Recurrence of Nonmenstrual Toxic Shock Syndrome: Clinical Manifestations, Diagnosis, and Treatment

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We report 3 cases of recurrent nonmenstrual toxic shock syndrome (TSS) and review the clinical manifestations, diagnosis, and treatment. The primary sites of infection were the genital tract (in a patient who underwent cesarean delivery), the upper respiratory tract, and a breast abscess. In all 3 patients, the initial illness was not recognized to be TSS; only after development of recurrent illness with desquamation was this diagnosis entertained. Strains of *Staphylococcus aureus* that were isolated from 2 patients produced TSS toxin-1, whereas the third strain produced staphylococcal enterotoxin B. All 3 patients lacked antibody to the implicated toxins at the time of presentation with recurrent illness. Nonmenstrual TSS can occur in a variety of clinical settings and may be recurrent. The presence of desquamation during a febrile, multisystem illness could suggest this diagnosis and should prompt the clinician to obtain appropriate cultures for *S. aureus*.

Toxic shock syndrome (TSS) is an illness defined by the occurrence of fever, rash, hypotension, multiple organ system dysfunction, and desquamation. The clinical setting of TSS is characterized as being either nonmenstrual or menstrual, with the latter setting having received more attention since the disease was first characterized in 1978 [1]. The incidence of menstrual TSS in the United States peaked in 1980 and has decreased significantly during the past 20 years [2]. Although tampon use during menstruation remains relatively common among patients who experience TSS, nonmenstrual cases actually accounted for 55% of all cases identified by Gaventa et al. in 1989 [3], and the incidence of nonmenstrual TSS has remained relatively constant while the incidence of menstrual TSS has decreased [2]. TSS has been reported to occur in association with use of barrier contraceptives, vaginal and cesarean delivery, upper and lower respiratory tract infection, soft tissue infection, endovascular infection, and visceral abscesses [4–6]. This wide variety of physical sites and clinical settings underscores the importance of considering TSS in the differential diagnosis of febrile illnesses associated with rash, hypotension, and multiple organ system dysfunction.

Recurrent menstrual TSS is a well-described phenomenon, initially found to occur in as many as one-third of patients who have TSS [7]. Two conditions are required for recurrence of TSS: persistent colonization with a toxigenic strain of *Staphylococcus aureus* and persistent absence of neutralizing antibody. Recurrent TSS develops exclusively among patients who fail to develop a humoral immune response to the implicated staphylococcal toxin [8]. Patients who remain susceptible to TSS can be identified by means of antibody testing, and recurrences of menstrual TSS can be reduced by having patients abstain from the use of tampons and by treatment with an antistaphylococcal antibiotic. On the other hand, recurrence of nonmenstrual TSS is rare for uncertain reasons. We report 3 cases of recurrent nonmenstrual TSS, review the published lit-

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erature, and summarize important aspects of the diagnosis and treatment of this disease.

METHODS

Assays for TSS toxin 1 (TSST-1) and staphylococcal enterotoxin B (SEB). Staphylococcal isolates were cultivated by means of the membrane-over-agar method, as described elsewhere [9]; this method of cultivation yields high levels of TSST-1 and enterotoxins. Culture supernatants were tested for TSST-1 by use of competitive ELISA [9]. SEB was detected by use of double immunodiffusion assay with commercially available reagents (Sigma; Toxin Technology).

Assays for antibody to TSST-1 and SEB. Antibody to TSST-1 was quantitated by use of direct ELISA. In brief, microtiter plates (Immulon I; Dynatech) were coated with TSST-1 at a concentration of 0.5 μg/mL in carbonate-bicarbonate buffer with a pH of 9.6; TSST-1 was purified as described elsewhere [10]. After washing with phosphate-buffered saline that contained Tween and bovine albumin, serial dilutions of the patient’s serum samples were added to the plate and incubated at room temperature overnight. Plates were washed again and goat anti-human IgG conjugated to alkaline-phosphatase (Cappel) was added. After incubation at 37°C for 3 h, plates were washed and substrate solution was added (p-nitrophenyl phosphate in diethanolamine buffer). Plates were read when a 1:64 dilution of a positive control (Sandoglobulin; Sandoz) achieved an optical density (OD) of 1.0 at 405 nm. In this assay, the anti–TSST-1 titer of a sample is the highest dilution that yields OD > 0.2 × OD of the positive control. A titer of ≤1:4 represents an absence of protective antibody in this assay.

Antibody to SEB was assayed after coating plates with SEB (Sigma), at 0.5 μg/mL, by use of similar methods. Because of nonspecific color development, serial dilutions of samples and controls were added to both coated and uncoated wells, with the ODs of the latter subtracted from the former.

CASE REPORTS

Patient 1. A 32-year-old woman presented to an emergency room with complaints of headache, chills, myalgia, and shortness of breath, which had progressed over 48 h. Eighteen days before the onset of illness, she had undergone an elective cesarean section for delivery of a full-term infant. On the first day after delivery, she developed a temperature of 39.7°C, dyspnea, and myalgia. No hypotension was noted, and examination of her skin, lungs, abdomen, abdominal wound, uterus, and perineum revealed nothing remarkable. The findings of laboratory studies included a normal WBC count with an increase in band forms, normal results of liver function tests and urinalysis, and a blood gas analysis that showed a partial pressure of oxygen (P_{O_2}) of 75 in room air. Results of cultures of blood and urine samples were negative; vaginal and wound samples were not obtained for culture. Cefotetan was administered for a possible surgical wound infection. She continued to have high fever, tachypnea, and hypoxia on postoperative days 2–4, and she developed edema of her hands and feet. A chest radiograph revealed a prominent interstitial pattern consistent with pulmonary edema. Her tachypnea improved after treatment with furosemide. Because of concerns about pulmonary embolism, heparin was administered intravenously. Lower-extremity venous Doppler studies and a ventilation-perfusion scan were nondiagnostic, and heparin therapy was discontinued. A thoracic echocardiogram revealed nothing abnormal. On the fifth postpartum day, her fever resolved. Therapy was changed from cefotetan to orally administered erythromycin to treat for possible atypical pneumonia. She was discharged 1 week after surgery with the diagnosis of fever of uncertain etiology after cesarean section and noncardiogenic pulmonary edema.

The patient felt healthy after she was discharged. She developed extensive peeling of the skin on both hands, which she did not report to her health care providers. She did well until day 17 postpartum, when she developed myalgias, chills, headache, hand swelling, nausea, abdominal pain, and episodes of cough and shortness of breath. The next evening, she developed a high fever and reported to a local hospital. On examination, she was toxic-appearing and in moderate distress. Her temperature was 40.3°C, her pulse was 152 beats/min, her blood pressure was 105/62, and her respiratory rate was 44 breaths/min. Her examination also revealed a fine, erythematous rash on her thorax and abdomen, clear lungs, and a nontender abdomen with a well-healed incision. Laboratory studies disclosed a WBC count of 13.7 × 10^3 cells/mm^3, with 72% neutrophils and 16% band forms. The patient’s serum creatinine level was 1.7 mg/dL. The chest radiograph showed pulmonary edema.

The patient was admitted to the intensive care unit and treated with ticarcillin–clavulanate and erythromycin for sepsis syndrome of uncertain etiology. During the 24 h after admission, multiple fluid boluses and treatment with dopamine were required to maintain a systolic blood pressure of >90 mm Hg. A CT scan of the pelvis showed a slightly enlarged uterus but no fluid collection. A diagnosis of TSS was entertained, and the patient was transferred to Dartmouth-Hitchcock Medical Center, Lebanon, NH.

At the time of transfer, her vital signs were essentially unchanged; she continued to have high fever, tachycardia, tachypnea, and borderline hypotension despite 6 μg/kg per min of dopamine. She remained toxic-appearing. There was a diffuse erythroderma and desquamation of the skin over her lips and fingertips. The lung and heart examinations did not reveal abnormalities. Her surgical incision was well healed, but her lower abdomen was tender on deep palpation. Pelvic examination
revealed a slightly enlarged uterus and cervical motion tenderness, a brown-gray cervical discharge, and mucosal hyperemia. Laboratory studies disclosed a WBC count of \(12.9 \times 10^3\) cells/mm\(^3\), with 51% neutrophils and 39% bands. Electrolytes were within normal limits, and creatinine levels had decreased to 1.3 mg/dL. Prothrombin time was slightly elevated, at 13.6 s. The remainder of the results of a screen for disseminated intravascular coagulation were negative. An arterial blood gas analysis obtained on 4 L of \(O_2\) by means of nasal cannula showed a pH of 7.43, partial pressure of carbon dioxide (\(PCO_2\)) of 31, and \(PO_2\) of 82. Serum calcium, magnesium, and phosphorus levels were all low, at 7.4 mg/dL, 0.64 mM/L, and 2.3 mg/dL, respectively. The results of liver function tests and a urinalysis were normal.

Recurrent TSS in the setting of postpartum endometritis was diagnosed. The patient was treated with iv clindamycin and aztreonam. Because of persistent hypotension that required dopamine, she was also treated with a single dose of iv immunoglobulin (IVIG; 230 mg/kg). During the next 48 h, she became afebrile and normotensive, and her oxygenation improved. The results of cultures of blood and urine samples were negative, but cultures of samples of a uterine aspirate and vaginal fluid yielded \(S. aureus\). She was discharged from the hospital on the sixth day with instructions to complete a 10-day course of amoxicillin-clavulanaate.

The strain of \(S. aureus\) obtained from this patient was found to be a producer of SEB; the strain did not produce TSST-1. An acute-phase serum specimen obtained before administration of IVIG lacked antibody to SEB, whereas serum obtained after IVIG showed a high antibody titer. The patient completely recovered, but she had to undergo cholecystectomy for acute cholecystitis <2 weeks after her second hospitalization.

**Patient 2.** A 51-year-old man presented to an emergency room with throat and neck pain and dysphagia, which had started on the morning of admission. He subsequently developed fever, chills, myalgia, nausea, vomiting, and diarrhea during the day. At arrival, he appeared acutely ill. His temperature was 40.9°C, his pulse was 152 beats/min, his respiratory rate was 28 breaths/min, and his blood pressure was 160/50; his blood pressure subsequently dropped to 74/30 despite iv administration of fluids. Erythroderma of his neck and upper thorax was evident. Examination of his oropharynx revealed poor dental hygiene, gingivitis, pharyngeal erythema, and dry mucous membranes. His neck was tender and there was fullness, without fluctuance, over the right submandibular gland. There were bibasilar rales. There was no murmur. There was mild right upper quadrant tenderness. The remainder of his examination revealed nothing abnormal.

Laboratory studies disclosed the following values: WBC count, \(14.7 \times 10^3\) cells/mm\(^3\); hemoglobin, 15.0 g/dL; platelet count, 84,000 platelets/mm\(^3\); prothrombin time, 14.2 s (control, 12.7 s); and fibrin split products, 10–40 μg/mL. The results of liver function tests and serum levels of creatinine and amylase were normal. Serum magnesium and calcium levels were low, at 0.9 mg/dL and 7.2 mg/dL, respectively, and creatine phosphokinase (CPK) levels were elevated, at 890 U/L. An arterial blood gas analysis showed pH of 7.42, \(PCO_2\) of 30, and \(PO_2\) of 75 on 2 L of \(O_2\), by means of nasal cannula. Urinalysis showed cloudy urine with >30 WBCs and 0 RBCs per high-power field. The chest radiograph showed mildly increased vascular markings.

The patient was thought to have postanginal sepsis (Lemierre’s disease) and was treated empirically with broad-spectrum antibiotics. Evaluation of his oropharynx and neck by means of laryngoscopy, CT scan, and Doppler studies revealed no abscess or venous thrombosis. The results of a Panorex film of his teeth were negative. Because of continued hypotension, a pulmonary artery catheter was placed; it demonstrated a high cardiac output and a low systemic vascular resistance, consistent with sepsis. Administration of antibiotics and fluids gradually improved his hemodynamics. The results of cultures of blood, urine, and stool samples and of a streptococcal throat screen were negative. The patient was felt to have a dental or pharyngeal source of sepsis, and he was switched to iv penicillin G. After 7 days of therapy, he was switched to orally administered penicillin VK and discharged. A sputum sample was obtained for culture on day 3 of hospitalization; it grew moderate \(S. aureus\), but the physician did not change course or plan on the basis of this result.

Eleven days after discharge, the patient returned to the hospital with a 1-day history of sore throat, neck pain, fever, myalgia, and arthralgia. He had been taking orally administered penicillin until the day before readmission. He reported having developed a desquamative rash that involved his hands, feet, and scrotum 1 day after his previous discharge. Examination revealed a temperature of 39.0°C, pulse of 90 beats/min, a respiratory rate of 20 breaths/min, and blood pressure of 80/30. He appeared acutely ill. There was erythema over the anterior and left lateral aspects of his neck and upper chest, with warmth and fullness over his left neck. His pharynx was erythematous. Examinations of his chest, heart, and abdomen were unrevealing. His distal extremities were cool. There was desquamation of skin over his hands, feet, and scrotum. Laboratory investigation demonstrated leukocytosis with a left shift and normal serum chemistries except for hypocalcemia. The findings on a chest film were unchanged from previous films; a repeat CT scan of his neck revealed no mass or abscesses.

A diagnosis of recurrent TSS was entertained and vancomycin was administered. The patient had persistent hypotension that required iv administration of large volumes of fluids, but his condition gradually improved. The results of cultures of blood and urine samples were negative; culture of a nasal swab yielded \(S. aureus\) despite several days of therapy with
vancomycin. Mupirocin ointment was applied to his nares, and he was instructed to shower with an antibacterial soap. After 7 days of therapy, he was discharged on these medications plus rifampin.

The isolate of \textit{S. aureus} obtained from the nasal swab was tested for production of TSST-1 and the results were positive. A serum specimen obtained during his second hospitalization was tested for antibody to TSST-1; the antibody titer was found to be <1:4 (undetectable). The results of follow-up nasal cultures were negative for \textit{S. aureus}. A late convalescent anti–TSST-1 titer, obtained 1 year after these episodes, remained <1:4.

\textbf{Patient 3.} A 33-year-old woman developed fever and myalgia 11 days after she gave birth vaginally. Three days after she became ill, she saw her nurse midwife because of persistent symptoms. An examination showed a temperature of 38.8°C and a tender right breast. The patient retrospectively recalled having had a generalized rash that she had thought was "prickly heat" (i.e., heat rash). Orally administered erythromycin was prescribed for suspected mastitis. Her symptoms improved, and a repeat examination on completion of 10 days of therapy showed resolution of her abnormal physical findings.

One week after discontinuing erythromycin therapy, the patient developed recurrent myalgia and arthralgia. She also reported having difficulty with breast-feeding, but she denied experiencing breast redness or tenderness. Her physician prescribed erythromycin over the telephone for possible recurrent mastitis. During the next 24 h, however, she developed shaking chills and a temperature of 40.0°C, as well as neck and back stiffness and orthostatic dizziness. She presented to a local emergency room, where examination revealed her to be toxic-appearing, with a temperature of 38.2°C, a pulse of 100 beats/min, blood pressure of 130/60, and a respiratory rate of 24 breaths/min. The findings of analyses of her head, throat, lungs, and heart were unremarkable. Her right breast was slightly engorged but without abnormal discharge. Right axillary adenopathy was present. The remainder of her examination was unrevealing: laboratory studies revealed a WBC count of 20.7 \times 10^3 cells/mm$^3$, with 68% neutrophils and 26% band forms. Erythrocyte sedimentation rate was 73 mm/h. Levels of serum electrolytes, calcium, creatinine, and CPK and the results of liver function studies were normal. Urinalysis revealed 1+ protein, 2+ ketones, and 1+ blood. Analysis of CSF drawn via lumbar puncture proved normal. A chest radiograph did not reveal any abnormalities.

The patient was admitted and treated with cefazolin and fluids. Her fever and myalgia resolved within 48 h of initiation of treatment. The results of cultures of blood, urine, and CSF samples were negative. A vaginal culture yielded what was described as “usual vaginal flora.” A rapid streptococcal screen and an antistreptolysin O titer returned negative results. Subsequent examinations of the breast did not suggest mastitis.

The patient remained afebrile, and she was discharged on orally administered cephalexin and ibuprofen. She subsequently developed peeling skin on her hands and feet.

Eight weeks after delivery, and only a few days after completing a 2-week course of cephalexin, she developed recurrent fever, arthralgia, and generalized weakness. On physical examination, she was noted to have a desquamative rash that involved her hands and feet. Her temperature was 38.8°C. There was slight erythema of the right nipple, but no abnormal discharge. A small, nonfluctuant mass, several centimeters in diameter, was noted in the superior aspect of the breast. An ultrasound of the breast was nondiagnostic. Dicloxacillin was prescribed for a possible breast abscess. During the next few days, however, she developed progressive weakness and continued to experience fever and myalgia. She sought medical attention at a local emergency room. Physical examination was remarkable for a temperature of 37.1°C, a pulse of 108 beats/min, and blood pressure of 80/40. There was desquamation of the skin on the soles of her feet. Her right breast was indurated but without erythema, discharge, or tenderness. There was diffuse muscle tenderness. The findings of examinations of her head and neck, chest, heart, and abdomen were unremarkable, and findings of the remainder of a physical examination were normal. Laboratory studies disclosed a WBC count of 24.5 \times 10^3 cells/mm$^3$ and an erythrocyte sedimentation rate of 125 mm/h. The serum sodium level was 129 mM/L and the calcium level was 7.9 mg/dL. Her serum creatinine level was markedly elevated, at 5.3 mg/dL. The results of liver function tests and the levels of serum CPK were normal. Despite the negative result of ultrasound, needle aspiration of the breast yielded 10 mL of a tan fluid, culture of which yielded \textit{S. aureus}.

The patient was admitted to the hospital with a diagnosis of a breast abscess complicated by TSS. She was treated with cefazolin and fluids and the breast abscess was incised and drained. She improved rapidly and her renal function normalized. She was discharged from the hospital after 72 h with the instruction to complete a 2-week course of therapy with cephalexin.

The \textit{S. aureus} isolate was subsequently shown to produce TSST-1. A serum specimen drawn at the time of admission showed an anti–TSST-1 titer of <1:4. A convalescent-phase serum sample, obtained 5 weeks after discharge (>2 months after her initial presentation) continued to show an anti–TSST-1 titer of <1:4. Late convalescent testing, performed 2.5 years after her initial illness, showed her to have an anti–TSST-1 titer of 1:256, which is a protective level of antibody titer.

\textbf{DISCUSSION}

The clinical syndrome known as “TSS” was first defined by Todd in 1978 [1] and came into the public spotlight in 1980.
when an association was made between tampon use and increased risk [11, 12]. The Centers for Disease Control’s (CDC) case definition of “definite” TSS requires the presence of fever, rash, hypotension, multisystem disease, and desquamation, with the latter occurring 1–2 weeks after the onset of illness; absence of 1 criterion constitutes “probable” TSS [13]. Staphylococcal toxin production and acute and convalescent antibody testing may be useful in supporting the diagnosis, with the characteristic findings being the presence of a toxigenic strain of S. aureus in the absence of acute-phase antibody. Toxicologic and serologic test results are not currently part of the CDC case definition, but alternative case definitions that incorporate these data have been proposed [14].

Nonmenstrual TSS and menstrual TSS are now reported with almost equal frequency. Until 1981, nonmenstrual TSS accounted for only 7% of cases reported to the CDC [13]; by 1990, however, nonmenstrual TSS constituted 45% of reported TSS cases [13], and this probably underrepresents the actual percentage of nonmenstrual cases because of reporting bias. This shift has been variably attributed to changes in tampon fiber composition, changes in absorbency, better recognition of early menstrual TSS, and a heightened awareness of TSS in clinical situations other than during menstruation [15].

The epidemiology, pathogenesis, and clinical spectrum of menstrual TSS and nonmenstrual TSS have been compared. Kain et al. [16] observed higher rates of previous antibiotic treatment and hospital exposure among patients with nonmenstrual TSS than among patients with menstrual TSS; these patients are presumably predisposed to colonization with toxigenic strains of S. aureus. Two of the patients we studied had been hospitalized in the days before their first episode of TSS. In both menstrual and nonmenstrual disease, colonization or infection with a toxin-producing Staphylococcus species initiates a systemic inflammatory response if neutralizing antibody to the toxin is lacking. The toxins, as immunologic “superantigens,” are potent inducers of tumor necrosis factor and IL-1, and this is probably integral to the pathogenesis of illness [10, 17–20]. Both menstrual TSS and nonmenstrual TSS can be caused by toxins other than TSST-1, especially SEB [21–24], which was the case in one of the patients we assessed. The diseases caused by the various toxins are indistinguishable on clinical grounds.

Recurrent menstrual TSS is a phenomenon that has been well described [12, 16, 25]. Davis et al. [26] showed that after an episode of menstrual TSS, roughly two-thirds of women who were not treated with an antistaphylococcal antibiotic and who continued to use tampons developed recurrent TSS during the next 5 months. This extraordinary rate of recurrence reflects (1) continued colonization with a toxin-producing strain of S. aureus in the absence of antibiotic therapy, (2) continued increased risk (by uncertain mechanisms) because of tampon use, and (3) persistent immunologic susceptibility to the toxin. Davis et al. [12, 26] showed that treatment with an antibiotic regimen that is effective against S. aureus decreased the likelihood of recurrent menstrual TSS during the ensuing months. Several groups of investigators have shown, however, that many women with menstrual TSS, probably on the order of two-thirds, do not develop a protective level of antibody during the months after acute illness [8, 26–28], which makes it clear that elimination of staphylococcal carriage is important in decreasing the risk of recurrent disease. The failure of many patients with TSS to seroconvert is particularly striking in light of the fact that the majority of healthy adults have protective antibody to TSST-1 without having had an illness suspected to have been caused by toxin-producing S. aureus [29–32].

There have been several previous reports of recurrent TSS in nonmenstrual settings [16, 33–39] (A. Chow, personal communication). These cases and the cases of TSS described in this report are summarized in table 1.

In patient 1, the source of the patient’s initial infection immediately postpartum was not definitively identified, although diagnoses of wound infection and endometritis were considered. We cannot classify this illness as “definite” TSS because rash, hypotension, and multiple organ system failure were not well documented in the medical record. Highly suggestive of the diagnosis, however, were fever, myalgia, hypoxemia (consistent with pulmonary edema or early sepsis syndrome), and desquamation that occurred 1 week after the onset of illness. Early initiation of empiric antibiotics may have altered the course of her first episode, including prevention of its more severe manifestations. The patient’s subsequent presentation fulfilled the standard diagnostic criteria for nonmenstrual TSS, including fever, erythroderma, mucosal hyperemia, hypotension, and multiple organ system involvement; figure 1 summarizes the chronology of the patients’ course of recurrence. The isolation of a S. aureus strain that produced SEB and the patient’s lack of protective antibody to this toxin are additional evidence in support of the diagnosis of TSS.

This case is similar to other cases of TSS that have been recognized as occurring within hours to weeks after childbirth. Postpartum TSS, in patients who have undergone either vaginal or cesarean delivery, as well as those who have had therapeutic abortions, has been recognized since the early 1980s [5]. In these cases, the primary sites of S. aureus have been mastitis, infected abdominal wounds, episiotomy infections, and endometritis. Vaginal and skin colonization with S. aureus have been proposed as initial risk factors for development of TSS, followed by disruption of mucosal or cutaneous host defenses at the time of parturition. Lochia, like menstrual detritus, are postulated to harbor adequate nutrients for bacterial multiplication and toxin production. Reingold et al. [5] described 31 patients with vaginal or postpartum TSS. The 21 postpartum
<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (y), sex</th>
<th>Clinical setting</th>
<th>Antibiotics administered during first illness</th>
<th>Interval to second illness</th>
<th>Antibiotics administered during second illness</th>
<th>S. aureus toxin</th>
<th>Comments</th>
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<tr>
<td>[36]</td>
<td>20, F</td>
<td>Laparotomy wound infection</td>
<td>Pen/Gm; Oxa</td>
<td>6 days</td>
<td>Czid/Tm</td>
<td>NT</td>
<td>Status post salpingo-oophorectomy after ruptured ectopic pregnancy</td>
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<tr>
<td>[35]</td>
<td>18, F</td>
<td>Postpartum endometritis, episiotomy infection</td>
<td>Amp/Cfox/GM; Naf/Tm/Mtz</td>
<td>11 days</td>
<td>Vm/Gm/Mtz</td>
<td>NT</td>
<td>Status post forceps delivery with 4 degrees perineal laceration; patient did not complete orally administered therapy prescribed after first episode</td>
</tr>
<tr>
<td>[33]</td>
<td>26, M</td>
<td>Upper respiratory infection</td>
<td>Naf/Rif</td>
<td>49 days</td>
<td>Naf</td>
<td>NT</td>
<td>5 total episodes in a mentally retarded patient with IgA deficiency</td>
</tr>
<tr>
<td>[34]</td>
<td>46, F</td>
<td>Laparotomy wound infection</td>
<td>Vm; Naf; Dcl</td>
<td>10 days</td>
<td>Vm; “a cephalosporin”</td>
<td>TSST-1</td>
<td>Receiving cisplatin for ovarian cancer</td>
</tr>
<tr>
<td>[16]; Chow*</td>
<td>37, F</td>
<td>Pharyngitis</td>
<td>None</td>
<td>1 month</td>
<td>None</td>
<td>TSST-1</td>
<td>—</td>
</tr>
<tr>
<td>[16]; Chow*</td>
<td>35, F</td>
<td>Vaginitis</td>
<td>Em</td>
<td>2.5 months</td>
<td>Cfaz</td>
<td>TSST-1</td>
<td>No association with tampon use or menstruation</td>
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<tr>
<td>[37]</td>
<td>20, M</td>
<td>Infected sebaceous cyst</td>
<td>Clox</td>
<td>5 months</td>
<td>Not stated</td>
<td>TSST-1</td>
<td>Initial illness recognized as being TSS; recurrent infection of cyst with phenotypically identical S. aureus</td>
</tr>
<tr>
<td>[39]</td>
<td>6, F</td>
<td>Sinusitis</td>
<td>Ctax/Oxa; Tc-Clv/Vm</td>
<td>6 weeks</td>
<td>Tic-Clv; Rif/Crad</td>
<td>NT</td>
<td>HIV infection; source of infection not evident at first admission, but S. aureus recovered from maxillary sinus at second admission; Treated with IVIG during both episodes and monthly thereafter</td>
</tr>
<tr>
<td>[38]</td>
<td>34, F</td>
<td>Postpartum</td>
<td>Pen + Chl; Em/Mtz</td>
<td>2 weeks</td>
<td>Gm</td>
<td>NT</td>
<td>Status post vaginal delivery; S. aureus resistant to antibiotics used in initial illness</td>
</tr>
<tr>
<td>Present report</td>
<td>32, F</td>
<td>Postpartum endometritis</td>
<td>Ctan; Em</td>
<td>12 days</td>
<td>Tic + Clv/Em; Cm/Atm</td>
<td>SEB</td>
<td>Status post cesarean section; treated with IVIG</td>
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<tr>
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<td>51, M</td>
<td>Pharyngitis</td>
<td>“Broad-spectrum” antibiotics; Pen</td>
<td>11 days</td>
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<td>TSST-1</td>
<td>Initial diagnosis of postanginal sepsis</td>
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<tr>
<td>Present report</td>
<td>33, F</td>
<td>Mastitis, breast abscess</td>
<td>Em</td>
<td>7 days</td>
<td>Cfaz; Clex</td>
<td>TSST-1</td>
<td>Status post vaginal delivery; 3 episodes of illness</td>
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</table>

**NOTE.** Amp, ampicillin; Atm, Aztreonam; Cfa, cefazolin; Cfox, cefoxitin; Chl, chloramphenicol; Clex, cephalaxin; Clox, cloxacillin; Cm, clindamycin; Cpt, cephradine; Cta, cefotetan; Ctx, cefotaxime; Czid, ceftazidime; Dcl, dicloxacillin; Em, erythromycin; Gm, gentamicin; IVIG, intravenous immunoglobulin; Mtz, metronidazole; Naf, nafcillin; NT, not tested; Oxa, oxacillin; Pen, penicillin; Rif, rifampin; S. aureus, Staphylococcus aureus; TSS, toxic shock syndrome; SEB, staphylococcal enterotoxin B; Tic-Clv, ticarcillin/clavulanate; Tm, tobramycin; TSS toxin 1; Vm, vancomycin.

* Personal communication.
Figure 1. Chronology of patients’ course of recurrence of nonmenstrual toxic shock syndrome (TSS). A, A 32-year-old woman who developed fever and hypoxemia 24 h after cesarean section. She was treated empirically for possible wound infection and her condition improved. At 17 days postpartum, she presented with endometritis and full-blown TSS with desquamation. B, A 52-year-old man admitted with complaints of throat and neck pain, fever, myalgia, and gastrointestinal symptoms. He was treated for sepsis (possibly from a pharyngeal source) and his condition improved. He was readmitted 11 days later with recurrent symptoms and desquamation. C, A 33-year-old woman treated for 2 episodes of fever, rash, and arthralgia associated with postpartum mastitis. Eight weeks postpartum, she was admitted with TSS and a breast abscess. Desquamation was noted at that time. Solid bars, inpatient received iv antibiotics; open bars, outpatient received orally administered antibiotics; checked bars, desquamation; shaded circles, TSS diagnosis considered.

patients with TSS in their report could be separated into 2 subsets: those who became ill within 3 days of delivery (7 patients) and those whose onset of disease occurred ≥2 weeks postpartum (14 patients). A significant association was found between postpartum tampon use and the incidence of TSS in the latter subset.

At initial presentation, patient 2 fulfilled the criteria for probable TSS, with fever, myalgia, vomiting and diarrhea, erythroderma, and hypotension, as well as evidence for multiple organ system dysfunction. An oropharyngeal or deep neck abscess, fasciitis, myonecrosis, septic phlebitis, sinusitis, tracheitis, and pneumonia were all considered in the differential diagnosis but were not identified in exams or studies. Cultures of sputum samples yielded S. aureus, but because pneumonia and sinusitis were not suggested by clinical findings, this organism was considered to be a colonizing strain and was not targeted for therapy. Desquamation occurred 1 week after the onset of illness, which suggested (in retrospect) the diagnosis of TSS. The patient’s illness recurred 1 day after completion of >2 weeks of treatment with penicillin (parenteral followed by oral administration). A strain of S. aureus that produces TSST-1 was isolated from nasal swabs, and the patient was shown to lack antibody to TSST-1 at the time of his second presentation.

A variety of S. aureus respiratory infections have been reported previously to culminate in TSS, including sinusitis, pharyngitis, tonsillitis, laryngotracheitis, pneumonia, and lung abscess [5, 40–49]. Patients with antecedent influenza or respiratory syncytial virus infection may be particularly predisposed to staphylococcal superinfection, and, consequently, to TSS [50, 51].

The third patient met the major diagnostic criteria for “probable” TSS during both of her hospitalizations. Delayed development of a desquamative rash supports the retrospective diagnosis of probable TSS at the time of her initial presentation.
During her second hospitalization, when a staphylococcal breast abscess was found, fever, hypotension, and multiple organ system dysfunction (myalgia, hypocalcemia, and renal insufficiency) were also present, which fulfilled criteria for probable TSS. Laboratory evidence supporting the diagnosis of recurrent TSS consisted of the isolation of a TSST-1–producing strain of *S. aureus* and a lack of protective antibody. These findings are essentially pathognomonic of the diagnosis of TSS.

In addition to this case, there have been 5 previous reports of mastitis and TSS in both the immediate puerperium and the later postpartum period [5, 52–55]. The range of time until onset of illness is 1–3 weeks after delivery; the patient we studied first became ill 11 days postpartum. In all cases, a tender, engorged breast was noted, but a fluctuant mass or abscess was not clinically obvious at the time of initial presentation. Cultures of breast milk samples may yield staphylococci before obvious abscess formation [52]. Incision and drainage of any obvious abscess or breast tissue suspected of harboring toxin-producing *S. aureus* has been deemed essential to therapy.

The patients that we have described illustrate several points about the clinical features of recurrent nonmenstrual TSS. First, clinicians must consider the diagnosis of TSS that occurs under circumstances that don’t involve menstruation and tampon use in order to make the diagnosis, in male and female subjects of all ages. Infection with toxin-producing *S. aureus* was suspected at the time of initial presentation in only 2 reported cases of recurrent nonmenstrual TSS [16, 37]. As a result, empiric antibi-otic therapies were not specifically directed against treating or eradicating toxin-producing staphylococci. Second, the benign appearance of surgical wounds can be deceptive at the time a patient presents with TSS, yet toxin-producing staphylococci can be isolated from samples of such wounds [5]. Primary sites of infection caused by toxin-producing *S. aureus* strains may require aggressive surgical drainage, even in the absence of a well-defined abscess or fluid collection, as was the case for the patient we studied who had mastitis. Third, clinicians must remember that desquamation occurs during the early convalescent and not during the acute phase of illness. Absence of desquamation initially does not go against the diagnosis, but desquamation at the time of recrudescence may be an important clue to the diagnosis.

These cases occurred in clinical settings that were similar to cases of nonmenstrual TSS reported previously. The apparently higher rate of recurrence in menstruation-related disease reflects the recurrent nature of a predisposing factor—namely, menstruation. The fact that tampon use further increases the risk probably reflects enhanced production of TSST-1 in the presence of a tampon, as tampons do not increase the likelihood of staphylococcal colonization [56–58]. It may also be easier to eradicate staphylococcal colonization from some sites, such as surgical wounds, than to eliminate staphylococcal coloni-

zation of mucus membranes. Different rates of seropositivity or seroconversion to toxins that cause nonmenstrual TSS (i.e., toxins other than TSST-1) might also contribute to differences in recurrence rates. Finally, an element of bias might favor the diagnosis or the reporting of recurrent menstrual TSS.

The cases of TSS that we describe suggest several ways in which the laboratory can be used to assist in the diagnosis and management of suspected TSS. Physicians should request that the laboratory identify all staphylococci, especially from nasopharyngeal and vaginal cultures, in which staphylococci may otherwise be dismissed as “normal flora.” Production of specific staphylococcal toxins, including TSST-1 and SEB, can be determined readily, and this can be useful information if accompanied by serologic test results that demonstrate a lack of antibody to the putative toxin at the onset of illness. Lack of seroconversion after acute illness may be used as a marker for individuals who are at risk for recurrent TSS. One of the 2 patients with TSST-1–induced disease had developed anti–TSST-1 by 2.5 years after her illness, which provided her with significant reassurance. Finally, antimicrobial susceptibility of causative staphylococci should be determined, although most cases in the United States, and all of the cases we studied, have the common phenotype of resistance to penicillin and sensitivity to methicillin.

Failure to eradicate colonization with *S. aureus* predisposes the patient to recurrent TSS. Treatment of patients with nonmenstrual TSS should be geared toward eradicating toxigenic strains of *S. aureus*. In some circumstances, this may require a more protracted antibiotic course than would otherwise be chosen for a clinical syndrome. A prospective clinical trial addressing the question of duration of therapy required for eradication of carriage of toxin-producing staphylococci will not be feasible because of the low incidence of TSS. Previous studies have generally recommended a 2-week course of antistaphylococcal antibiotics when elimination of carriage was deemed important. Use of combination therapy (e.g., with mupirocin, rifampin, or both) might further decrease the risk of recurrence by eliminating carriage, but this has not been studied. The decision to treat TSS with a prolonged course of therapy will follow only from the recognition that a patient has a toxigenic staphylococcal infection, a fact that has not been apparent initially in most cases of recurrent nonmenstrual TSS published elsewhere.

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**References**


