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The Clinical Spectrum of Toxic Shock Syndrome

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Toxic shock syndrome (TSS) is a recently recognized acute multisystem illness that may recur. Epidemiologic links with menstruation and use of tampons have been identified. We report the cases of seven patients (six women and one man), 12 to 31 years old, seen over nine months, who met the criteria for TSS. Four were menstruating at onset. All had hypotension, fever, erythematous rash and distal desquamation. A prodrome of myalgias and diarrhea occurred in all patients. Clinical features of the acute illness included pharyngitis, conjunctivitis, leukocytosis and renal dysfunction (7), hepatobiliary abnormalities (6), mental confusion (6) and coagulopathy (4). In three patients, examination of cerebrospinal fluid showed abnormalities. The illness progressed in three patients to adult respiratory distress syndrome and significant cardiac dysfunction. Staphylococcus aureus *was isolated from mucosal sites in six. The disease recurred in two. There were no deaths. Possible transmissibility was illustrated by two patients, a married couple, with simultaneous illnesses. Pathophysiologic features of TSS suggest a toxicogenic cause. Management consists of early recognition, vigorous fluid resuscitation, inotropic support as needed, discontinuation of tampon use and treatment with antistaphylococcal antimicrobic drugs.*

TOXIC SHOCK SYNDROME (TSS) is an acute febrile illness involving multiple organ systems and associated with hypotension and rash. Since this entity was first described in 1978,[1] a striking increase in reported frequency has occurred.[2-7] Epidemiologic data indicate an association with menstruation and, in particular, the use of tampons.[3,4] *Staphylococcus aureus* has been isolated from mucous membranes of affected patients, but the cause of TSS remains unclear. However, the clinical features of the syndrome suggest a toxicogenic cause.

Between December 1979 and August 1980 we saw seven patients, admitted to the University of California, Davis (UCD), Medical Center in Sacramento, whose illnesses were consistent with a diagnosis of TSS. The diagnoses were made in conformity to a definition of the syndrome recently proposed by the Surgeon General of the United

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ABBREVIATIONS USED IN TEXT

ARDS = adult respiratory distress syndrome
BUN = blood urea nitrogen
CPK = creatine phosphokinase
CSF = cerebrospinal fluid
DIC = disseminated intravascular coagulation
GGT = gamma glutamyl transferase
LDH = lactate dehydrogenase
MLNS = mucocutaneous lymph node syndrome
PCWP = pulmonary capillary wedge pressure
PEEP = positive end-expiratory pressure
PT = prothrombin time
PTT = partial thromboplastin time
SEB = staphylococcal enterotoxin B
TSS = toxic shock syndrome
UCD = University of California, Davis

States. The criterial which must be fulfilled to meet this definition are outlined in Table 1.

Our experience with these seven patients illustrates not only the potential seriousness of the illness but also the wide clinical spectrum of the syndrome. Several patients with acute, life-threatening diseases are included in this series. Recurrent disease with variably severe symptoms occurred in two of the patients. Finally, two patients, one of whom was male, show a potential for either transmissibility or common-source acquisition of the syndrome that, to our knowledge, has not previously been reported.

The following selected cases are representative of the broad range of clinical involvement seen in TSS.

Reports of Cases

CASE 1. A 19-year-old woman, previously in good health, was admitted to the UCD Medical Center in shock. Six days earlier, she had sustained second degree facial burns, which had been treated topically with silver sulfadiazine. Three days before admission, nausea, vomiting and watery diarrhea developed. On the morning of admission, she woke with painful, cold extremities and profound weakness. There was no history of fever, chills, exposure to infectious diseases, travel or intravenous use of drugs. Menses had been regular, with the last period 20 days previously.

On admission, she appeared acutely ill, with a pulse of 140 beats per minute, no palpable blood pressure, respiratory rate of 40 per minute and a temperature of 39.1°C (102.4°F). She was confused and complained of severe myalgias in her back and legs. Second degree burns without exudate were present on the face, and an evanescent erythematous macular rash was seen on the trunk and thighs. There was bilateral purulent conjunctivitis. The nose, mouth and throat were dry and the tongue was coated and pink. The neck was supple. There was no lymphadenopathy. Both lung fields were clear. The heart sounds were normal without murmurs or extra sounds. Initial examination of the abdomen disclosed diffuse tenderness with normal bowel sounds; however, two hours later, bowel sounds were absent. Pelvic examination showed no abnormalities except for a thin white vaginal discharge. The extremities were cold with poor capillary filling.

Initial laboratory values were as follows: leukocyte count 20,900 per cu mm (50 percent segmented neutrophils, 43 percent band neutrophils, 2 percent lymphocytes, 4 percent metamyelocytes and 1 percent myelocytes); blood urea nitrogen (BUN) 37 and creatinine 2.4 mg per dl; sodium 134, potassium 4.2, chloride 94 and carbon dioxide 14 mEq per liter; serum aspartate aminotransferase 140 IU per liter; bilirubin 1.8 mg per dl; serum amylase 148, lactate dehydrogenase (LDH) 425, gamma glutamyl transferase (GGT) 60 and creatine phosphokinase (CPK) 4,180 IU per liter (MB fraction less than 1.5 percent); lactate 1.2 mEq per liter; prothrombin time (PT) 13.7 sec (control 11.5); partial thromboplastin time (PTT) 51.4 sec (control 35 to 40) and fibrinogen 380 ± 25 mg per dl. Fibrin monomers and fibrin split products were not detected. Analysis of urine showed 1+ proteinuria; 25 to 50 erythrocytes and 12 to 25 leukocytes per high-power field, and 2+ bacteriuria. The cerebrospinal fluid (CSF) contained 10 leukocytes per cu mm (8 polymorphonuclear neutrophils and 2 mononuclear cells), glucose 59 mg per dl and protein 19 mg per dl. No organisms were seen on Gram stain. An electrocardiogram showed sinus tachycardia. An x-ray study of the chest showed no abnormalities.

Treatment was initiated with intravenously

TABLE 1.—*Criteria for the Diagnosis of Toxic Shock Syndrome**

- Fever (temperature ≥38.9°C [102°F])
- Erythematous macular rash
- Desquamation during recovery phase
- Systolic blood pressure of 90 mm of mercury or lower for an adult
- Involvement of at least four organ systems
- Reasonable evidence for the absence of meningococcal infection, Rocky Mountain spotted fever, bacteremia or other known diagnostic possibility

*Adapted from Update on Toxic-Shock Syndrome. FDA Drug Bulletin 10:3 Nov 1980.

given normal saline and methylprednisolone 30 mg per kg of body weight, followed by three doses (15 mg per kg of body weight) at six-hour intervals; nafcillin 150 mg per kg of body weight, gentamicin 5 mg per kg of body weight and chloramphenicol 65 mg per kg of body weight were given per day. Initial hemodynamic measurements after insertion of a Swan-Ganz catheter included the following: central venous pressure 9 and pulmonary capillary wedge pressure (PCWP) 12 mm of mercury; cardiac output 8.7 liters per minute; systemic vascular resistance 388 and pulmonary vascular resistance 46 dyne•sec•cm^{-5}, and mixed venous oxygen tension 45 mm of mercury. Heart rate was 120 per minute and blood pressure 68/40 mm of mercury following administration of 11 liters of fluid during the first three hours. Dobutamine and large volumes of crystalloid were required to maintain the systolic blood pressure at 85 mm of mercury during the first 36 hours.

Hypoxic respiratory failure occurred on the second hospital day, requiring intubation and mechanical ventilation with positive end-expiratory pressure (PEEP). Additionally, the cardiac output fell to 3.6 liters per minute and remained low until day 4. Tests for disseminated intravascular coagulation (DIC) remained abnormal for seven days. The feces became guaiac-positive and the hematocrit fell to 15.8 percent, necessitating blood transfusion. Jaundice was noted on day 4. A gall bladder scan showed normal biliary function.

Initial blood, urine and CSF cultures yielded no growth. Cultures of the feces grew 3+ coliforms. *Staphylococcus aureus* in pure culture was isolated from swabs of the facial burn and the conjunctival exudate. Cultures of cervix and vaginal discharge were negative for *S aureus* and *Neisseria gonorrhoeae,* as were cultures of throat and rectal swabs.

She improved gradually during the second week and was extubated on day 13. After a convalescence complicated by pulmonary embolism she was discharged on day 26. Two weeks after discharge, desquamation of the palms and soles occurred, and an area of alopecia on the scalp was noted. There has been no recurrence of illness in eight months of follow-up, but progessive diffuse alopecia of the scalp persisted for six months.

CASE 2. A 30-year-old woman was admitted to hospital in shock. Two days earlier the sudden onset of watery diarrhea and vomiting had occurred. Abdominal pain, myalgias and arthralgias developed. On the day of admission, a rash appeared on the extremities. Treatment, consisting of fluid resuscitation and intravenous administration of penicillin and amikacin, was initiated after blood, urine and CSF specimens for culture had been obtained in another hospital, and the patient was transferred to the UCD Medical Center.

A physical examination on admission showed an acutely ill woman with a blood pressure of 70/50 mm of mercury, pulse 112 per minute and temperature 36.3°C (97.6°F). A macular petechial rash was present on the forearms and lower extremities. The neck was supple. The conjunctivae were injected, and the pharynx was dry and injected without exudate. No lymph nodes were palpable. Both lung fields were clear. Findings of a cardiovascular examination were within normal limits except for hypotension, tachycardia and somewhat diminished pulses in the cool, moderately cyanotic extremities. The abdomen was diffusely tender with decreased bowel sounds; no masses or enlarged organs were palpated. Pelvic examination was normal except for thick vaginal discharge containing a small amount of blood. A neurologic examination showed no abnormalities.

Laboratory data were as follows: leukocyte count 14,600 per cu mm (31 percent segmented neutrophils, 48 percent band neutrophils, 5 percent lymphocytes and 1 percent metamyelocytes); serum creatinine 3.9 and BUN 58 mg per dl; serum asparate aminotransferase 120, LHD 364 and GGT 584 IU per liter, and albumin 2.3 grams per dl. The PT was 13.3 sec (control 11.0 sec), PTT 57.4 sec (control 35 sec), fibrinogen 220 mg per dl and fibrin split products positive in a titer of 1:40. The platelet count was 48,000 per cu mm. Analysis of urine showed blood and albumin, with 6 to 12 leukocytes per high-power field seen in the sediment. A study of CSF showed no abnormalities.

A Swan-Ganz catheter was inserted, and the PCWP was 12 mm of mercury following volume resuscitation. Cardiac output by thermodilution was 7.5 liters per minute.

Penicillin, tobramycin and chloramphenicol, as well as methylprednisolone, were given. Vigorous intravenous fluid therapy and inotropic agents were required during the first 48 hours. Fever developed (temperature to 39.3°C [102.7°F]) on day 2 and persisted for ten days. Pulmonary infiltrates, hypoxemia and progressive decrease in lung compliance appeared on day 3, requiring intubation and institution of mechanical ventilation

with PEEP. On day 4, the platelet count fell to 12,000 per cu mm, and platelets were transfused. Bilateral pleural effusions containing 25,200 erythrocytes and 1,400 leukocytes per cu mm (2 percent polymorphonuclear neutrophils) and having the biochemical characteristics of a transudate developed.

Cultures of blood, CSF, urine, pleural fluid, feces, skin lesions and vaginal secretions were negative. In addition, the CSF was negative for serological evidence of pneumococcal, meningococcal or *Hemophilus influenzae* antigen by counterimmunoelectrophoresis. *S aureus* was isolated from nasopharyngeal cultures. Bone marrow, examined at the nadir of thrombocytopenia was hypercellular, with granulocytic hyperplasia and normal megakaryocyte content. Titers of antibody to *Herpes simplex* virus, type 1 (HSV-1) showed a fourfold increase, but other viral titers were negative.

The patient's hospital course in the second week of illness was one of gradual improvement. Antimicrobic drugs were discontinued on days 5 (chloramphenicol) and 14 (penicillin and tobramycin). Skin lesions cleared without scarring. She was discharged on day 19 and when seen a month later reported patchy alopecia, desquamation of the palms, soles, face and neck, amenorrhea and easy fatigability.

CASE 3. A 31-year-old man was the husband of the patient described in case 2. An identical illness developed the same day as his wife's, though diarrhea was more severe in his case.

Initially, the clinical features were similar to those of his wife, with pronounced hypotension, tachycardia and diffuse muscle tenderness. Several purpuric lesions were noted over his patellae and the dorsa of the feet, but, in general, he did not have the striking petechial rash that developed in his wife. A mucopurulent conjunctivitis was present. On day 2, a brightly erythematous and diffuse macular rash appeared on his trunk.

Laboratory findings in this patient were similar to those seen in case 2, except that pronounced thrombocytopenia did not develop. Results of CSF examination were slightly abnormal, with 5 leukocytes per cu mm (3 polymorphonuclear neutrophils and 2 mononuclear cells) but normal protein and glucose values. On day 2, there were 22 leukocytes per cu mm (19 mononuclear cells) noted, with other CSF values normal. Cultures of blood, CSF, urine and feces were negative. Conjunctival cultures were positive for *Staphylococcus epidermidis*. Viral titers showed a fourfold rise against HSV-1.

The clinical course of the disease in this patient was otherwise similar to that described in case 2; mental confusion developed and cleared after a week, and respiratory complications were less severe. Treatment was the same in both cases.

Discussion

The clinical diagnosis of TSS is based on the criteria listed in Table 1. The cases of our seven patients (six women and one man, aged 12 to 31 years) met these criteria and demonstrate the clinical spectrum of this syndrome. A prodrome of malaise, myalgias and watery diarrhea progressed to an acute systemic illness with fever, hypotension, pharyngitis, conjunctivitis, leukocytosis and rash with subsequent desquamation in all patients. Four of the seven were menstruating at the time of admission to the hospital.

Three patients were moribund when admitted to our hospital and required massive crystalloid infusions to achieve and maintain blood pressures of 80 to 85 mm of mercury systolic. Further, in these three, adult respiratory distress syndrome (ARDS) developed, which required intubation, mechanical ventilation with high fraction of inspired oxygen (FIO_2) and PEEP. In contrast, the other four patients were acutely ill but responded very well to less invasive supportive measures. Two of them (patients 4 and 6) clearly had manifestations of the disease a month before admission and had been managed adequately as outpatients. There were no deaths or significant sequelae in our series.

The range of systemic involvement in this multisystem illness is broad (see Table 2). All patients had cardiovascular collapse at the time of admission. Four responded to mild fluid resuscitation while two had evidence of profound myocardial dysfunction and three required inotropic support with dobutamine. Swan-Ganz catherization in three patients showed low to normal PCWP and, initially, high cardiac outputs that quickly fell in two of these three. The CPK was elevated in four patients; however, when the myocardial fraction was assayed in patient 1, it was consistently below 1.5 percent of the total CPK.

Renal dysfunction was present in all patients. Sterile pyuria, hematuria and azotemia were seen in six patients and proteinuria in four. All renal abnormalities resolved after fluid resuscitation, suggesting that prerenal factors may have been

predominant in the pathogenesis of these findings. No urinary infection was found.

Hepatobiliary abnormalities occurred in six patients, characterized by elevated levels of transaminases, GGT and alkaline phosphatase. Hyperbilirubinemia occurred in five patients. A radionuclide gall bladder scan in patient 1 demonstrated a functioning biliary tract and a follow-up chole-

TABLE 2.—*Clinical and Laboratory Manifestations of Toxic Shock Syndrome in Seven Patients*

	Patients						
Prodrome	1	2	3	4	5	6	7
Gastrointestinal							
Nausea and vomiting	+	+	+	+	+	+	+
Diarrhea	+	+	+	+	+	+	+
Mucosal							
Conjunctivitis	+	+	+	+	+	+	+
Pharyngitis	+	+	+	+	+	+	+
Glossitis	+	−	+	+	+	+	+
Vaginitis discharge	−	+	0	+*	+	+	+
Menstruating at onset	−	−	0	+	+	+	+
Fever (temperature ≥38.9°C [102°F])	+	+†	+	+	+	+	+
Cardiovascular							
Hypotension (BP <90 mm of mercury systolic)	+	+	+	+	+	+	+
Tachycardia (P>110 beats/min)	+	+	+	+	+	+	+
Peripheral cynanosis	+	+	+	−	+	−	−
Myocardial depression (CI <3.3 L/min/m²)	+	+	−	NA	NA	NA	NA
Respiratory							
Adult respiratory distress syndrome	+	+	+	−	−	−	−
Hypoxemia (Po_2 <50 Torr)	+	+	+	−	NA	NA	NA
Required mechanical ventilation	+	+	+	−	−	−	−
Renal							
Azotemia (creatinine 1.6 mg/dl)	+	+	+	+	+	−	−
Proteinuria	+	+	NA	+	−	+	−
Hematuria	+	+	NA	+	+	+	−
Pyuria	+	+	NA	+	+	+	+
Hepatobiliary							
Hepatomegaly	+	−	−	−	+	+	+
SGOT >2×normal	+	+	+	NA	+	+	+
Bilirubin >1.6 mg/dl	+	−	−	NA	+	+	+
Amylase >150 IU/liter	+	−	−	+	−	+	−
Hematologic							
Leukocytosis (leukocytes >14,000/cu mm)	+	+	+	+	+†	+	+
Thrombocytopenia (platelets <10^5/cu mm)	+	+	+	NA	−	−	−
PT and PTT >4 standard deviations above normal	+	+	+	NA	+	NA	−
Musculoskeletal							
Myalagias	+	+	+	+	+	+	+
Arthralgias	+	+	+	+	−	+	+
CPK >2×normal	+	−	+	NA	+	+	NA
Neurologic							
Delirium	+	+	+	+	+	−	+
Aseptic meningitis	+	−	+	−	+	NA	NA
Recovery phase							
Rash	+	+	+	+	+	+	+
Desquamation	+	+	+	+	+	+	+
Patchy alopecia	+	+	+	−	−	−	+
Recurrent attacks	−	−	−	+	−	+	−
Amenorrhea	+	+	0	−	NA	−	−
Staphylococcus aureus isolated							
Vagina	−	−	0	+	+	+	+
Other mucosal site	+‡	+§	−	−	−	−	−

BP = blood pressure; CI = cardiac index; CPK = creatine phosphokinase; NA = data not available; P = pulse; Po_2 = partial pressure of oxygen; PT = prothrombin time; PTT = partial thromboplastin time; SGOT = serum glutamic oxaloacetic transaminase (serum aspartate aminotransferase); + = positive findings; − = negative findings; 0 = not applicable.

*First episode only.
†Developed on second hospital day.
‡Conjunctiva, facial burns.
§Nasopharynx.

cystogram (after oral administration of contrast medium) in patient 6 showed a normal gall bladder. Clinical pancreatitis with hyperamylasemia developed in three patients. Diffuse abdominal tenderness was seen in six patients, although definite signs of peritonitis did not develop in any of them.

Disseminated intravascular coagulation with prolonged coagulation times and peripheral platelet consumption occurred in three patients, while a coagulopathy without platelet consumption was seen in a fourth. Gastrointestinal bleeding occurred in the three patients with DIC, requiring blood transfusion in patients 1 and 2. Additionally, patient 2 required platelet transfusions. A bone marrow aspirate done at the nadir of thrombocytopenia in patient 2 showed a hypercellular marrow with granulocytic hyperplasia but normal megakaryocytes. This suggests either relative suppression of megakaryocyte precursors, with or without peripheral platelet consumption, or failure of platelet release from the bone marrow.

Six patients displayed delirium or mental confusion, severe enough in two to necessitate the use of soft restraints for self-protection. Three patients with abnormal CSF also had clinical courses consistent with aseptic meningitis. Counterimmunoelectrophoresis of the CSF failed to detect antigens of *N meningiditis, S pneumoniae* or *H influenzae*. CSF cultures for bacteria and fungi were negative in all cases. All patients recovered without neurologic sequelae.

Diffuse and severe myalgias were a prominent complaint in six patients, with pronounced muscle tenderness persisting as long as seven to ten days a frequent finding. Although several of our patients also experienced intermittent arthralgias, none manifested inflammatory arthropathies.

In six of our patients, *S aureus* was isolated from mucous membranes. Four of these isolates were from vaginal secretions, all in menstruating women. Of the two women with negative vaginal cultures, one was not menstruating at the onset of illness (patient 1) and one did not have vaginal cultures taken until the third day of illness and after antimicrobial drugs had been given (patient 2). One woman (patient 1) had *S aureus* isolated from the conjunctivae as well as from clean facial burns; in patient 2, the organism grew from nasopharyngeal swabs. In no patient was staphylococcal bacteremia observed.

The convalescent phase of TSS was characterized by recurrence of disease with menses in two patients in whom *S aureus* had been isolated in vaginal cultures and by amenorrhea in two others. Additionally, prominent patchy alopecia was observed in four patients, which lasted six months in patient 1. All patients experienced distal desquamation within two weeks of the onset of illness. The findings we report are in agreement with those of others who have described the clinical features of TSS.[3-5,8,9]

Cause and Pathogenesis

The precise cause and pathogenesis of TSS are as yet unknown. However, the similarity between TSS and so-called staphylococcal scarlet fever,[10-12] the lack of demonstrable bacteremia in patients otherwise having all the hallmarks of septic shock, and the association with *S aureus* colonization or local infection strongly suggest a contributory or causal role for staphylococcal exotoxin or exotoxins. *Staphylococcus aureus* isolates from five patients in Todd's series produced an epidermal toxin, which those authors suggested might account for the characteristic skin involvement in TSS.[1] A different pyrogenic exotoxin derived from *S aureus* has been described and characterized by Schlievert and co-workers.[13] The original isolate that produced this toxin was grown from vaginal cultures of an adult patient diagnosed as having Kawasaki's disease.[14] In retrospect, the clinical manifestations in that patient were entirely compatible with TSS. Distinct from other known staphylococcal toxins, the toxin isolated from this patient's organism produced fevers in both rabbits and mice, was a potent mitogen but did not produce exfoliative changes in suckling mice. Further, Schlievert observed enhanced host susceptibility to damage by endotoxin—"either lethal shock or myocardial and liver damage."[13]

The possibility of a toxin or toxins either directly or indirectly causing the multisystem failure seen in TSS is an attractive hypothesis. In three of our patients the course was consistent with severe toxicogenic shock. Each of these patients was in shock when admitted to hospital and massive fluid resuscitation was required to achieve normal cardiac filling pressures. Initially, cardiac output was elevated but fell rapidly, with pronounced cardiac dysfunction and persistently low systemic vascular resistance. Elsberry and his colleagues[15] have described similar findings in monkeys with either staphylococcal enterotoxin B

(SEB) or endotoxin from *Escherichia coli*. Shock caused by *E coli* endotoxin occurred rapidly and resulted in increased systemic vascular resistance. Conversely, in the shock associated with SEB, the cardiovascular collapse occurred more slowly and systemic vascular resistance consistently remained slightly below normal.[15] This model is consistent with findings observed in our patients. The slower onset of cardiovascular collapse with SEB may explain why TSS patients have a prodrome of several hours before presenting in shock. Additionally, the persistently low systemic vascular resistance observed with SEB is consistent with similar findings in our patients.

The gastrointestinal symptoms early in the course of TSS are similar to those reported in staphylococcal toxin-mediated gastroenteritis. Subsequent hepatocellular dysfunction, hyperamylasemia and gastrointestinal bleeding are most likely related to the hypotension during the shock phase of TSS and the resultant development of DIC. Whether the hematologic abnormalities are directly related to the presence of a toxin, or are a result of microvascular phenomena induced by shock is unclear. It seems probable that the dermatologic findings in TSS also have a toxicogenic basis, but support for this contention must await more definitive characterization of the responsible agent or agents.

Epidemiologic studies have pointed out a statistical association between tampon use and the development of TSS.[3] Asymptomatic vaginal ulcerations have been described in tampon users.[16] *Staphylococcus aureus* has been found in the normal vaginal flora of 5 percent of women.[17] Ulceration of the vaginal mucosa as a result of tampon use may provide the point of entry for *S aureus* or its exotoxin. However, in 42 percent of our patients we were unable to implicate vaginal *S aureus*. Thus, the vaginal mucosa, although perhaps a common site, is not the exclusive point of entry of toxin. Isolation of *S aureus* from de-epithelialized skin in our first patient raises the possibility that colonization of compromised tissue at any site may result in an environment favorable to generation and absorption of a toxin or toxins. Such a mechanism may have been responsible for the development of TSS in Todd's and earlier cases,[1,10,11] in which TSS occurred in association with focal staphylococcal infections.

Transmissibility is suggested by our cases 2 and 3: TSS developed in the husband within 12 hours of the disease's occurrence in his wife. *Staphylococcus aureus* was cultured from a mucosal site in the wife but could not be cultured from the husband. No other causative or epidemiologic factors could be implicated to account for their illnesses, which were virtually identical in presentation and course and fulfilled all the criteria for TSS. To our knowledge, this is the first reported case of TSS in a consort.

Some investigators have raised the possibility of viral synergy in the pathogenesis of TSS,[8] and several reports have described either clinical or serological evidence of infection with herpesvirus concomitant with the acute illness.[6,8] In cases 2 and 3 there was a fourfold rise in viral titers against HSV-1, without clinical evidence of local or disseminated infection. It is unclear whether this represents a nonspecific response to acute illness, a concurrent subclinical infection or a potential predisposing factor to the development of TSS.

In only one of our patients (case 5) was lymphadenopathy present. Interestingly, in this our youngest patient, the manifestations combined features of TSS and the mucocutaneous lymph node syndrome (MLNS) or Kawasaki's disease.[18] MLNS is characterized by fever unresponsive to antimicrobic drugs, conjunctivitis, pharyngitis, strawberry tongue, fissured lips, peripheral edema, cervical lymphadenopathy and desquamative erythematous rash on the extremities. The major differences between TSS and MLNS are the hypotension associated with TSS, and the lymphadenopathy and indurative nature of the rash on the extremities in MLNS. Recently, several cases of MLNS have been reported in adults.[14,19-23] Most, if not all, of these cases also fit the criteria for TSS. Significant hypotension was a presenting feature in most of the patients with "adult Kawasaki disease." Cardiac dysfunction has been reported in 5 percent to 15 percent of patients with MLNS.[24,25] It is tempting to speculate that a similar mechanism of staphylococcal toxin-mediated myocardial damage links these cases with those in our series who had evidence of significant myocardial dysfunction. Patchy alopecia in the recovery period, as observed in several of our patients, has also been reported in MLNS.[25] Twenty-five percent of the patients reported by Kawasaki in 1974 had *S aureus* isolated from throat cultures,[18] another finding that guides speculation on the possible relationship of these syndromes in a spectrum of

Staphylococcus-associated diseases. Further study will be required to establish the likelihood of such a relationship.

Prevention

Strategies for the prevention of TSS remain of unproved value. Identification of those at high risk of contracting TSS by virtue of vaginal carriage of *S aureus* is a possible approach that cannot be justified until more data on the carriage rate in the normal population have been accumulated. Moreover, such an approach would not aid in identifying potential victims whose disease is not associated with menstruation or a vaginal route of acquisition of the disease. However, in those at risk for recurrent disease, detection and eradication of vaginal *S aureus* should be considered. In view of the epidemiologic association with use of tampons and the recurrent nature of the illness, we have advised our TSS patients not to use tampons.

Treatment

Treatment of TSS must include recognition and early aggressive management of the life-threatening manifestations of the disease, specifically those related to the serious hemodynamic compromise that develops in most patients. Signs of myocardial dysfunction should be sought and monitored appropriately, and our experience points out the potential requirement for inotropic drug support in some patients. In view of the reports of serious cardiac sequelae in patients with MLNS and the possible relationship of that disease to TSS, patients with TSS who have cardiac dysfunction during their acute illness should be followed for several months, with careful attention paid to cardiac status. Although antimicrobial drug therapy has not been known to alter the course of the acute illness, a favorable effect on the incidence of recurrent disease, as suggested by some investigators, cannot be excluded.[3] Therefore, our practice is to include in the management of TSS treatment with a β-lactamase-resistant antistaphylococcal drug for seven to ten days.

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