (6/12) compared with 9.4% in 64 adults. The mortality rate in this report was 66.7% in both children and adults, very similar to the data reported by the follow-up surveillance report by the Ontario Group A Streptococcal Study Group.[56] From the above data, the incidence and mortality rate of streptococcal TSS varied according to the geographic location. More population-based studies are needed to explain this discrepancy.

Clusters of invasive GAS infection, including streptococcal TSS, in households, nursing homes, and hospitals have been described.[50,58,73-75] A family cluster of streptococcal TSS involving three children caused by a single clone documented further person-to-person transmission and risk in household contacts.[58] Results of population-based active surveillance suggest that the rate of secondary invasive group A β-hemolytic streptococci infection is approximately 2.9 cases per 1000 household contacts, almost 200 times the risk in the general population.[50,72] The risk of colonization in the household is associated with younger age and 4 or more hours of contact with an infected person per day, but the risk of disease is greatest in the elderly despite the low carriage rate.[50] Because of insufficient data, the use of chemoprophylaxis for household contacts of persons with invasive GAS infection remains inconclusive at present.[75] Physicians should base the decisions regarding chemoprophylaxis on their assessment of the risk associated with each individual case.

M types 1 and 3 were the most common strains isolated from cases of streptococcal TSS, but other types and some nontypable strains have also been isolated. M types 1 and 3 are also commonly isolated from asymptomatic carriers, and individuals with pharyngitis, and scarlet fever.[76] However, in different geographic areas, the M type strains may be different.[77] In the Israel cohort,[60] the microbiologic characteristics were the predominance of M3 type and the paucity of M1 type. Streptococcal pyrogenic exotoxins (SPEs) A, B, and C have been associated with severe invasive GAS infections and streptococcal TSS.[76] In Taiwan, SPEA was present in only 13% of streptococcal TSS-associated strains while SPEB was present in all the invasive isolates.[78]

Varicella is an important risk factor for invasive GAS infections in previously healthy children.[72] About 15% of children with invasive GAS disease had a history of varicella in the month prior to their illness, and this was usually associated with a soft-tissue infection. Varicella-associated cases occurred more in children aged <10 years. The attack rate for invasive GAS in children within 2 weeks after chickenpox was 5.2 per 100 000. Overall, chickenpox was associated with a 58-fold increased risk of acquiring invasive GAS[56] infection.

A relationship between the use of NSAIDs and the development of TSS caused by GAS and *S. aureus* has been reported.[58] NSAIDs can impair granulocyte function and enhance production of cytokines. NSAIDs may mask signs of disease progression by relieving pain, reducing swelling, and suppressing fever, thus contributing to a delay in diagnosis.[79] In a recent study from Yorkshire, UK, 92% of patients with streptococcal TSS had used NSAIDs. This further supported the association between NSAIDs and the development of TSS.[80]

3. Pathogenesis

TSS is thought to be a superantigen-mediated disease. Superantigens are a group of proteins that can activate the immune system by bypassing certain steps in the usual antigen-mediated immune response sequence (figure 1). Superantigens are not processed within the antigen-presenting cell before being presented to T cells. Instead, they bind directly to molecules of the MHC class II, which requires recognition of only one element of the T-cell receptor (Vβ) to trigger a massive T-cell activation, 5–30% of the entire T-cell population, whereas, conventional antigens activate only about 0.01–0.1% of the T-cell population.[81] The net effect is a massive release of cytokines.

Superantigens have also evolved diverse mechanisms for binding to the MHC class II molecule.[83] Most bind exclusively at the β chain, some at the α chain, and some both. Most staphylococcal enterotoxins (SEs) bind HLA-DR preferentially, whereas many

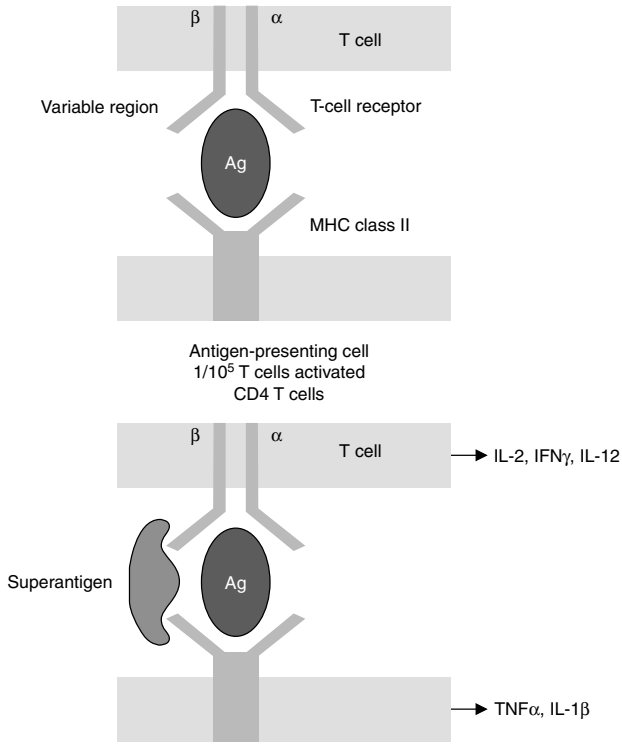

Fig. 1. Contrasting mechanisms of conventional antigen (Ag) [upper panel] and superantigen presentation (lower panel). Superantigen is not processed by antigen-presenting cell before being presented to T cells. **IFN**γ = interferon-γ; **IL** = interleukin; **TNF**α = tumor necrosis factor-α (reproduced from Llewelyn and Cohen,[82] with permission from Elsevier).

SPEs bind better to DQ. Differences between HLA-DR and DQ alleles might lead to differences between individuals in susceptibility to particular superantigens.[3,8] After binding to T-cell receptors and MHC class II molecules on antigen-presenting cells, superantigens trigger T-cell activation that results in the release of cytokines, including tumor necrosis factor-α (TNFα), interleukin (IL)-6, interferon-γ, and IL-2. Other results of T-cell activation are recruitment of further T and B cells to the site of infection and co-activation of the antigen-presenting cell, resulting in further release of mediators such as IL-1 and TNFα.[84,85] Massive cytokine release is believed to be responsible for the most severe features of TSS, such as fever, hypotension, tissue injury, and shock.[82,86]

Staphylococcal TSST-1 and SEs (A, B, C, D, E, and H) are the family of superantigens and are the major toxins associated with staphylococcal TSS.[87,88] TSST-1 is responsible for 75%, SEB for 23%, and SEC for about 2% of patients with TSS.[87,88] TSST-1 is found in >90% of menstrual TSS cases and about 50% of nonmenstrual TSS cases. Various SEs are found in the other 50% of nonmenstrual TSS.[89] The staphylococcal TSS often develops from a site of colonization rather than infection. The role of *S. aureus* in implicating TSS is well described:

- vaginal isolation rate of *S. aureus* in 98% of patients with menstrual TSS compared with 8–10% carriage rate in healthy control individuals;
- isolation of *S. aureus* from other sites in nonmenstrual TSS;
- recurs more frequently in the absence of antistaphylococcal antibodies.[90]

Factors in the vagina in the presence of hyperabsorbable tampons enhance the production of TSST-1 such as neutral pH, oxygen tension, carbon dioxide tension, and low magnesium levels.[91] Menstrual blood flow is associated with elevated protein, and the acidic vaginal environment reaches a pH of 7. The introduction of a tampon into the normally anerobic vaginal environment raised oxygen tension to atmospheric levels, and at the same time carbon dioxide levels recovered from low levels to high levels associated with blood flow.[92] All patients with menstrual TSS had undetectable antibodies against TSST-1 at the onset of disease. Nonmenstrual TSS can occur in association with primary *S. aureus* infection, including postsurgical, postpartum, or postabortion infection,[93] burns,[68] focal infections, such as pneumonia, or antecedent influenza infection.[16]

SPEs (A, B, C, F [mitogenic factor], G, H, and J and streptococcal superantigen), the family of superantigens, are the major toxins associated with streptococcal TSS.[94-96] Some other virulence factors such as peptidoglycan, lipoteichoic acid, and killed streptococci are capable of inducing mononuclear cells to produce TNFα, *in vitro*.[95,96] The portals of entry for GAS infection include the vagina, pharynx, mucosa, and skin, accounting for 50% of cases, and frequently at sites of minimal or inapparent local trauma. The portal of entry is unknown in 50% of invasive disease.[94,95] Streptococcal pharyngitis rarely develops into streptococcal TSS but has been reported.[95] Infections with viruses such as varicella and influenza[93,94] provided portals in some patients. Adherence of the streptococci to the pharyngeal wall and then colonization are related to surface structures such as lipoteichoic acid and fibronectin-binding proteins. The M protein protects the streptococci from phagocytosis.[94,95]

As group A streptococcus invades the blood, M protein is shed from its surface and forms a complex with fibrinogen. A recent study shows that the M protein-fibrinogen complexes bind to integrins on the surface of polymorphonuclear leukocytes, activating these cells to adhere to endothelium, and resulting damage to the underlying endothelium leads to a clinical feature characteristic of the streptococcal TSS.[97] Herwald et al.[98] also blocked the pathologic effects of M protein by injecting a peptide that prevents fibrinogen from interacting with integrin on polymorphonuclear leukocytes.

4. Host Immunity

The host-pathogen interaction, the virulence factors, and the absence or presence of immunity determines the epidemiology, clinical syndrome, and outcome. The absence of antibodies to the superantigens appears to be a major risk factor for the development of both staphylococcal and streptococcal TSS and explains partly why not all patients exposed to virulent strains develop TSS.

The prevalence of antibodies against TSST-1 is >90% in adults but lower in the pediatric population.[69] In one study, the prevalence of antibodies to TSST-1 was 47% at age 1 year, 58% at age 5 years, and 70% by age 10 years.[99] In a burns unit in the UK, only 50% of the children aged <4 years had antibodies to TSST-1 on admission, which reflected the low prevalence of antibodies in children.[67,68] Transplacentally-acquired antibodies were evident in 90% of infants.[99] Mucosal colonization with TSST-1 producing *S. aureus* strains may result in antibody formation since 90% of adults have antibodies to TSST-1 without having TSS. An inability to generate anti-TSST-1 antibodies after an episode of staphylococcal TSS predisposes patients to recurrent episodes and may be due to the ability of TSST-1 to suppress immunoglobulin-secreting cells[86] through two possible mechanisms. First, superantigen activation of CD4+ T cells results in T helper-1 cytokine release (IL-2, IFN-γ, and TNFβ), with minimal T helper-2 response. Since T helper-2 subsets produce cytokines such as IL-4 and IL-5 that support B-cell proliferation and differentiation, lack of a T helper-2 response may inhibit production of neutralizing antibodies and inhibit extracellular bacterial clearance. Second, TSST-1 can induce T cell-dependent B-cell apoptosis, but only when exposed to high levels of toxin. This may explain why the infection did not resolve in some patients, and why in some patients TSS is recurrent.[86]

The association between the lack of antibodies to SPEs in healthy individuals and the development of invasive streptococcal disease has been established.[100] The presence of antibodies to SPEs has been shown to decrease the risk of severe infection. Antibodies to the M protein confer protection against invasive infection by enhancing phagocytosis.[94,95] Low levels of protective anti-M1 and anti-superantigen neutralizing antibodies in plasma may contribute to host susceptibility to invasive streptococcal infection but do not modulate disease outcome. The absence of a high rate of invasive infection due to the presence of significant herd immunity against the virulence factors responsible for streptococcal TSS (figure 2). This partly explains why epidemics have not occurred and how GAS infection can cause different clinical manifestations.[95] In addition, researchers have discovered that a person's MHC class II haplotype affects the regulation of cytokine release in response to superantigen, which can affect the outcome

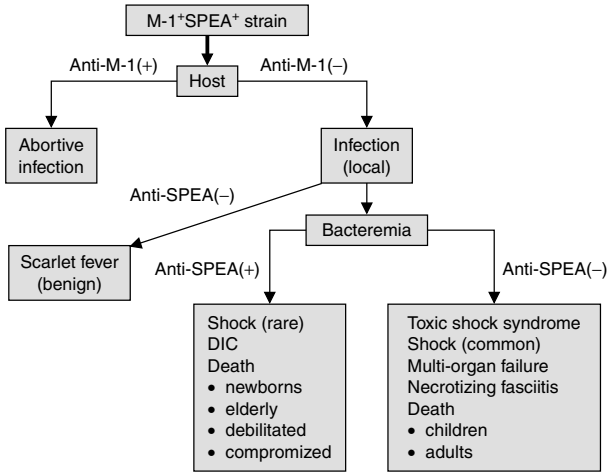

Fig. 2. Pathogenesis of scarlet fever, bacteremia, and toxic shock syndrome. **Anti-M-1(+)** = the presence of antibody to M protein type 1; **Anti-M-1(–)** = the absence of antibody to M protein type 1; **Anti-SPEA(+)** = antibody to SPEA; **Anti-SPEA(–)** = no antibody to SPEA; **DIC** = disseminated intravascular coagulation; **M-1+SPEA+** = a group A streptococci strain that contains M protein type 1 and SPEA; **SPEA** = streptococcal pyrogenic exotoxin A.

of invasive GAS infection.[101] Patients with a DRB1*1501/DQB1*0602 haplotype seem to have an attenuated inflammatory cytokine response to the GAS superantigen and thus have protection against the development of severe systemic disease. Host factors have to be involved in the manifestations of GAS infection.[101]

5. Clinical Features

Both TSSs caused by *S. aureus* or *S. pyogenes* are characterized by an acute illness with fever, rapid-onset hypotension, rapidly accelerated renal failure, and multisystem organ involvement. Clinical case definitions are presented in tables III and IV. Staphylococcal TSS differs from streptococcal TSS in a number of aspects.[71,102] Table V summarizes the differences. The presence of profuse watery diarrhea, vomiting, generalized erythroderma, conjunctival injection, and severe myalgias are more frequent in staphylococcal TSS. Local or deep-seated soft tissue infections, such as cellulitis, abscess, myositis, or necrotizing fasciitis, are associated with increasing pain and commonly occur with streptococcal TSS. The presence of a foreign body at the site of infection is common in staphylococcal TSS. Both can occur without an identifiable focus of infection, or with any form of invasive infections such as pneumonia, osteomyelitis, pyogenic arthritis, or endocarditis. Recurrent episodes of TSS occur in both menstrual and nonmenstrual forms of staphylococcal TSS but not in streptococcal TSS. TSS can be confused with meningococcemia, Rocky Mountain spotted fever, septic shock, Kawasaki disease, ehrlichiosis, scarlet fever, measles, and systemic lupus erythematosus.[102]

5.1 Staphylococcal TSS

The onset of illness is abrupt, with fever, chills, malaise, headache, myalgias, muscle tenderness, vomiting, diarrhea, and dizziness or syncope. Diffuse erythroderma develops within 24–48 hours. Confusion, somnolence, irritability, and agitation may also occur. Muscle tenderness, conjunctival hyperemia or hemorrhages, and beefy red edematous mucous membranes have also been noted.[71] Desquamation of skin occurs in 7–14 days. In menstrual TSS, edema and erythema of the inner thigh and perineum with a normal uterine and adnexal examination may be noted. In nonmenstrual TSS, another focus of infection may be present. Laboratory abnormalities include an increase in immature neutrophils, thrombocytopenia, and anemia. Disseminated intravascular coagulation may be present. Elevated blood urea nitrogen and creatinine, abnormal liver function tests, hypocalcemia, hypoproteinemia, and elevated creatine phosphokinase may be present, which will return to normal within 7–10 days of disease onset.[71] Blood cultures are positive in <5% of patients. Cultures from the sites of infection are usually positive and should be obtained.[102]

In patients with nonmenstrual TSS, there was a higher rate of previous antibiotic treatment and hospital exposure, predisposing to colonization with toxigenic strains of *S. aureus*.[104] In addition, patients with nonmenstrual TSS may have a delayed onset of symptoms, more frequent CNS manifestations, less frequent myalgia and arthralgia, and a higher degree of anemia.[104]

The surgical wound responsible for postoperative TSS typically has no signs of inflammation, because the production of TNFα by macrophages inhibits neutrophil mobilization.[71] In postoperative cases, the organism usually originates from the patient's own colonization disrupted by surgery or trauma. The incubation period for postoperative TSS is 2–4 days but can be as short as 12 hours.[71]

Recurrent menstrual TSS has been well described, and has been found to occur in as many as one-third of patients who have TSS. Persistent colonization with a toxin-producing strain of *S. aureus* and the persistent absence of neutralizing antibodies contributes to the development of recurrent TSS. This occurs among patients who fail to develop a humoral immune response to the staphylococcal toxin. Patients can be identified by means of antibody testing, and recurrences can be reduced by abstaining from tampon use and by treatment with an anti-staphylococcal antibiotic.[71,104,105] However, recurrence of nonmenstrual TSS is rare but several cases have been reported.[71,104,105]

Table III. Staphyloccocal toxic shock syndrome: clinical case definition[103]

Fever: temperature ≥38.9°C (102.0°F)
Rash: diffuse macular erythroderma
Desquamation: 1–2 weeks after onset, particularly palms and soles
Hypotension: systolic blood pressure ≤90mm Hg for adults; lower than fifth percentile for age in children aged <16y; orthostatic drop in diastolic blood pressure of ≥15mm Hg from lying to sitting; orthostatic syncope or orthostatic dizziness
Multisystem involvement (three or more of the following):
gastrointestinal: vomiting or diarrhea at onset of illness
muscular: severe myalgia or creatinine phosphokinase level greater than twice the upper limit of normal
mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
renal: serum urea nitrogen or serum creatinine level greater than twice the upper limit of normal or urinary sediment with ≥5 white blood cells per high-power field in the absence of a urinary tract infection
hepatic: total bilirubin, AST, or ALT level greater than twice the upper limit of normal
hematologic: platelet count $<100 \times 10^9$/L ($<100 \times 10^3/\mu L$)
CNS: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent
Negative results on the following tests, if obtained:
blood, throat, or cerebrospinal fluid cultures; blood culture may be positive for *Staphlyococcus aureus*
serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles
Case classification:
probable: a case with five of the six aforementioned clinical findings
confirmed: a case with all six of the clinical findings, including desquamation. If the patient dies before desquamation could have occurred, the other five criteria constitute a definitive case

5.2 Streptococcal TSS

Persons of all ages can be affected, and most children do not have any predisposing underlying disease. Pain is the most suggestive symptom of streptococcal TSS and is abrupt in onset and severe, with preceding tenderness. Flu-like symptoms characterized as fever, chills, myalgia, nausea, vomiting, and diarrhea are present in 20% of patients. Fever is the most common early sign. Confusion, combativeness, or coma are manifest in some patients. Eighty percent of adults have a localized soft tissue infection that may progress to necrotizing fasciitis or myositis and require surgical debridement, fasciotomy, or amputation.[95] Laboratory data may reveal organ dysfunction and usually hepatic or renal impairment. Hypoalbuminemia, hypocalcemia, elevated creatinine kin-

Table IV. Streptoccocal toxic shock syndrome: clinical case definition[3]

1. Isolation of group A β-hemolytic streptococci
(a) from a normally sterile site (e.g. blood, cerebrospinal fluid, peritoneal fluid, tissue biopsy specimen)
(b) from a nonsterile site (e.g. throat, sputum, vagina)
2. Clinical signs of severity
(a) hypotension: systolic blood pressure <90mm Hg in adults or lower than the fifth percentile for age in children
And
(b) two or more of the following signs:
renal impairment: creatinine level >177 μmol/L (≥2 mg/dL) for adults or two times or more the upper limit of normal for age
coagulopathy: platelet count $<100 \times 10^9$/L ($\leq 100 \times 10^3/\mu L$) or disseminated intravascular coagulation
hepatic involvement: ALT, AST, or total bilirubin levels two times or more the upper limit of normal for age
adult respiratory distress syndrome
a generalized erythematous macular rash that may desquamate
soft tissue necrosis, including necrotizing fasciitis or myositis, or gangrene
An illness fulfilling critera 1(a), 2(a), and 2(b) can be defined as a definite case. An illness fulfilling criteria 1(b), 2(a), and 2(b) can be defined as a probable case if no other cause for the illness is identified

Table V. Features of staphylococcal toxic shock syndrome (TSS) and streptococcal TSS in children[82,93]

Characteristics	Staphylococcal TSS	Streptococcal TSS
Superantigen toxins	TSST-1 (menstrual TSS), SEs A, B, C1-3, D, E (nonmenstrual TSS), SEG-1 (Kawasaki disease)	SPEs A, G, H, J, SSA, MF, SMEZ
Predisposing factors	Tampons, burns, wounds	Varicella, NSAID, wounds
Associated sites of infection	Superficial, such as impetigo, burns, diaper rash, genital tract, surgical-site infection	Deep, such as site of blunt trauma, necrotizing fasciitis, myositis, septic joint, surgical site infection
Soft tissue infection	Rare	Common
Abrupt severe pain	Rare	Common
Rash	Very common	Less common
Vomiting, diarrhea	Very common	Less common
Elevated creatinine kinase	Rare	Common in fasciitis/myonecrosis
Bacteremia	<5%	60%
Desquamation	7–14 days	Less common
Mortality	3–5%	5–10%

MF = mitogenic factor; **SEs** = staphylococcal enterotoxins; **SMEZ** = streptococcal mitogenic exotoxin 2; **SPEs** = streptococcal pyrogenic exotoxins; **SSA** = streptococcal superantigen; **TSST-1** = TSS toxin-1.

ase, and increased immature neutrophils are present. Blood cultures are positive in 60% of cases.[95] Cultures from sites of infection are usually positive and remain so for days even after appropriate antibiotics.[102]

Children aged <10 years with invasive streptococcal disease are more likely to present with bacteremia without focus, osteomyelitis, or a CNS infection and are less likely to present with necrotizing fasciitis or endocarditis/pericarditis.[61] Cellulitis and upper respiratory infection are also common syndromes. In contrast with adults, necrotizing fasciitis occurs in only 4% of children.[56]

The initial clinical presentation of patients with streptococcal TSS is often nonspecific and many patients have been treated as outpatients on one or more occasions before admission.[72] Physicians should have a high index of suspicion for this syndrome especially in persons at increased risk, such as children with varicella or a chronic underlying illness. Clues suggesting streptococcal TSS may include the absence of respiratory signs or a contact history, more localized or severe pain rather than generalized myalgia, and the presence of a skin lesion or history of blunt trauma at the site of pain.[72]

6. Management

Management of a child with TSS includes hemodynamic stabilization and specific antimicrobial therapy to eradicate the bacteria. Immediate and aggressive management of hypovolemic shock caused by capillary leakage, vasodilatation, and fluid loss is the most important aspect of treatment in children. Fluid resuscitation with large volumes of crystalloid solutions (such as isotonic sodium chloride, lactate Ringer) or colloidal solutions is important and is the mainstay of treatment. Patients frequently require multiple boluses of fluid because of severe volume depletion and ongoing capillary leakage. Inotropic agents such as dobutamine, dopamine, and norepinephrine may be needed if fluid resuscitation alone is insufficient to ensure adequate perfusion of vital organs. Appropriate management of associated problems such as renal failure and adult respiratory distress syndrome is also critical.

Initial parenteral antibiotic coverage for both GAS and *S. aureus* infection should be instituted promptly because of the similarity to the clinical appearances of streptococcal and staphylococcal TSS.[102]

6.1 Antibiotic Therapy for Staphylococcal TSS

In addition to hemodynamic stabilization, a thorough search for possible sites of staphylococcal infections is mandatory to eliminate any preformed toxin and to prevent synthesis of new toxins. Vaginal examination and removal of a tampon or other foreign body are mandatory. Surgical wounds should be considered as possible reservoirs of infection, even if no superficial signs of local infection or purulent discharge are present. Infected wounds should be opened and debrided, and any packing should be removed. Abscesses need to be drained and irrigated. Culture specimens from all possible sites should be obtained. High-dose β-lactamase-resistant anti-staphylococcal antibiotics are indicated to eradicate the organism and prevent recurrences.[71,104] Nafcillin, oxacillin, and first-generation cefalosporins (cephalosporins) are the first-line agents for *S. aureus*. Vancomycin should not be used routinely as initial empiric therapy because methicillin (meticillin)-resistant *S. aureus* causes <1% of cases of staphylococcal

TSS.[102] However, methicillin-resistant *S. aureus* recently emerged as a community pathogen and thus raised an important issue of initial empiric antibiotic therapy in these patients.

Clindamycin, erythromycin, rifampin (rifampicin), and fluoroquinolones have been shown to reduce TSST-1 by 90%, whereas β-lactamase inhibitors, including nafcillin and first-generation cefalosporins, increase TSST-1 in culture, probably by lysis or increased cell membrane permeability.[106] Thus, the use of clindamycin in combination with a β-lactamase-resistant antistaphylococcal agent results in a potentially beneficial effect by decreasing the synthesis of TSST-1.

Antimicrobial therapy should be continued for at least 10–14 days to eradicate the organism and prevent recurrences.[105] Antibiotics do not shorten the duration of an acute illness but they can decrease the organism load and the rate of relapse.[71,105] The total duration should be based on the usual duration established for the underlying focus of infection.[102]

6.2 Antibiotic Therapy for Streptococcal TSS

In addition to hemodynamic stabilization, patients with suspected necrotizing fasciitis should have urgent surgical intervention for fasciotomy and debridement. Intravenous penicillin G (200 000–400 000 U/kg/day) in four to six divided doses is the drug of choice for GAS infection.

Despite the susceptibility of GAS to penicillin, the outcome among individuals who have streptococcal TSS remains poor. In a mouse model of streptococcal myositis, penicillin was ineffective when treatment was delayed; the clindamycin-treated group had significantly better survival rates even if treatment was delayed.[107] The failure of penicillin to eradicate the organisms may be due to the slow replication rate of the organisms when a large inoculum is present, or due to the inoculum effect. The large inocula may reach stationary growth phase rapidly and diminish the expression of penicillin-binding proteins, the target sites for penicillin activity. Clindamycin is more effective because:

- the antimicrobial activity is not affected by the inoculum size;
- it acts by inhibiting protein synthesis, is not dependent on penicillin-binding proteins, and thus also inhibits the synthesis of antiphagocytic M protein and bacterial toxins (SPEs), subsequently reducing the superantigenicity of SPEs;
- it has a longer postantibiotic effect than β-lactams such as penicillin.[102,107,108]

Thus, clindamycin (25–40 mg/kg/day in three or four divided doses) administered intravenously is recommended in addition to penicillin as therapy for severe, invasive GAS infections. Clindamycin should not be used alone as initial empiric therapy because 1–2% of *S. pyogenes* are resistant to clindamycin.[102]

6.3 Adjunctive Therapy

Intravenous immunoglobulin (IVIG) [1–2 g/kg given once] may be beneficial when given in addition to appropriate antimicrobial therapy. *In vitro*, IVIG can inhibit T-cell activation by blocking or inactivating staphylococcal and streptococcal superantigens, resulting in a decrease in the production of inflammatory cytokines.[109] *In vivo*, several case reports have been published in which IVIG administration in TSS correlated with clinical improvement.[110] The Ontario Group A Streptococcal Study Group conducted a comparative observational study of the effect of IVIG on 30-day survival in 21 patients with streptococcal TSS. IVIG-treated patients were more likely than control individuals who received only antimicrobials to survive for both 7 days (90% vs 50%) and 30 days (67% vs 34%). This observational study posed some difficulties in the interpretation of results, as to the comparability of the treatment and the control group. Multivariate analysis revealed that IVIG administration and a lower Acute Physiology and Chronic Health Evaluation II score were associated with survival; the odds ratio for survival associated with IVIG therapy was 8.1 (95% CI 1.6, 45). IVIG therapy enhanced the ability of patient plasma to neutralize bacterial mitogenicity and reduced T-cell production of IL-6 and TNFα. These findings supported the theory that IVIG could effectively neutralize bacterial toxins *in vivo* and nonspecifically inhibit cytokine synthesis and immune activation.[111]

Thus, as IVIG may be an effective adjunctive therapy for diseases associated with superantigens, the neutralizing activity against purified superantigens was studied for five IVIG preparations. It is of interest that there was great variation in the neutralizing activity of different brands and batches of immunoglobulin preparation. Neutralization of SPEA activity was significantly lower than that of other streptococcal superantigens for all brands tested.[112] Despite this, complete neutralizing activity may be achieved by optimizing the type and dose of IVIG used.

Darenberg et al.[113] further demonstrated that staphylococcal superantigens are not inhibited as efficiently as streptococcal superantigens by IVIG, and hence, a higher dose of IVIG may be required for therapy of staphylococcal TSS in order to achieve protective titers and clinical efficacy.

Several therapy regimens aimed at modifying the host's responses to sepsis have met with limited success. Activated protein C has direct anti-inflammatory properties, including blocking the production of cytokines by monocytes and blocking cell adhesion. The use of recombinant activated protein C in the treatment of sepsis has been studied in adult patients and is currently being studied in pediatric patients.[114] The use of high-dose corticosteroids in adult patients with sepsis does not improve survival and

may worsen outcome by increasing the frequency of secondary infections. Low-dose hydrocortisone was effective in one study in adult patients with septic shock but this was not confirmed by other studies.[115]

7. Recent Developments

Recent studies have undertaken the development of toxoid vaccines that may protect against the immunobiologic effects of pyrogenic toxin superantigens, through antibody neutralization.[116,117] These toxoids are not biologically toxic in standard animal models of streptococcal TSS, and they are not superantigenic when tested against human mononuclear cells. The toxoids are highly effective in inducing toxin-specific neutralizing antibodies, capable of neutralizing superantigenicity and protecting animals from streptococcal TSS.[116,117]

Two regions of marked sequence homology in the tertiary structure of superantigens have been identified in the SEs/SPEs.[118] Research with peptides constructed to mimic these regions showed that both peptides, and antibodies produced against the peptides, had blocking activity against a range of bacterial superantigens.[119] The mechanism of action is probably by blocking the superantigen MHC class II binding interaction.[118] This approach has encouraging results in animal models of TSS, but needs further clinical trials.

Researchers have also produced a murine monoclonal antibody against TSST-1.[120] In animal models, this monoclonal antibody neutralized various superantigen activities induced by TSST-1 and SEs (SEA and SEB) in human peripheral blood mononuclear cells and protected against TSST-1- and SE-induced lethality.[120-122] Further studies should be conducted to elucidate the mechanisms as well as the application to clinical cases.

8. Conclusion

TSS is the best example of superantigen-mediated disease. Superantigens have also been implicated in the etiology of clinical syndromes, such as Kawasaki disease, atopic dermatitis, autoimmune diseases, and some skin diseases. We have yet to understand how new superantigens generated by toxins from staphylococci and streptococci arise. The spectrum of disease results from differences in the immune response of the host. Therapeutic strategies should include agents that can inhibit these superantigens.

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