TOXIC-SHOCK SYNDROME IN MENSTRUATING WOMEN

Association with Tampon Use and Staphylococcus aureus and Clinical Features in 52 Cases

Kathryn N. Shands, M.D., George P. Schmid, M.D., Bruce B. Dan, M.D., Deborah Blum, M.D., Richard J. Guidotti, M.D., Nancy T. Hargrett, Ph.D., Roger L. Anderson, Ph.D., Dianne L. Hill, M.S., Claire V. Broome, M.D., Jeffrey D. Band, M.D., and David W. Fraser, M.D.

Abstract To determine the risk factors associated with toxic-shock syndrome (TSS) in menstruating women, we conducted a retrospective telephone study of 52 cases and 52 age-matched and sex-matched controls. Fifty-two cases and 44 controls used tampons (P<0.02). Moreover, in case-control pairs in which both women used tampons, cases were more likely than controls to use tampons throughout menstruation (42 of 44 vs. 34 of 44, respectively; P<0.05). There were no significant differences in brand of tampon used, degree of absorbency specified on label, frequency of tampon change, type of contraceptive used, frequency of sexual intercourse, or sexual intercourse during menstruation. Fourteen of 44 cases had one or more definite or probable recurrences during a subsequent menstrual period. In a separate study, Staphylococcus aureus was isolated from 62 of 64 women with TSS and from seven of 71 vaginal cultures obtained from healthy controls (P<0.001). (N Engl J Med. 1980; 303:1436-42.)

T XIC-SHOCK syndrome (TSS) was first described in 1978 by Todd et al., who reported seven cases in children eight to 17 years old. The illness was characterized by high fever, headache, confusion, conjunctival injection, a scarlatiniform rash, subcutaneous edema, oliguria, and hypotension. These symptoms were usually accompanied by sore throat, vomiting, watery diarrhea, and shock. During recovery, all patients had fine desquamation of affected skin, particularly of palms and soles. Toxin-producing strains of Staphylococcus aureus, Phage Group I, were recovered from various body sites in each of five children with TSS who were studied prospectively, and an association between this organism and TSS was suggested.

In January 1980, Andrew G. Dean, M.D., and Jeffrey P. Davis, M.D., state epidemiologists in Minnesota and Wisconsin, reported five and seven cases of TSS, respectively, to the Center for Disease Control (CDC). Dr. Davis noted that most of his cases occurred in women and that most of the onset took place during a menstrual period.

From February 1 to May 23, 1980, 43 additional cases of TSS were reported to the CDC.² Like Davis' cases, these patients were older than Todd's cases, ranging in age from 13 to 52 years, and they were almost exclusively women (95 per cent). There was a striking association with menses: 38 (95 per cent) of 40 women from whom a menstrual history was obtained became ill within five days after the beginning of a menstrual period. Like Todd's cases, a majority (33 of 45, 73 per cent) of patients from whom cultures were obtained had Staph. aureus isolated from the throat, cervix, vagina, or rectum. Many of these patients had only one or two cultures performed, and Staph. aureus was not the subject of a systematic search.

Announcement of these data² resulted in the reporting of more than 100 suspected cases of TSS to the CDC. The striking association with menses continued in these suspected cases. Because of this association and because of observations by Davis and others that a large number of these women used tampons, we undertook a case-control study to examine various factors relating to the menstrual period that might be associated with the development of TSS.

When all of 16 women in this study who had vaginal cultures performed had Staph. aureus isolated from these cultures, we reviewed the literature on vaginal isolation of this organism. Studies of the normal vaginal flora³-¹¹ cite isolation rates for Staph. aureus ranging from zero to 17 per cent; most report rates of less than 5 per cent. None of these studies, however, were conducted during the menstrual period; we therefore undertook a second study to determine the prevalence of Staph. aureus in the vaginas of healthy women during menstrual periods.

Methods

Case Definition and Selection

In February 1980, one of us (K.N.S.), in collaboration with Dr. James K. Todd and Dr. Neal A. Halsey at the University of Colorado, Denver, developed a case definition based on cases reported to the CDC and to Dr. Todd. This case definition was circulated to other physicians who were familiar with TSS, including Dr. Davis, for comments. The case definition, thus revised, appears in Table 1.

The cases that we studied were drawn from approximately 100 suspected cases of TSS reported to the CDC from May 23 to June 28, 1980. We reviewed the medical records of these suspected cases or discussed the clinical history in detail with the attending physician. We selected cases that had clinical features and laboratory results meeting the case definition.

Because TSS, especially in menstruating women, is a newly recognized entity, we include at the end of the Methods section a typical case report and a general description of the illness.

Fifty-three cases met the case definition. All cases were female and between the ages of 12 and 49 years. One case did not have onset of the illness during a menstrual period, and she was excluded from the study. We administered a telephone questionnaire to the 52 remaining cases and to 52 age-matched controls. Controls were chosen by cases with TSS from among friends who were within three years of their own age.

Questionnaire

We asked cases and controls about their marital status, fecundity, contraceptive methods, frequency of sexual intercourse, sexual intercourse during menstruation, use of tampons or sanitary nap-
Table 1. Case Definition of Toxic-Shock Syndrome.

<table>
<thead>
<tr>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever: temperature ≥38.9°C</td>
</tr>
<tr>
<td>Rash: diffuse macular erythrodema</td>
</tr>
<tr>
<td>Desquamation of palms and soles one to two weeks after onset of illness</td>
</tr>
<tr>
<td>Hypotension: systolic blood pressure &lt;90 mm Hg for adults or below fifth percentile by age for children below 16 years of age, orthostatic drop in diastolic blood pressure &gt;15 mm Hg from lying to sitting, or orthostatic syncope</td>
</tr>
<tr>
<td>Multiorgan involvement — three or more of the following:</td>
</tr>
<tr>
<td>Gastrointestinal: vomiting or diarrhea at onset of illness</td>
</tr>
<tr>
<td>Muscular: severe myalgia or creatine phosphokinase level at least twice the upper limit of normal for laboratory</td>
</tr>
<tr>
<td>Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia</td>
</tr>
<tr>
<td>Renal: blood urea nitrogen or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria (&gt;5 white cells per high-power field) in the absence of urinary-tract infection</td>
</tr>
<tr>
<td>Hepatic: total bilirubin, SGOT,* or SGPT† at least twice the upper limit of normal for laboratory</td>
</tr>
<tr>
<td>Hematologic: platelets &lt;100,000 per cubic millimeter</td>
</tr>
<tr>
<td>Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent</td>
</tr>
</tbody>
</table>

*SGOT denotes serum aspartate aminotransferase.
†SGPT denotes serum alanine aminotransferase.

Inkins during menstruation, brand and absorbency of tampon or napkin used, and use of deodorized tampons. We also asked about usual menstrual patterns, including quantity and duration of menstrual flow, frequency of tampon or napkin change, and patterns of tampon or napkin use during menstrual periods and during an index menstrual period. The index period for cases was the menstrual period coincident with onset of the illness, and the index period for controls was the period immediately preceding the interview. Cases were asked in a separate questionnaire about the recurrence of symptoms characteristic of TSS, the temporal relation of these recurrent symptoms to a menstrual period, the use of feminine deodorant sprays, and the frequency of douching.

Tampons

We interviewed the six major tampon manufacturers in the United States, who made all the tampons used by cases and controls. Manufacturers supplied information on materials contained in their products, manufacturing practices, and marketing history.

We asked patients with TSS to mail to the CDC any unused tampons remaining in the box that was used at the time of illness. We also purchased tampons of all brands from commercial sources in Atlanta. Two hundred sixty-four of these tampons were placed aseptically into sterile jars containing 150 ml of brain-heart-infusion broth, incubated at 37°C, and observed daily for seven days for evidence of turbidity. Turbid samples were transferred to blood-agar plates for isolation and identification of microorganisms.

Staph. aureus Prevalence Study (Study 2)

Cases for this study were those reported to the CDC after May 23, 1980, who had a vaginal culture performed before the administration of antimicrobial therapy. The control group was composed of 71 women who visited one of seven family-planning clinics or a single private physician's office in major cities in the United States. All these women were menstruating at the time of the visits. Staph. aureus isolates from cases were sent to the CDC in any manner deemed appropriate by the laboratory personnel who processed the cultures.

 Cultures from controls were obtained with a dry swab from the anterior nares, the vaginal introitus, and the posterior vaginal pool. Swabs were inserted into Cary-Blair transport mediums for mailing to the CDC. At the CDC, swabs were removed and inoculated onto blood agar and to mannitol-salt agar. Plates were incubated at 37°C and observed at 24 and 48 hours for growth. Suspected staphylococcal colonies on mannitol-salt agar (on the basis of colonial morphology, pigmentation, and fermentation of mannitol) and on blood agar (on the basis of pigmentation and hemolysis) were separately picked to triple sugar-iron agar and tested for catalase and tube-coagulase activity. Colonies positive for both were identified as Staph. aureus. These isolates were phage-typed and tested for antimicrobial sensitivities. We arbitrarily classified original microbial plate counts as follows: scant growth, 0 to 10 colonies; 1+, 11 to 50 colonies; 2+, 51 to 100 colonies; and 3+, more than 100 colonies.

Statistical Analysis

In the analysis of these data, a variety of descriptive and inferential statistical analyses were performed, including univariate matched logistic regression as a descriptive technique and multivariate matched logistic regression models for inferential analyses.

The statistical significance of differences seen in cross-tabulations was examined with a matched-pair-analysis, McNemar test with continuity correction. An estimate of the individual risk associated with each factor, an odds ratio, and confidence intervals for that ratio were found by means of linear logistic regression for matched studies.

Case Report

In the afternoon of the third day of her menstrual period, a previously healthy 15-year-old girl suddenly had shakiness, chills, fever, diffuse severe myalgia, lower abdominal pain, and vomiting. She also noted mild dysuria. When examined in an emergency room that evening, she had a temperature of 38.3°C and diffuse abdominal and costovertebral angle tenderness. The white-cell count was 12,600 per cubic millimeter with 86 percent neutrophils, 7 percent band forms, 3 percent lymphocytes, 3 percent monocytes, and 1 percent atypical lymphocytes. Urinalysis showed 20 to 25 white cells per high-power field, and a urine culture was ordered but not performed. A presumptive diagnosis of acute pyelonephritis was made, and the patient was given ampicillin to take orally at home.

That night she had watery diarrhea without blood or mucus approximately every two hours. Over the next two days the patient became increasingly ill; her temperature rose to 40°C, and vomiting and diarrhea continued. On the third day of illness, she became lethargic.

On admission to a hospital, the oral temperature was 39°C, the heart rate was 152 beats per minute, and the blood pressure was 120/0 mm Hg. Within several hours the blood pressure dropped to 70/40 mm Hg, and she was disoriented and combative. Physical examination revealed an acutely ill girl with marked bilateral conjunctivitis, diffuse abdominal tenderness without signs of peritonitis, minimal, and a urine culture was ordered but not performed. A presumptive diagnosis of acute pyelonephritis was made, and the patient was given ampicillin to take orally at home.

The heart rate was 152 beats per minute, and the blood pressure was 120/0 mm Hg. Within several hours the blood pressure dropped to 70/40 mm Hg, and she was disoriented and combative. Physical examination revealed an acutely ill girl with marked bilateral conjunctivitis, diffuse abdominal tenderness without signs of peritonitis, minimal, and a urine culture was ordered but not performed. A presumptive diagnosis of acute pyelonephritis was made, and the patient was given ampicillin to take orally at home.

The white-cell count was 13,000 per cubic millimeter with 28 percent neutrophils, 68 percent band forms, 1 percent metamyelocytes, 1 percent lymphocytes, 1 percent monocytes, and 1 percent eosinophils. The hematocrit was 43.8 percent, and the platelet count was 170,000 per cubic millimeter. The urine had a specific gravity of 1.024 and contained 30 to 35 white cells per high-power field, one to two red cells per high-power field, and 1 protein and bilirubin. The serum sodium level was 132 mmol per liter, the potassium level was 4.7 mmol per liter, the chloride level was 95 mmol per liter, and the carbon dioxide content was 15.1 mmol per liter. The blood urea nitrogen level was 66 mg per deciliter (24 mmol per liter), and the creatinine level was 7.6 mg per deciliter (672 μmol per liter). The serum aspartate aminotransferase (SGOT) level was 30 U per liter (0.24 μmol · sec⁻¹ per liter), the total bilirubin level was 15 μmol per liter, and the creatinine phosphokinase level was 814 IU per liter (13 μmol · sec⁻¹ per liter). The prothrombin time was 14.2 seconds (control, 9.9 seconds), the partial thromboplastin time was 33 seconds (control, 25.5 seconds), and the fibrin-split products were greater than 40 μg per milliliter. The cerebrospinal fluid was normal. A stool smear contained zero to one neutrophil per high-power field.

The New England Journal of Medicine
Downloaded from nejm.org at CDC Public Health Library & Information Center on November 2, 2011. For personal use only. No other uses without permission.
From the NEJM Archive. Copyright © 2010 Massachusetts Medical Society. All rights reserved.
DESCRIPTION OF TSS

This patient had most of the features of TSS. The syndrome typically begins abruptly with fever, vomiting, diarrhea, and sometimes rigors. The temperature is frequently above 40°C, and the patient may have abdominal pain. Hypotension develops within 72 hours; the drop in blood pressure may occur abruptly. There is a diffuse, blanching, macular erythematous rash, which is often attributed to the flush of fever; it may also go unnoticed. The rash may later evolve into a more discrete macular exanthem, which has been attributed to a drug-related eruption.

There is variable but prominent mucous-membrane involvement, with pharyngeal, conjunctival, or vaginal hyperemia. Sore throat may be a presenting symptom or may occur later in the course of the illness. A vaginal discharge, though difficult to detect in menstruating women, may be observed. When tampons are found in place and removed by medical personnel, they are frequently noted to emit a foul odor. Diffuse myalgia is almost always present, and many women complain of exquisite skin or muscle tenderness when touched or moved.

Initial laboratory findings often reveal hyponatremia, abnormal urinary sediment, and evidence of renal and hepatic abnormalities. Most patients have leukocytosis with a strikingly high proportion of immature neutrophils. Most of the women have thrombocytopenia, although petechiae are uncommon. The creatine phosphokinase level is often elevated, occasionally to extremely high levels, and some patients have been noted to have myoglobinuria. Many patients have marked hypocalcemia, and a few actually have tetany.

Photophobia, arthralgias and joint effusions, hepatomegaly, hyperamylasemia, pericarditis, paresthesias, vasculitis, and the adult respiratory-distress syndrome, and central-nervous-system effects, including seizures, have also been reported.

Patients may require enormous volumes of fluid (e.g., 8 to 12 liters per day) and vasopressor therapy to maintain perfusion. Much of this fluid is sequestered outside the intravascular space, and many patients become edematous.

The majority of patients recover within seven to 10 days; desquamation occurs within one to two weeks, most prominently on the palms and soles but also on the face, trunk, and tongue. The skin may peel in large sheets, and the denuded fingertips may be more sensitive than usual. Several patients have also had hair and nail loss.

RESULTS

The mean age of cases and controls was 27 years. Twenty-nine (56 per cent) of the cases and 26 (50 per cent) of the controls were married.

The earliest onset of illness was in December 1976, and the latest was in June 1980. One woman became ill in 1976, one in 1977, two in 1978, 11 in 1979, and 37 in 1980. Cases were reported from 20 states and were widely distributed geographically. Clinical features are summarized in Table 2.

The mean duration from onset of the menstrual period to onset of the illness was 3.8 days (Fig. 1). The mean duration of menstruation (± S.D.) was 5.7 ± 1.0 days for cases and 5.2 ± 1.4 days for controls.

All 52 cases used tampons during the index period,
as compared with 44 (85 per cent) of 52 controls (P<0.02) (Table 3). The eight controls who did not use tampons used napkins or minipads. Seventeen cases (33 per cent) and 17 controls (39 per cent) used napkins or minipads or both in addition to tampons.

Because of the significant difference in tampon use between cases and controls, we attempted to identify additional risk factors in case-control pairs in which both the case and the control used tampons. Among such pairs, more cases than controls used tampons every day and night throughout the index menstrual period (P<0.05; odds ratio, 9.1) (Table 4). When tampon use throughout the index period was compared with intermittent use or no use, the difference between cases and controls was also significant (P<0.001) (Table 5). The odds ratio for this analysis was 16.1 (95 per cent confidence limits, 5.7 to 44.8).

Information supplied by tampon manufacturers revealed that before 1977, all tampon products were made of rayon or a blend of rayon and cotton. Since 1977, 44 per cent of tampon products, representing 65 per cent of the estimated market, have contained more absorbent synthetic materials, including polyacrylate fibers, carboxymethyl cellulose, high-absorbency rayon-cellulose, and polyester foam. There were no significant differences between cases and controls in brand of tampon used, absorbency of tampon used, use of deodorized tampons, or use of brands containing high-absorbency materials.

No differences were found between cases and controls in amount or duration of menstrual flow or in frequency of change of tampon. Women who used "super" tampons changed them as often as did women who used "regular" tampons. Women who became ill early in their menstrual cycle (by the fourth day) did not differ significantly from those who became ill later in the menstrual cycle (Day 5 or later) in brand of tampon, absorbency, or frequency of change.

Information on contraceptive use was provided by 49 cases and 49 controls. Significantly fewer cases (15 of 49, 31 per cent) than controls (23 of 49, 47 per cent) used contraceptives (P<0.05), but no one method of contraception accounted for this difference (Table 6). No significant differences were found between cases and controls in frequency of sexual intercourse or sexual intercourse during menstruation.

Data on recurrences were obtained for 49 cases (94 per cent); 44 of these women were considered to be at

![Figure 1. Day of Menstrual Period on Which Clinical Illness Began.](image)

Table 3. Tampon Use in Case-Control Pairs.*

<table>
<thead>
<tr>
<th>Controls</th>
<th>Cases</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>44</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NO</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*P<0.02
Table 4. Tampon Users With Continuous Tampon Use in Case-Control Pairs During Index Period.*

<table>
<thead>
<tr>
<th>Cases</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>16</td>
<td>2</td>
</tr>
</tbody>
</table>

*P<0.05

risk for recurrence, since the elapsed time from the initial episode of TSS to the time of questioning was at least one month. These data on recurrences were grouped into three categories (Table 7). Eleven of the 44 women considered to be at risk (25 per cent) had had at least one definite recurrence; three other women (7 per cent) had had a probable recurrence. The remaining 30 women at risk (68 per cent) had not had recurrences, although two of them had had myalgia and one or more gastrointestinal symptoms with a subsequent menstrual period, and one had had fever and myalgia. The median time from initial episode to first recurrence was two months (range, one to 41 months).

Of the 14 women with a definite or probable recurrence, five had had multiple recurrences. The maximum number of recurrences in cases to date is five. All single recurrences and all but one of the multiple recurrences occurred during a menstrual period. In five of the 14 women (36 per cent), the first episode of TSS was the most severe, as measured by physician visits or hospitalization. In six women (43 per cent), initial and subsequent episodes were of equal severity, and in three (21 per cent) the initial episode was not as severe as a subsequent one.

Data on feminine-deodorant sprays and frequency of douching were obtained from 37 cases (71 per cent). No cases used feminine deodorant sprays, and three (8 per cent) of the 37 douches during the week before the onset of TSS.

Twenty cases had vaginitis or a vaginal discharge noted in their charts. Of these, 12 had vaginal cultures performed; all 12 yielded Staph. aureus. Four additional patients who were not noted to have vaginitis or discharge also had vaginal cultures performed; all four yielded Staph. aureus. Thus, of the 16 vaginal cultures performed before the administration of antibiotic therapy, 16 (100 per cent) yielded Staph. aureus.

More than 100 additional cases of TSS were reported to the CDC in the month after completion of this study. Of these, 48 were classified as definite cases and had vaginal cultures performed before the administration of antibiotics. Forty-six (96 per cent) of the 48 cultures yielded Staph. aureus. In the study and nonstudy cases combined, 62 (97 per cent) of 64 vaginal cultures yielded Staph. aureus.

In contrast, in the control group, Staph. aureus was isolated from seven (10 per cent) of 71 vaginal cultures performed (P<0.001). Thirteen (18 per cent) of the 71 women were found to carry Staph. aureus in the anterior nares. Only one of the seven women with positive vaginal cultures had a positive anterior-nares culture. Seven (10 per cent) of the 71 women had Staph. aureus isolated from the vaginal introitus. Four of the seven women with positive vaginal cultures had positive introital cultures. In all instances in which Staph. aureus was isolated from more than one body site, the isolates had the same phage type and antimicrobial-sensitivity patterns.

Table 6. Types of Contraceptives Used by Cases and Controls.

<table>
<thead>
<tr>
<th>Type of Contraceptive</th>
<th>Cases *</th>
<th>Controls *</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>34 (69)</td>
<td>26 (53)</td>
</tr>
<tr>
<td>Oral</td>
<td>2 (4)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Intrauterine device</td>
<td>2 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>2 (4)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Foam or condom or both</td>
<td>3 (6)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Vaginal insert</td>
<td>0 (0)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>4 (7)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (4)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Figures in parentheses denote percentages.

Thirty-six Staph. aureus isolates from cases were forwarded to the CDC for phage typing and antimicrobial-sensitivity testing. Thirty-three (92 per cent) of these 36 were found to be resistant to penicillin and ampicillin and sensitive to 20 other antimicrobials tested. One isolate was sensitive to penicillin and ampicillin, one was intermediate in sensitivity to these two antibiotics, and one was resistant to erythromycin in addition to penicillin and ampicillin. In the control group, four of seven isolates (57 per cent) were resistant to penicillin and ampicillin, two were resistant to tetracycline as well as to penicillin and ampicillin, and one was resistant to clindamycin, lincomycin, tetracycline, and oxacillin in addition to penicillin and ampicillin. There was no characteristic phage type or group found among either the case or control isolates.

No tampons currently marketed in the United States are sterilized. Although Staph. epidermidis and bacillus species were recovered frequently, none of 264 unused tampons were found to harbor Staph. aureus.

**DISCUSSION**

TSS is a distinct clinical entity that is being recognized with increasing frequency. It is similar in some
respects to scarlet fever, Kawasaki’s disease, meningococemia, and Rocky Mountain spotted fever, but the composite picture of severe illness observed in retrospect is characteristic. Several recently reported cases of “adult Kawasaki’s disease” were probably cases of TSS.14-16

Although TSS was initially described as a disease of children and adolescents with an equal sex distribution,1 it is now apparent that TSS is much more common in women than in men. Moreover, it is strikingly associated with the menstrual period. Although cases of TSS may have occurred in previous years, its occurrence in menstruating women appears to be a relatively new phenomenon. Reports of cases that met our case definition, except for the fact that some had Staph. aureus isolated from blood cultures, appeared in the literature before publication of Todd’s report.17-20 With one possible exception, however, these cases did not occur in menstruating women. The possible exception was a woman who had vaginal blood loss associated with a septic abortion.19 We have received no reports of TSS in menstruating women before 1974, and we believe that the many recent reports of TSS represent more than just recognition or recall artifact.

Our first study suggests that tampon use, especially continuous use throughout the menstrual period, may be one factor that accounts for the increased risk in women. Tampon use by itself is not sufficient to cause TSS, because tampon use is extremely common and the incidence of the disease is low. Tampon manufacturers estimate on the basis of marketing data that 70 to 80 per cent of American women use tampons, whereas Davis has estimated that the incidence of TSS is 6.2 per 100,000 menstruating women per year, by extrapolation from surveillance data in Wisconsin.21 Clearly, some additional factor or factors must be necessary for the development of TSS.

The second study reported here strongly supports Todd’s hypothesis that Staph. aureus is the causative agent in TSS. Also in accord with this hypothesis are the findings that the two men who met our case definition had osteomyelitis and a focal abscess caused by Staph. aureus and that the woman in our study who had onset at a time other than during her menstrual period had a purulent wound infection that was not cultured but might have been caused by Staph. aureus.

Because all the blood cultures performed on patients reported here were negative for Staph. aureus, it is likely that the syndrome is produced, again as suggested by Todd, by a toxin elaborated by the organism.

If toxigenic Staph. aureus is responsible for TSS, the use of tampons might predispose persons to the disease by one of several mechanisms. A blood-soaked tampon at body temperature is a suitable culture medium for Staph. aureus and may also enhance toxin production. Constituent materials of certain tampons may stimulate or permit growth of Staph. aureus or provide a substrate that encourages toxin production. Absorption of the toxin may be facilitated by vaginal ulcerations, which have been observed in women who use tampons.22 Although it is possible that an inherently contaminated tampon introduces the organism, the occurrence of cases among users of all brands of tampons and the absence of positive cultures for Staph. aureus from a large number of unused tampons make this possibility unlikely. It is possible that the tampon transports the organism from the hands or perineum into the vagina, but this possibility has not been studied.

Only 31 per cent of the cases in this study used any birth-control method. This rate was considerably lower than the rate of 70 per cent among all women in this country.23 It is possible that contraceptive use may protect against the development of TSS. Specifically, oral contraceptives are associated with light menstrual flow24 and may decrease the risk of TSS if a heavily saturated tampon provides a better culture medium than does a lightly saturated tampon. However, there were no differences between cases and controls in the use of oral contraceptives or in their subjective evaluation of the volume of menstrual flow or the number of tampons used per day. Thus, we are unable to explain this finding at present.

In this study, the selection of controls from among the friends of the cases made it likely that our cases and controls would be highly concordant. This close matching adds further credence to the finding that tampon use is associated with TSS, but it may have obscured true differences in marital status, fecundity, choice of tampon brands, frequency of intercourse, intercourse during menstruation, and use of contraceptives. In addition, questioning cases and controls about menstrual periods at different times may have obscured differences in tampon brands used.

Aside from ascertainment bias, possible explanations for the recent increase in cases include the introduction of new tampon products, a change in constituent materials, and a change in the causative organism. In the past several years, synthetic “superabsorbent” materials have been incorporated into tampon products. Data from this study show no significant differences between cases and controls in the use of products containing these new materials, but further evaluation is in progress. We are also looking

Table 7. Recurrence Categories for Toxic-Shock Syndrome.

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Temperature ≥38.9°C</th>
<th>Rash</th>
<th>Vomiting or diarrhea</th>
<th>Myalgia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite recurrence</td>
<td>Desquamation and at least three of four major criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable recurrence</td>
<td>Desquamation and two of four major criteria or Three of four major criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No recurrence</td>
<td>Two major criteria or fewer; no desquamation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
for toxin production and genetically selective mutations in the Staph. aureus isolates from cases.

Because our data suggest that the use of tampons (especially continuous use throughout the menstrual period) is associated with the development of TSS in menstruating women, we offer the following recommendations.

Women who have not had TSS have a low risk of its development (6.2 cases per 100,000 menstruating women) and probably do not need to change their patterns of tampon use. However, if they want to reduce an already small risk, they might use tampons for only part of the day or night, or for only part of the menstrual period.

Women who have had TSS are at considerable risk for recurrences and should not use tampons at least until Staph. aureus has been eradicated from the vagina. The possibility that a toxigenic strain of Staph. aureus can be carried in the anterior nares or elsewhere and lead to reinfection of the vagina has not been examined and needs further assessment.

We are indebted to the many physicians across the country who reported cases to us, and in particular to Dr. Patricia DuBose for providing us with the information used in the case report; to Mr. Wesley Lee, Drs. Carl Tafeen, Hubert Harris, Spiro Galioussis, Steve Burkman, Hugh Anwyl, and Marshall Goldberg, Ms. Patty Knadler, Drs. Thomas Britton and Robert Kothenbeutal, Ms. P. J. Viles, Ms. Marilyn Epstein, Ms. Anita K. Highsmith, and Ms. Betty W. Holland for help with the second study; to Ms. Helen Kline and Ms. Burnese Harper for assistance in the preparation of the manuscript; and to Dr. John V. Bennett for guidance and supervision.

REFERENCES