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Toxic Shock Syndrome

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *Despite the scrutiny of astute physicians over many years, new clinical entities continue to be recognized. Examples can be found in every discipline of medicine and include legionnaires' disease, pseudomembranous colitis, glucagonoma, eosinophilic fasciitis (Shulman's syndrome), idiopathic hypertrophic subaortic stenosis and primary hyperaldosteronism. Obviously, there is still scope for inquiring physicians to make a contribution to medical progress. Among the newly identified syndromes is the toxic shock syndrome, which has recently received much attention in medical publications and the popular press. For this Grand Rounds we have asked Dr. Donald Ganem to review this syndrome.*

DR. GANEM:† The first report identifying toxic shock syndrome (TSS) as a discrete nosologic entity was that of Todd and his colleagues in 1978.[1] They described a severe acute illness characterized by fever, profound hypotension and a scarlatiniform rash with subsequent desquamation in a group of seven children between 8 and 17 years of age. In many of the affected children, oliguria and azotemia developed, and there was laboratory evidence of disseminated intravascular coagulation. Most also had pronounced mucosal hyperemia, abdominal discomfort and watery diarrhea; one child died. Although blood cultures were negative in all cases, five of the patients had either colonization (upper respiratory or vaginal) or overt infection (of soft tissue or pleural space) with *Staphylococcus aureus*. Because of the similarity of some aspects of the clinical syndrome to known exotoxin-induced diseases (such as scarlet fever and staphylococcal scalded-skin syndrome), and because of the frequent recovery of *S aureus*, the authors postulated that the disease was a result of systemic absorption of a locally produced staphylococcal exotoxin, and so named the disease toxic shock syndrome. In support of this hypothesis, they reported that all five of their *S aureus* isolates elaborated a heat-labile epidermal toxin that could be demonstrated by inoculation of neonatal mice. Although subsequent studies have shown that this particular toxin is not unique to TSS-related strains (see below), most experts continue to accept the pathogenesis as proposed by Todd and co-workers,[1] and hence the syndrome still bears its original name.

The first clear description of TSS was thus not in menstruating females, the group that has since come to be so closely associated with the disease, but in young children (of both sexes). In a sense, this was fortunate because the presence of overt staphylococcal infection in some of these children made obvious the causative relationship of the

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ABBREVIATIONS USED IN TEXT
CDC = Centers for Disease Control
TSS = toxic shock syndrome

disease to *S aureus*. Such a relationship might have been less obvious had one merely to rely on the association between the clinical syndrome and the recovery of *S aureus* from the complex microbial environment of the vagina.

It is unlikely that TSS is an entirely new disease, although there are sound reasons to believe that its incidence has greatly increased in recent years. In retrospect, several published cases[2-4] of so-called staphylococcal scarlet fever may in fact have represented TSS. More recent reports of Kawasaki disease occurring in adults[5-7] are almost surely bona fide examples of TSS. Nevertheless, it remains true that before 1979, reports of TSS-like illnesses were extremely rare. However, beginning in late 1979, physicians in several state health departments[8] began receiving increasing numbers of reports of a severe illness occurring in young women, again characterized by high fever, abdominal complaints, myalgias, diffuse macular erythema and (often) refractory hypotension. Virtually all women (95 percent) had onset of symptoms during menses.[8] These reports were forwarded to the Centers for Disease Control (CDC), which has since maintained a national surveillance system. Figure 1 illustrates the major rise in the number of TSS cases reported to the CDC between 1979 and 1980.[9] It is unlikely that this increase was due solely to failure of physicians to recognize or report the condition in the past. Analysis of the reports by region indicated that cases were appearing throughout the country, without major concentration in any one locale. Similar cases were also reported in Canada,[10] Western Europe and Scandinavia.[9] In the ensuing

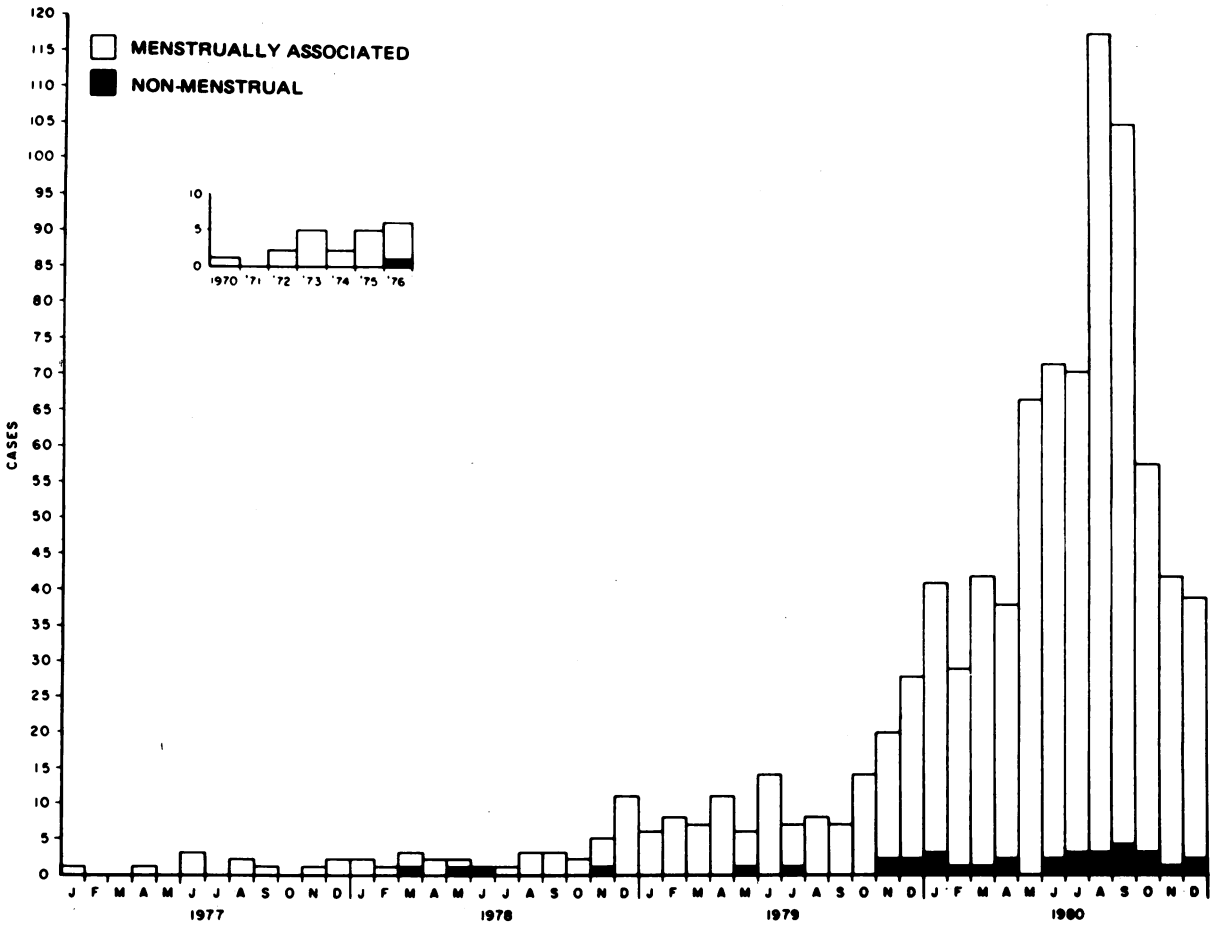

Figure 1.—Reported cases of toxic shock syndrome, by date of onset, in the United States, January 1970 through December 1980. The case definition requires four major criteria (fever, hypotension, rash and desquamation), involvement of three organ systems and absence of evidence for other causes. (Reprinted with permission from Centers for Disease Control and Morbidity Mortality Weekly Rep 30:25, Jan 30, 1981.)

sections we shall consider the clinical and epidemiologic features of TSS, with particular emphasis on their relation to its cause and pathogenesis.

Clinical Presentations

In early 1980, investigators at the CDC[11-13] and the Wisconsin State Health Department[14] initiated case-control studies of TSS to characterize better its clinical course and to attempt to identify risk factors for its acquisition. Central to this undertaking was the establishment of a rigorous case definition, to be certain that all included cases were indeed examples of the same illness. The criteria for inclusion in the CDC study[9] are given in Table 1 and are virtually identical to those used by other investigators.[14,15] In addition to the findings of fever, scarlatiniform rash and desquamation, the CDC required the presence of hypotension and involvement of at least three extracutaneous organ systems for inclusion.

These entry criteria ensure uniformity of disease and, thus, make possible meaningful assessment of risk factors. However, they also preselect a group of severely affected patients and, thus, may depict only one end of a spectrum of clinical presentations. Indeed, as experience with this entity grows, less severe forms are being recognized with increasing frequency.[16] It is important to realize that, for precisely this reason, these criteria were not intended to be diagnostic commandments for use in daily practice. Nevertheless, they do allow description of many of the varied clinical manifestations of this remarkable syndrome. Most obvious is the rash, which is macular, erythematous, blanches on pressure and is nonpruritic. Characteristically, desquamation, which is most pronounced over the palms and soles, occurs during convalescence. In this regard, the lesions are like those of Kawasaki disease and, of course, of scarlet fever. Rarely, hair and nail loss have been reported.

Gastrointestinal involvement is often pronounced, with diffuse abdominal pain, vomiting and (especially) diarrhea being commonly reported.[13-15,17] The latter is usually watery, without blood or fecal leukocytes being evident. Prominent mucous membrane involvement is frequent, with conjunctival, pharyngeal and vaginal hyperemia the usual findings. Patients often complain of pronounced musculoskeletal pains, most typically myalgias. These can involve the muscles of the abdominal wall, giving rise to abdominal tenderness. Perhaps most important of all the extracutaneous findings, however, is renal involvement, which can present in many forms. At one extreme is acute renal failure, with azotemia and oliguria, often occurring in combination with profound hypotension. Even in the absence of hypotension, however, other abnormalities, including pyuria and hematuria, can be observed; these are *not* related to direct infection of the urinary tract by the staphylococci. Neurologically, transient encephalopathic changes characterized by altered or depressed mentation, disproportionate to the degree of fever or hypotension, are often observed. Again, examination of cerebrospinal fluid documents that these symptoms are not the result of direct bacterial invasion of the central nervous system.[12]

Laboratory abnormalities are numerous but generally nonspecific. Leukocytosis and moderate thrombocytopenia are common, as are mildly elevated serum transaminase levels. Azotemia, hematuria and pyuria have already been mentioned above. Two other laboratory findings are of note. About 40 percent of severely ill patients

TABLE 1.—*Toxic Shock Syndrome Case Definition**

Fever (temperature ≥38.9°C [102°F]).

Rash (diffuse macular erythroderma).

Desquamation, one to two weeks after onset of illness, particularly of palms and soles.

Hypotension (systolic blood pressure ≤90 mm of mercury for adults or <5th percentile by age for children 16 years of age or younger, or orthostatic syncope).

Involvement of three or more of the following organ systems:

- Gastrointestinal (vomiting or diarrhea at onset of illness).
- Muscular (severe myalgia or creatine phosphokinase level ≥2×ULN).
- Mucous membrane (vaginal, oropharyngeal or conjunctival hyperemia).
- Renal (blood urea nitrogen or creatinine levels ≥2× ULN, or ≥5 leukocytes per high-power field—in the absence of a urinary tract infection).
- Hepatic (total bilirubin, serum asparate aminotransferase or serum alanine aminotransferase levels >2× ULN).
- Hematologic (platelets ≤100,000 per cu mm).
- Central nervous system (disorientation or alterations in consciousness without focal neurological signs when fever and hypotension are absent).

Negative results on the following tests, if obtained:

- Blood, throat or cerebrospinal fluid cultures.
- Serological tests for Rocky Mountain spotted fever, leptospirosis or measles.

ULN = upper limits of normal

*Adapted from Morbidity Mortality Weekly Rep.[12,p442]

will have serum creatine phosphokinase levels more than twice the normal range; a few patients with very high levels have also had myoglobinuria.[13] In addition, hypocalcemia has also been observed, with a few patients becoming symptomatic and requiring replacement therapy.[13] The mechanism underlying this phenomenon is not known.

In its milder forms, TSS may closely resemble Kawasaki disease, an illness that generally occurs in young children and is characterized by fever, macular rash with subsequent desquamation, musculoskeletal complaints and mucosal abnormalities similar to those outlined above. Indeed, as previously noted, several adult cases initially felt to represent Kawasaki disease are now classified as examples of TSS. However, the syndromes are distinguishable on clinical and epidemiologic grounds. Hypotension and renal failure are not characteristics of Kawasaki disease, and pyuria, when present, is of urethral rather than renal origin. Analysis of urine aspirated from the bladders of these children shows no abnormalities.[18] Conversely, lymphadenopathy—a major criterion for the diagnosis of Kawasaki disease—is usually absent in TSS. Lastly, the epidemiologic features of the diseases are often helpful in separating the two. Kawasaki disease occurs almost exclusively in young children, most cases ocurring within the first four years of life.[18] While TSS may occur in children,[1] Kawasaki disease rarely, if ever, affects adults.

The other diagnosis most commonly entertained in cases of TSS is scarlet fever. In addition to the rash, many of the other associated physical findings of scarlet fever, including pharyngitis, circumoral pallor and even the classic "strawberry tongue" can be seen in TSS.[15] Again, the typical epidemiologic setting and the absence of pharyngeal group A streptococci are the most useful differential features. When headache, disorientation and thrombocytopenia dominate the clinical features, the condition can resemble meningococcemia or even Rocky Mountain spotted fever; where abdominal pain and hypotension predominate, intraabdominal infection with Gram-negative sepsis can be suggested.[13] Usually, however, the characteristic rash allows ready differentiation from these other entities.

Epidemiologic Features

The striking association of TSS with menses (Figure 1) immediately suggested that factors related to menstruation might be responsible for the recent wave of cases of this illness. Having established strict criteria for diagnosis, several groups[13,14] began examining their cases for the presence of risk factors associated with the development of TSS. Age-matched controls were selected from either acquantances of the patients[11-13] or from women attending gynecologic clinics.[14] Detailed questions were asked concerning tampon use and other hygienic practices during menses, sexual habits, contraception, previous menstrual problems, past vaginal infection and many other variables. The only major differences detected between cases and controls involved tampon use and contraceptive practices. Although 75 percent to 80 percent of control women used tampons with periods, more than 97 percent of patients were tampon users.[13,14] Among women using only one brand of tampon, one large study[12] reported a significant association between the use of Rely tampons and the development of TSS. Because of these data, this brand was withdrawn from the market in September 1980. However, it is to be emphasized that almost 30 percent of TSS cases in the same study occurred in users of tampon brands other than Rely. Among tampon users, more TSS patients than controls used tampons continuously throughout their entire period.[13] No differences were found between groups in the absorbency of the tampons used, or the volume or duration of menstrual flow; further, no relationship was noted between marital status or sexual practices and the risk of TSS development.[13,14] The only other factor that differentiated cases from controls was the finding that contraceptive use was significantly less frequent in patients than in controls. However, no one method of contraception could be shown to account for the difference, and the reasons for this finding—independently noted in two separate studies[13,14]—remain obscure at present. Speculations that contraceptive use is somehow protective against the development of TSS are premature.

Etiology and Pathogenesis

Greatly aided by the previous association of TSS in children with local *S aureus* infection,[1] evidence implicating staphylococci in the menses-related form was rapidly forthcoming. In the large CDC study,[13] *S aureus* was isolated from vaginal cultures in 97 percent of TSS cases, as compared with 10 percent of controls (cultured during a normal menstrual period). Though most of the

early isolates belonged to phage group I,[1] more extensive surveys show no unique phage group among responsible strains.[13,14] Likewise, the antibiotic susceptibilities of these staphylococci show no unusual features; most produce β-lactamase and are susceptible to nafcillin, cephalosporins and vancomycin.[6,13,15]

Many groups are now actively investigating the available isolates from TSS cases, searching for the putative toxin or other markers that might differentiate these strains from conventional *S aureus* isolates. Cohen and Falkow[19] have described two polypeptides (with molecular weights of 30,000 and 33,000, respectively) present in TSS strains that specifically react with antisera from patients convalescing from TSS. It has been suggested that such proteins could be subunits of the putative toxin of TSS, or simply antigenic markers associated with such strains. However, they were detected in only 78 percent of TSS isolates; they were also demonstrated in 25 percent of control *S aureus* strains.[19] More work is needed to define fully the relationship, if any, of these antigens to TSS.

Very recently, two groups[20,21] have reported the identification of apparently novel staphylococcal toxins from TSS isolates. Bergdoll and co-workers[20] have described a toxin, designated enterotoxin F, that was produced by 94 percent of TSS-related *S aureus;* only 5 percent of non-TSS-strains elaborated this material. This low-molecular weight, acid-stable protein was detected by virtue of its enterotoxigenic properties following intragastric injection in monkeys. Direct laboratory demonstration of a TSS-like illness induced by enterotoxin F has not yet been reported, however, and its role in the pathogenesis of this disease remains to be defined.

Schlievert and associates[21] have isolated from the growth medium of TSS strains a protein of molecular weight 22,000, which they term exotoxin C. This material was detected by virtue of its pyrogenicity in rabbits and its ability to enhance the susceptibility of inoculated animals to lethal shock caused by *Salmonella* endotoxin. All 28 TSS-related strains examined were positive for exotoxin C production; 16 percent of non-TSS strains (including several vaginal isolates from healthy women with no history of TSS) also produced this activity. No published data are available at present concerning the enterotoxigenic properties of exotoxin C, and the relationship of this protein to enterotoxin F requires clarification. Because both proteins are immunogenic,[20,21] serological as well as functional assays can, in principle, be developed to study this question. Again, as for enterotoxin F, inoculation of experimental animals with exotoxin C does not reproduce all of the clinical features of TSS.[21] Thus, its contribution to the pathogenesis of this syndrome is likewise a subject requiring further investigation.

It is not unexpected that occasional isolates from normal persons can be found to elaborate this candidate toxin or toxins in vitro; the existence of such asymptomatic carriers in no way refutes the possibility that the proposed toxin or toxins cause or contribute to the symptoms of TSS. It does, however, suggest that other bacterial or host factors are also important in its pathogenesis. Such factors could, for example, affect the ability of the organism to colonize a particular site (such as the vagina) or modulate the amount of toxin produced, absorbed from, or inactivated at such a site. The complete enumeration of all such factors may prove to be a formidable undertaking. Nonetheless, the identification of these novel toxins appears to be a promising first step in this direction.

Thus, although *S aureus* is almost certainly causally associated with TSS, clear delineation of the pathogenesis of this disease is still lacking. In view of this, one can speculate about the role tampons play in the development of TSS. Direct introduction of the organism into the vagina on the surface of the tampon has been excluded by the failure to recover *S aureus* from all brands of tampon cultured to date.[12,13] Tampon use has been shown to produce vaginal mucosal drying and even microulcerations[22]; and, though the latter usually resolve rapidly, they could be involved in allowing establishment of infection or enhancing absorption of a putative toxin. Unfortunately, such hypotheses, while attractive, remain untestable at present.

Prognosis and Treatment

The overall fatality rate from TSS has been reported to be approximately 8 percent.[9] It is likely that this figure will decline as awareness of this entity among physicians grows and milder forms of the disease are recognized.[16]

One of the striking features of TSS, at least in its menses-related form, is the propensity of patients to have recurrences. In two large series,[13,14] approximately 30 percent of women recovering from an episode of TSS experienced another epi-

sode with a subsequent period. The median time to recurrence was two months following the initial episode, though recurrences up to 41 months later have been documented.[13] Multiple recurrences were not infrequent. Usually the severity of the recurrent illness is less than that of the initial episode, but exceptions to this rule are frequent.

The proper management of a case of TSS includes, of course, careful physical examination, with particular attention to localized foci of infection (especially of skin and soft tissues). Meticulous pelvic examination in females is mandatory; tampons, if present, should be removed and vaginal cultures obtained. Cultures of blood and of any evident soft tissue foci of infections are likewise essential. The role of nasal, axillary and pharyngeal cultures[15] (in the absence of local signs of infection) has not been adequately assessed. The usual supportive measures for hypotension and renal insufficiency should be promptly undertaken where these are present.

No prospective study on antibiotic use in treating TSS has yet appeared, but retrospective examination of cases already reported[13,14] has yielded helpful insights into this question. Because of the retrospective nature of the available data, it is not possible to ascertain whether the administration of appropriate antibiotic drugs ameliorates an overt acute episode of TSS. However, it is clear that patients who received β-lactamase-resistant antibiotic drugs had significantly fewer recurrences than patients who did not. In one study,[14] only 1 of 16 women so treated experienced a recurrence within the first three months, while 9 of 13 untreated women had recurrences during this interval.

Another important reason to include antibiotic therapy at the earliest suspicion of TSS is the occasional presence of *S aureus* bacteremia.[15] While this is uncommon, bacteremic patients cannot be reliably differentiated from nonbacteremic cases on clinical grounds alone. Thus, at present, early parenteral therapy with β-lactamase-resistant antibiotic agents is strongly recommended.

Women who have had TSS are advised[13] not to return to tampon use for several months following the episode, if ever. Although this issue has not been carefully studied, it is prudent to verify by repeat culture that *S aureus* has been eradicated from the vagina before resumption of tampon use can be considered. Should such women opt to resume the use of tampons, using them intermittently (for example, for only part of the day or only part of the period) is advised. Obviously, such recommendations may be revised when more is known about the biology of TSS-related staphylococci and the natural history of their carriage in the female reproductive tract.

REFERENCES

1. Todd J, Fishaut M, Kapral F, et al: Toxic-shock syndrome associated with phage-group-I staphylococci. Lancet 2:1116-1118, Nov 25, 1978

2. Aranow H, Wood W: Staphylococcic infection simulating scarlet fever. JAMA 119:1491-1495, 1942

3. McCloskey R: Scarlet fever and necrotizing fasciitis caused by coagulase-positive hemolytic *Staphylococcus aureus,* phage type 85. Ann Intern Med 78:85-87, 1973

4. Durmet W, Schallibaum E: Scarlet fever-like illness due to staphylococcal infection. Lancet 2:1227-1229, 1960

5. Everett E: Mucocutaneous lymph node syndrome in adults. JAMA 242:542-543, 1979

6. Milgram K, Palmer E, Slovin S, et al: Kawasaki's disease in a healthy young adult. Ann Intern Med 92:467-470, 1980

7. Schlossberg D, Kandra J, Kreiser J: Possible Kawasaki's disease in a 20-year-old woman. Arch Dermatol 115:1435-1436, 1979

8. Toxic-shock syndrome—United States. Morbidity Mortality Weekly Rep 29:229-230, 1980

9. Toxic-shock syndrome—United States. Morbidity Mortality Weekly Rep 30:25-30, 1980

10. Toxic-shock syndrome—Canada. Morbidity Mortality Weekly Rep 30:36, 1981

11. Follow-up on toxic-shock syndrome, United States. Morbidity Mortality Weekly Rep 29:297-299, 1980

12. Follow-up on toxic-shock syndrome. Morbidity Mortality Weekly Rep 29:441-445, Sep 1980

13. Shands K, Schmid G, Dan B, et al: Toxic-shock syndrome in menstruating women—Association with tampon use and *Staphylococcus aureus* and clinical features in 52 cases. N Engl J Med 303:1436-1442, 1980

14. Davis J, Chesney P, Wand P, et al: Toxic shock syndrome—Epidemiologic features, recurrence, risk factors and prevention. N Engl J Med 303:1429-1435, 1980

15. Tofte R, Williams W: Toxic-shock syndrome—Clinical and laboratory features in 15 patients. Ann Intern Med 94:149-156, 1981

16. Siklos P, Carmichael D, Rubenstein D: Toxic-shock syndrome (Letter). N Engl J Med 304:1039, 1981

17. Fisher R, Goodpasture H, Peteriea J, et al: Toxic-shock syndrome in menstruating women. Ann Intern Med 94:156-163, 1981

18. Melish M: Kawasaki's syndrome—A new infectious disease? J Infect Dis 143:317-324, 1981

19. Cohen M, Falkow S: Protein antigens from *S. aureus* strains associated with toxic-shock syndrome. Science 211:842-844, 1981

20. Bergdoll M, Crass B, Reiser R, et al: A new staphylococcal enterotoxin, enterotoxin F, associated with toxic-shock syndrome *Staphylococcus aureus* isolates. Lancet 1:1017-1021, 1981

21. Schlievert P, Shands K, Dan B, et al: Identification and characterization of an exotoxin from *Staphylococcus aureus* associated with toxic-shock syndrome. J Infect Dis 143:509-516, 1981

22. Friedrich E, Siegesmund K: Tampon-associated vaginal ulcerations. Obstet Gynecol 55:149-156, 1980