

RISK FACTORS FOR STAPHYLOCOCCAL TOXIC-SHOCK SYNDROME

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Fifty-two cases of toxic-shock syndrome that occurred in January 1, 1976 through August 31, 1980, were reported to the Utah State Health Department between February 1 and August 31, 1980. The annual attack rate for Utah based on a six-month surveillance period was 14.4 per 100,000 women ages 12-49 years. All cases were in women who had onset of illness within two days of menses. Potential risk factors were investigated with a case-control study utilizing 29 women hospitalized with toxic-shock syndrome and 91 neighborhood female controls. Nine of the 29 (31%) women reported recurrences of similar illness. Use of tampons ($p = 0.012$) and use of a single brand of tampon—Rely—during the month of illness ($p < 0.005$, RR = 6.11) were associated with a significantly increased risk of acquiring toxic-shock syndrome. More controls were sexually active than women who had toxic-shock syndrome ($p < 0.05$, RR = 0.277). This epidemiologic investigation of toxic-shock syndrome in menstrual-age women has identified tampons generally and a single brand specifically as significant risk factors in acquiring toxic-shock syndrome.

retrospective studies; *Staphylococcus aureus*; tampons; toxic-shock syndrome

Toxic-shock syndrome was initially described as a clinical entity by Todd et al. (1) in 1978. The illness was described in seven children ages eight to 17 years, three of whom were males, and was characterized by high fever, headache, confusion, conjunctival hyperemia, a

scarlatiniform rash, subcutaneous edema, vomiting, watery diarrhea, oliguria, a propensity to acute renal failure, hepatic abnormalities, disseminated intravascular coagulation, and severe prolonged shock. During convalescence all survivors were reported to have fine desquamation of face, trunk, and extremities and peeling of palms and soles. Five patients, studied prospectively, grew *Staphylococcus aureus* related to phage-group I from mucosal or sequestered sites, but not from blood.

Prior to the report by Todd et al., others (2-4) had described similar clinical findings in association with a variety of localized *S. aureus* infections. In January 1980, Schrock, in a letter to infectious disease physicians in the United States and in a published letter to the editor (5),

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described similar clinical findings in three women and speculated about the possible associations of this syndrome with menstruation. In early February 1980, physicians in Utah began reporting cases of toxic-shock syndrome in young menstruating women, and at about the same time numerous similar reports from other states were made to the Centers for Disease Control (6). In May 1980, when it became increasingly apparent that menstruation and staphylococcal infection of the vagina might be associated with toxic-shock syndrome, we initiated a case-control study to evaluate systematically risk factors for toxic shock in menstruating women.

METHODS

Case Definition. Information describing a patient's illness was obtained by patient interview, review of medical records, and physician interviews. Patients included in this investigation had illness that conformed to the case definition proposed by the Centers for Disease Control (7) and which began within two days of menstrual flow.

Case finding and selection. Cases came to our attention through physician reporting and patient self-reporting. In February 1980, a Utah State Health Department Communicable Disease Newsletter (8) describing the illness was mailed to physicians, public health officials, and institutions delivering health care. In addition, toxic-shock syndrome received statewide attention from the media. Only patients who could be contacted and for whom hospital records were available were used in the case-control study. All women gave informed consent before participation in the study. None of the patients included in the case-control study died. The study was concluded in the summer of 1980 before the possible association of Rely brand tampons was publicly announced.

Control selection. Female controls, cho-

sen from the same neighborhood as the patient, had to have lived in the neighborhood at the time of the patient's illness. They were selected for the presence of menstrual periods, could not have been pregnant at the time of the patient's illness, and could not have had an illness consistent with toxic-shock syndrome. Controls were randomly chosen from the neighborhood by the method of Blake et al. (9). One control was selected per household and four controls per case were sought. If controls could not be obtained by systematically covering 28 houses, no further controls were sought.

Study design. All women were interviewed in person. When individuals less than age 18 were interviewed they were asked to answer the questionnaire in writing while the guardian followed on a second copy. The forms completed by underage individuals were examined only by the interviewer.

Questionnaires were administered by one of three interviewers. (A copy of the questionnaire may be obtained from the authors on request.) All interviewers received instructions on administering the questionnaire, and early administrations of the questionnaire were observed by one of us (MWK). Each interviewer attempted to ask questions of each subject in precisely the same manner. Additionally, in each set, the same person interviewed both the patient and the control subjects. Women who had had toxic-shock syndrome were asked to answer questions with reference to the month of their illness. Controls were asked to answer the questions with reference to the month that illness occurred in their associated patient. Patients and controls provided the following demographic information: age, marital status, occupation, estimated yearly income, number of children, number of people living in the home, and number of rooms in the residence. Risk factors evaluated pertained to subject's medical, menstrual and sexual history.

When tampon brand was evaluated as a risk factor, only patients and their control(s) who used a single brand during the menstrual period associated with illness (single exclusive brand user) were included in the analysis.

Statistical analysis. Attack rates were calculated using only Utah cases occurring from initiation of surveillance, February 1, 1980, until July 31, 1980. Denominator data were derived from 1977 projections (10) for the number of females age 12–49 years in Utah for 1980.

Data were analyzed using two methods. Breslow et al. (11) described a technique to estimate multiple relative-risk functions in matched case-control studies. This model permits simultaneous analysis of multiple discrete and continuous risk factors as well as interactions among risk factors and between risk factors and matching variables. The second method of analysis, described by Pike and Morrow (12) was used to evaluate a factor which was an all or none variable (tampon use). The analysis was performed by the Statistical Services Branch, Bacterial Disease Division, Centers for Disease Control.

RESULTS

Fifty-two cases of toxic-shock syndrome were reported to the Utah State Health Department officials from February 1, 1980 to August 31, 1980, with onset as early as January 1, 1976; 47 cases lived in Utah and five in Idaho. Twenty-nine patients met our criteria for inclusion in this study. Approximately two-thirds of the study cases occurred during intensive surveillance, February 1 through August 31, 1980. Twenty-eight Utah cases were reported from February 1, 1980 to July 31, 1980. Using this figure the annual attack rate per 100,000 is 14.4 for women age 12–49 years, 17.3 for women age 12–29 years, and 10.2 for women age 30–49.

Ninety-one controls were matched with

the 29 cases. Ten study cases were questioned within one month of illness, 17 cases within three months, 21 of 29 cases within six months, and 28 of 29 within 18 months. Controls were generally interviewed on the same day or within several days of the cases' interview. No statistically significant differences were found between the demographic characteristics of cases and controls (table 1).

Seven demographic characteristics and 37 risk factors were evaluated in 120 subjects. Women who had had toxic-shock syndrome answered all demographic and risk factor questions. Controls answered more than 99 per cent of the questions. The proportion of patients and controls answering "unknown" or "don't know" was less than 5 per cent and the two groups did not differ significantly in this regard. All eligible controls agreed to participate in the study.

Two significant differences were found when cases were compared to controls with respect to risk factors reflecting medical history, pregnancy, menstrual history, use of tampons or pads, use of contraception, bathing and hygienic habits, and sexual activity (table 2). More women in the control group (78 per cent) than study group (55 per cent) acknowledged sexual activity of any kind during the month prior to illness ($p < 0.05$, $RR = 0.277$, 95 per cent confidence limits = 0.074–1.046 using a matched linear logistic regression model).

Tampons were used more commonly by cases than by controls. While tampons were used by all patients, they were used by only 70 of 91 (77 per cent) controls ($p = 0.012$). Five major trade name brands were named by cases and controls (table 3). Fifteen of 24 cases (63 per cent) and 14 of 59 controls (24 per cent) who were single brand users, used Rely brand tampons (table 3). Use of Rely brand tampons was associated with a significantly increased risk of acquiring toxic-shock syndrome ($p < 0.005$, $RR = 6.11$, 95 per cent

TABLE 1
*Demographic characteristics of cases of toxic-shock syndrome, and controls, Utah, 1980**

Demographic characteristics	Cases (%)	Controls (%)
No.	29	91
Mean age (years)	25.6 ± 8.5†	29.1 ± 9.4
Married (no.)	20 (69)	65 (71)
Employed	8 (28)	23 (26)
Medically employed	3 (10)	2 (2)
Children:		
Mean no.	1.7 ± 1.6	2.25 ± 1.96
0	9 (31)	22 (24)
1-3	17 (59)	52 (57)
4	3 (10)	17 (19)
Persons living in house (mean)	4.9 ± 2.1	4.7 ± 1.8
Mean no. of rooms in home	6.0 ± 2.6	5.6 ± 2.5
Mean no. of persons per room	0.83 ± 0.36	0.80 ± 0.26
Income:		
<\$15,000	11 (38)	27 (29)
≥\$15,000	17 (59)	58 (64)
Unknown	1 (3)	6 (7)

* No statistically significant differences were found between cases and controls.

† Mean ± standard deviation.

confidence limits = 1.55 to 24.2, using a matched linear logistic regression model). Other brands were not used more frequently by cases than controls.

When only single-brand-using cases occurring after February 1, 1980 and their controls were evaluated, 11 of 17 cases (65 per cent) as compared to 11 of 43 controls (26 per cent) used Rely brand tampons exclusively ($p < 0.025$, RR = 5.29).

Risk factors and demographic factors were evaluated for association with Rely brand tampon usage by cross tabular analysis to see if confounding occurred. Six variables appeared to be potentially related to Rely brand tampon usage. Five of the six were then shown not to be associated with toxic shock syndrome, and therefore they could not have confounded the association between Rely brand tampon usage and the disease. Sexual activity, as noted before, did associate with toxic-shock; however, when it was evaluated in and out of the model with Rely brand tampon usage it had the same protective effect and thus did not confound the association between Rely and toxic-shock syndrome.

DISCUSSION

This epidemiologic investigation of toxic-shock syndrome in menstrual-age women has identified tampons generally and a single brand specifically as significant risk factors in acquiring toxic-shock syndrome. We also found that being sexually active was associated with a lower risk of toxic-shock syndrome. Use of tampons has been recognized as a risk factor by others (13, 14). However, the finding of an association of toxic-shock syndrome with a specific brand was not reported in either of these studies. Our results are similar to those reported by the Centers for Disease Control (7) in their study which found that Rely brand tampon use was associated with a significantly increased risk of developing toxic-shock syndrome. We and others (14) have found no association between toxic-shock syndrome and sexual intercourse during menses and no association between use of feminine deodorant sprays, suppositories, or douches the week before onset of illness and toxic-shock syndrome. In addition, we evaluated the use of these products during menses and found no association with

TABLE 2
Risk factors for toxic-shock syndrome—Utah, 1980

	Cases: Positive responders/ no. responding (%)	Controls: Positive responders/ no. responding (%)
Medical history		
Allergies	16/29 (55)	36/77 (47)
Dieted in month prior to illness	8/29 (28)	17/70 (24)
Weight loss of ≥ 5 kg with diet	7/28 (25)	8/71 (11)
Antibiotics in 2 weeks prior to illness	3/29 (10)	7/68 (10)
Ever had cold sores with menses	6/29 (20)	12/90 (13)
Ever had history of vaginal herpes infection	2/29 (7)	2/90 (2)
Preceding vaginal infection in past year	8/29 (28)	19/88 (22)
Menstrual and pregnancy history		
Pregnant in year before illness	9/29 (31)	27/90 (30)
Missed period in year before illness	12/29 (41)	37/89 (42)
Presently having periods	28/29 (97)	86/91 (95)
Using tampons during month of illness (or cases' illness)	29/29 (100)	70/91 (77)*
Contraception		
Uses contraception of any kind	14/29 (48)	35/91 (38)
Type used		
Pill	1/29 (3)	10/91 (11)
Intrauterine device	5/29 (17)	6/91 (7)
Bathing habits		
Uses tub	12/27 (44)	26/82 (32)
Uses shower	15/27 (56)	56/82 (68)
Sauna in previous year	8/29 (28)	16/87 (18)
Jacuzzi in previous year	2/29 (7)	19/87 (22)
Uses sauna or jacuzzi during menses	5/28 (18)	11/83 (13)
Hygienic habits		
Personal-private laundry	26/29 (90)	80/85 (94)
Uses douches	8/29 (28)	30/90 (33)
Douches during menses	0/28 (0)	3/85 (4)
Uses vaginal deodorant suppositories	0/29 (0)	1/91 (1)
Uses feminine spray deodorants	2/29 (7)	2/91 (2)
Uses vaginal sprays during menses	2/28 (7)	2/78 (3)
Sexual activity		
Sexually active	16/29 (55)	70/90 (78)†
Sexual intercourse during menses	10/29 (34)	26/86 (30)
More than one consort in year before illness	1/29 (3)	7/88 (8)
Sexual partner had genitourinary infection in year before illness	0/28 (0)	7/88 (8)
Other		
Family member/roommate with an illness in preceding 2 weeks	2/29 (7)	8/69 (12)
Synthetic/nylon insert in underwear	7/29 (24)	22/91 (24)

* Statistically significant, $p = 0.012$, chi square for matched case-controls with all or none variable.

† Statistically significant, $p < 0.05$, RR = 0.277, 95% confidence limits = 0.074–1.046 using the matched linear logistic regression model.

toxic-shock syndrome. Our results differ from others (13, 14) in that cases practiced contraception no less frequently than controls. Also, our finding that sexual activity during the month before ill-

ness was more common in controls than toxic-shock syndrome patients was not described by these investigators.

Differences between our findings and those of others could be due to differences

TABLE 3
*Tampon brand use of single-brand users,
 toxic-shock cases vs. controls, Utah, 1980*

Brand	Cases: n = 24 (%)	Controls: n = 59 (%)
Rely	15 (63)	14 (24)*
Playtex	2 (8)	7 (12)
Tampax	5 (21)	18 (30)
Kotex	2 (8)	17 (29)
OB	0 (0)	3 (5)

* RR = 6.11, $p < 0.005$, 95% confidence limits = 1.55 to 24.2 using the matched linear logistic regression model.

in selection of controls. Shands et al. (14) used "best friend" controls, while our design called for use of neighborhood controls selected by a predetermined standard process. Potentially similar demographic features, hygienic and sexual practices of best friends might hinder recognition of important risk factors.

Accuracy of recall of information asked for in the study is a potential problem since all women were not interviewed during or immediately after their illness. One case occurred in January 1976, and was not reported and interviewed until July 1980. However, the majority of patients were interviewed within four months of their illness. An additional potential recall bias relates to the possibility that patients who were more seriously ill during the time period in question may have selectively recalled certain details that were not accurately remembered by controls who did not experience a similar critical event at the time. We do not think that recall bias affected our results since when we controlled for recall bias by analyzing only single-brand-using cases and controls from February 1, 1980 on, the association between toxic-shock syndrome and use of Rely brand tampons persisted. Controls were generally interviewed within one week of the case interview so that any recall bias existed in the same direction for cases and controls. In addition, all data were collected before the release of information which suggested an increased risk of acquiring toxic-

shock syndrome associated with use of Rely brand tampons.

Our calculations of the incidence of toxic-shock syndrome in Utah resulted in higher figures than have been reported by others (13). We suspect that the variability in numbers of reported cases of this syndrome throughout the United States (15) is primarily a reflection of varying intensity of surveillance; however, different exposure to some risk factors such as specific tampon types or prevalence of "toxic" strains of staphylococci may also explain these differences.

The role of Rely tampons in the pathogenesis of toxic-shock syndrome is unclear. While this study and one other (7) have shown an increased risk of developing toxic-shock syndrome with the use of Rely tampons, 30-40 per cent of reported patients with toxic-shock syndrome were exclusive users of other tampon brands (7).

However, it appears that the syndrome is an illness seen predominantly in tampon-using menstruating women. Previous reports (13, 14) and studies at this institution (V. Noble, personal communication, 1981) implicate *S. aureus* in the development of toxic-shock syndrome. Cases of toxic-shock syndrome have certainly been recognized with increased frequency in recent years. Our finding of an association between toxic-shock syndrome and a particular type of recently marketed tampon argues for an important role for tampon characteristics in the pathogenesis of this illness.

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