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Division of Health Sciences Policy

Division of Health Promotion and Disease Prevention

INSTITUTE OF MEDICINE

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PREFACE

Although a relatively rare and recently described entity, the toxic shock syndrome has become a household word during the past two years. Few diseases have received such intense media coverage and there is little likelihood that public interest in this problem will wane in the near future. More than 1600 cases were reported nationally through April 1982. The case fatality rate for cases reported with onset in 1981 was about 3 percent. Although there are over 200 articles, letters, and other reports dealing with the toxic shock syndrome in the literature, fundamental knowledge concerning pathogenesis, epidemiology, management, and related areas is inadequate.

This report reviews our present knowledge concerning many of the clinical, epidemiological, pathological, microbiological, and other aspects of the toxic shock syndrome. Furthermore, we have attempted to point out where gaps in information and data exist. A portion of this report recommends where, in the opinion of the committee, research should be directed.

This committee received help and input from many members of the academic community, industry, and government. However, the staff of the Institute of Medicine, in particular Drs. Barbara Mandula and Enriqueta C. Bond, have been extremely helpful throughout the development of this report. We are very grateful to both Drs. Mandula and Bond for their continuing support and efforts.

In addition, I wish to acknowledge my appreciation to the members of the committee. Despite a wide variety of interests, busy schedules and responsibilities, meetings were held, deadlines were met and consensus achieved, always in an atmosphere of collegiality and openness.

During the tenure of this ten-member committee, two of our members died. Dr. Charles H. Rammelkamp, Jr., was our able chairman until December 1981, and Dr. Lowell A. Glasgow was an active participant in all of our activities until February 1982. With their passing, American medicine lost two of its leaders and we on the committee lost two of our ablest members.

Sheldon M. Wolff, M.D.
May 1982

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SUMMARY

Historical Background

The term toxic shock syndrome (TSS) was introduced in 1978 to describe an acute illness whose signs and symptoms include fever, rash, hypotension, involvement of various organ systems, and subsequent peeling of skin, especially on the palms and soles. A strong association has been shown between the occurrence of TSS and the presence of Staphylococcus aureus, a bacterial species known to cause various human illnesses.

Toxic shock syndrome came to public attention in the spring and summer of 1980 when it was reported preferentially to affect young menstruating women using tampons, some of whom died. In September, epidemiologic data indicated that Rely brand tampons were more likely to be associated with TSS than were other tampon brands. On September 22, 1980, the manufacturer of Rely tampons voluntarily withdrew them from the market. However, TSS cases continued to occur among users of other tampons. Also, up to 16 percent of reported cases were in children, males, and females who were not menstruating.

In early 1981 several public agencies and industry groups sought a critical and objective evaluation of available evidence related to TSS and suggestions for further research. The Institute of Medicine (IOM) agreed to undertake a project whose major goals were to:

- critically review and analyze available data related to TSS
- assess the feasibility of obtaining additional information
- stimulate research and suggest research strategies related to TSS.

Both government and industry provided support, with funding coming from the Centers for Disease Control (CDC), Food and Drug Administration (FDA), National Institute of Child Health and Human Development (NICHD), National Institute of Allergy and Infectious Diseases (NIAID), Johnson & Johnson, Inc., and the Procter & Gamble Company.

This report provides the findings and recommendations of the IOM Committee on Toxic Shock Syndrome. The committee addressed various questions related to TSS, including clinical features; patterns of occurrence in the United States, as determined primarily by surveil-

lance activities; risk factors associated with the illness, as determined primarily from case-control studies; the possible role of tampons; characteristics of the vagina as a local environment for S. aureus and other microorganisms; and the possible role of microbiological organisms and their toxins in the illness. Besides reviewing available data, the committee identified inadequacies in the data, and recommended studies to improve knowledge about TSS.

As part of its activities, the study committee organized a Conference on Toxic Shock Syndrome in November 1981. Among approximately 110 participants were more than 35 investigators who delivered papers, as well as representatives of industry, government agencies, and other interested groups. Appendix A contains the agenda and list of participants. Conference papers are available as Part 2 of the June 1982 issue of the Annals of Internal Medicine.

Case Definition and Clinical Features

Until a reliable laboratory marker for TSS is found, our understanding of the syndrome will be based primarily on what presumably are the most severe cases--those that meet the Centers for Disease Control (CDC) criteria for a "definite" case. Briefly, those criteria are specific findings of fever, rash, hypotension, involvement of three or more organ systems, and desquamation. A "probable" case lacks one of the criteria. Implicit to these criteria is the assumption that there is no evidence for other conditions that may be confused with TSS. Unless otherwise noted, data in this report refer to definite cases.

Various clinical and pathologic aspects of TSS need further study. Reported sequelae include abnormalities of renal function, cyanotic extremities, amenorrhea, and neuromuscular and neuropsychiatric changes. However, rigorous studies of sequelae have not been carried out. Recurrences have been noted in about 30 percent of menstrual TSS cases and have not been reported in nonmenstrual cases. The risk of recurrence has been reported to be decreased by cessation of tampon use and by treatment with beta-lactamase-resistant antibiotics, which are useful against bacteria that are resistant to penicillin.

Fatal TSS cases show pathologic changes similar to those found in shock from other causes. In addition, autopsy findings in TSS have noted characteristic ulceration of vaginal and other mucosal surfaces, and often hemophagocytosis. However, these findings were from fewer than 25 autopsies, which often were incomplete. Clinical and pathologic findings are consistent with a toxin-mediated illness, because neither bacteremia nor local extension of infection (e.g., peritonitis) is generally found.

Patterns of Occurrence of TSS Cases

Cases of toxic shock syndrome continue to occur. As of April 9, 1982, the CDC had reports of a total of 1660 cases of TSS in the United States, 92 percent of which were associated with menstruation; approximately 98 percent of the menstrual cases occurred among tampon users. Among the total cases with adequate data, 102 had onset between 1960 and 1978, 162 in 1979, 867 in 1980, and 492 in 1981.* A total of 88 deaths are known to have occurred, 15 of them before 1979, 13 in 1979, 44 in 1980, and 15 in 1981. The case fatality rate for cases reported with onset in 1981 was about 3 percent. Among the non-menstrual cases, about half have been in patients with skin lesions, postpartum infections, and surgical wound infections. Postpartum cases that occurred two to eight weeks after delivery were usually associated with tampon use. Women of ages 15 to 19 have accounted for approximately one-third of the menstrual cases. About 150 cases, most of them associated with tampons, have been reported from approximately a dozen countries worldwide.

The incidence rate† for TSS during any given time period is difficult to determine because the degree of reporting is markedly influenced by such factors as physician awareness and extent of publicity. Although the case criteria developed by the CDC appear reasonably adequate to separate TSS from diseases with some of the same signs and symptoms, the lack of a specific diagnostic test hinders reporting. In considering the national incidence rate of TSS before 1980, many people accept the view that the rate increased markedly in approximately 1979 among menstruating women who used tampons. Another possibility is that the illness was present in the past and occurred at about its current rate, but was not recognized. A suitable review of hospital records would probably resolve this question.

Uncertainty also remains about the true incidence rate in the United States during 1980 and 1981, and whether a marked decrease occurred after September 1980 when Rely brand tampons were no longer marketed. The CDC received reports of about 50 cases per month during 1981, a considerable decrease from the peak of 135 cases reported with onset in August 1980. However, Minnesota carried out continuous active surveillance for TSS from January 1980 to June 1981, and the number of cases reported per month remained relatively constant during that time,

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*The totals change frequently, as CDC receives reports of new cases and of those diagnosed retrospectively.

†The incidence rate is defined as the number of new cases of disease occurring in a population during a specified time period divided by the population at risk. For this report, the numerator is based on the reported number of TSS cases. The denominator is assumed to remain constant over the time periods of concern. There are difficulties in estimating an incidence rate, particularly in determining the numerator, where there is no continuous active community-wide surveillance.

with an annual incidence rate of about 2.3/100,000 population. The national rate based on cases reported to CDC for 1980 was about 0.38/100,000 population. For comparison, the 1980 United States incidence rate of legionellosis was 0.19/100,000 population, of rubella was 1.7/100,000, and of civilian primary and secondary syphilis was 12/100,000. Among menstruating women in Minnesota, estimated by surveys as the number of women who actually menstruated in the past three months, the TSS rate has been 8.9 menstrual cases per 100,000 menstruating women; age-specific incidence rates for women of ages less than 15 years, 15 to 24, and 25 years and over were respectively 2.3, 13.7, and 6.6/100,000 menstruating women.

If the Minnesota findings reflected the actual occurrence in the rest of the country, about 5000 cases of TSS would have been expected nationally during 1981, whereas 492 cases were reported by mid-April 1982. Many local factors, such as prevalence of the causative organism or susceptibility of the local population, in addition to active surveillance might explain the higher incidence rate in Minnesota compared with the rest of the country, but it seems likely that underreporting occurred nationally. Active surveillance in several parts of the country could provide an estimate of the extent of under- or overreporting.

Fewer than 50 TSS cases among non-whites and Hispanics have been reported to CDC. Non-whites and Hispanics account for less than 2 percent of menstrual cases and about 10 percent of nonmenstrual cases. A combination of factors related to individual susceptibility and habits, tampon use patterns, and recognition and reporting of TSS, may account for this observed difference in rates of menstrual cases among whites as compared with non-whites and Hispanics. Data on tampon use among non-whites are sparse, but they suggest that less common tampon use among blacks as compared with whites does not account for most of the observed difference in incidence rates for menstrual cases between blacks and whites. (Blacks are approximately 12 percent of the national population and account for less than 1 percent of menstrual TSS cases reported.)

Risk Factors

Infection or colonization with particular strains of S. aureus has been clearly associated with cases of TSS. These results are consistent with a causal role for the organisms, but such a causal role has not been proved.

Results of case-control studies of menstrual TSS cases indicate that use of tampons during menstruation is a risk factor for TSS. Four case-control studies showed a statistically increased risk for development of TSS with use of Rely tampons versus other brands, but cases have been reported with all major tampon brands and styles, and no decrease in incidence rate among menstruating women was seen in Minnesota after Rely was removed from the market. The Tri-State case-control study, the most detailed of the six case-control studies conducted to seek TSS risk factors for the menstrual cases, found that

use of high absorbency tampons increased the risk of developing TSS more than did use of lower absorbency tampons. There has not yet been a study that sought to replicate this finding. Further epidemiologic studies also are needed to determine whether intermittent rather than continuous tampon use during a menstrual period lessens risk.

Factors that have been found not to be associated with occurrence of TSS include perceived quantity of menstrual flow, douching, sexual activity during menstruation, and frequency of tampon changing. Continuous tampon use during menstruation (as opposed to intermittent use), a history of vaginal infection, and absence of any contraceptive use have been reported as significant risk factors in at least one study; however, in at least one other study these same factors were found not to be associated with an increased risk of acquiring TSS.

Tampons and TSS

Patterns of tampon use apparently changed after September 1980 among the approximately 50 million menstruating women in the United States. The total number of tampons sold in 1981 was about 4.5 billion, down about 10 percent from the 1979 and 1980 levels. Tampon use dropped about 25 percent in the few months following Rely's withdrawal from the market and by the end of 1981 was still about 10 percent below pre-September 1980 levels. Whereas 70 percent of menstruating women used tampons alone or used tampons plus napkins before September 1980, a year later the figure was about 60 percent. Furthermore, compared with a year earlier, many women seemed to have changed from only using tampons to using tampons and napkins. The few data available suggest that adolescents have decreased their tampon use slightly since September 1980.

The mechanism by which tampons increase a user's risk of getting TSS is not known. It has not been demonstrated that tampons are contaminated at the time of manufacture with TSS-associated S. aureus, and tampons apparently do not act by allowing menstrual fluid to reflux into the fallopian tubes. While tampons have been reported to induce vaginal lesions, these tampon-induced lesions appear to be different from the ulcerations characteristic of fatal TSS.

Association of TSS with Microorganisms and Toxins

Strains of S. aureus detected in TSS patients generally are phage group I or are untypeable, and are resistant to penicillin, cadmium, and arsenate. These TSS-associated S. aureus strains are apparently also found in nasal samples of healthy individuals and in the vaginal samples of up to 6 percent of normal women, so the mere presence of the organism is not sufficient to produce the syndrome. The possibility that other associated bacteria or factors are required for expression of the syndrome has not been adequately explored.

Two toxins, which may be the same or related proteins, have been found in more than 90 percent of TSS-associated strains tested

in vitro. These toxins, called pyrogenic exotoxin C (PEC) and staphylococcal enterotoxin F (SEF), have not been proved to have a role in producing the signs and symptoms associated with TSS, and have not been demonstrated in serum, vaginal secretions, menstrual fluid, or tissues from TSS cases. In preliminary tests, sera from TSS patients generally show significantly lower antibody titers to SEF than do sera from healthy persons. Attempts to develop an animal model for the syndrome are in progress.

Major Research Needs

- Because fewer than 500 cases of TSS have been reported for 1981 throughout the United States, multi-institutional collaborative research efforts should be undertaken to facilitate more effective study of many of the unanswered clinical and etiologic questions related to TSS. Aspects requiring particular attention concern evaluation of different treatment modalities, study of variability in clinical signs and symptoms and of host factors, and determination of types and numbers of anaerobic and aerobic organisms present in cases before antibiotic therapy is begun. In addition, patients should be followed to determine long-term sequelae associated with the syndrome, risk of recurrence, and patterns of vaginal flora.
- To more clearly delineate patterns of occurrence, active surveillance should be undertaken in several areas of the United States. Accompanying the active surveillance should be a retrospective review of hospital charts to determine incidence rates before the beginning of the active surveillance. The areas selected for study should include some with sizeable populations of non-whites and Hispanics.
- Additional studies concerning tampons as risk factors for TSS are needed. A comprehensive case-control study should be developed that would address additional tampon and non-tampon related risk factors, and would include microbiological and immunologic evaluation of cases and controls. Microbiological studies of sexual partners of cases could be included.
- Ways that tampons modify the vaginal environment need to be more intensively studied, with the same women followed through several menstrual cycles during which they are randomly assigned to use tampons or napkins. Interest in TSS has revealed that much remains to be learned about vaginal microbiology and physiology, especially during menstruation and during adolescence. Studies on the clinical status of the vagina, including microscopic, biochemical, and immunological studies of vaginal fluid, should be included.
- *In vitro* studies of the growth characteristics and patterns of toxin production of TSS-associated *S. aureus* should be continued, including the possible influence of tampons and tampon components.
- Further study of the prevalence of serum and local antibodies to SEF and PEC, both in normal persons and in TSS patients, may provide additional evidence concerning their role in TSS. Other factors related to host susceptibility to TSS-associated organisms

also need to be addressed. A suitable animal model should be developed.

• The susceptibility of adolescents should be considered in any studies undertaken to improve understanding of TSS. Adolescents may differ in relevant ways from adult women in vaginal physiology, aspects of behavior, and development of immunity to illness.

Prevention

Available data suggest steps that can lessen the chance of acquiring TSS, even though its etiology is not well understood. Among total cases reported to CDC with onset in 1981, 80 to 85 percent were associated with tampon use; it is likely that the number of cases would be markedly reduced in the absence of tampon use. Apparently fewer than one of 6,500 tampon users develops menstrual TSS in a year.* Other factors in addition to tampon use determine individual susceptibility. Although the syndrome is relatively rare, the consequences of TSS can be severe. Among the 492 cases with onset in 1981, 15 patients died.

In view of the relative rarity but possible severe consequences of TSS, we believe that information should be made available so that women can make informed decisions about tampon use. However, certain recommendations appear prudent at present. Women who have had TSS or who are postpartum should be advised not to use tampons. In addition, women 15 to 24 years of age should be made aware that they are apparently at a higher risk than older women. Furthermore, the use of high absorbency tampons should be minimized, one study having shown a positive association between tampon fluid capacity and risk of TSS. As research continues, it may be possible to design tampons that do not enhance the user's risk of acquiring TSS, or to identify those persons who are susceptible to the illness so that they can take specific preventive measures.

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*Using Minnesota's annual incidence rate of 8.9 menstrual cases per 100,000 menstruating women, we take 15/100,000 as an upper estimate of the rate among tampon users. The rate will vary with age and presence of other risk factors.

1

INTRODUCTION

Historical Background

Toxic shock syndrome (TSS) became widely known in the summer of 1980 as a potentially fatal illness suddenly striking previously healthy young women, especially adolescents, during menstruation.[1] Neither the illness nor the term "toxic shock syndrome" was really new. The term was introduced in 1978 by James Todd and his associates to characterize an illness whose signs and symptoms include fever, rash, lowered blood pressure, and subsequent peeling of skin on the palms and soles.[2] Cases that were probably the same syndrome can be traced back to 1927, and some cases of other atypical diseases, such as adult Kawasaki disease or staphylococcal scarlet fever, may have been TSS.[3-7]

Cases of TSS were first reported to the Centers for Disease Control (CDC) in early 1980, and the number of reported cases increased during subsequent months.[8-10] The first national newspaper accounts associating the illness with menstruation appeared in the late spring of 1980.[11,12] By early summer, the syndrome was associated with tampons,[9] a product that had received little public scrutiny in the past. During July and August 1980 increasing numbers of cases were reported to CDC, and there was no indication of a slowing in the reports. In September, results of two epidemiologic case-control studies indicated that there was statistically greater use of Rely brand tampons among women with the syndrome than among matched control women who had not had the syndrome.[10,13-15] On September 22, 1980, Procter & Gamble Company voluntarily withdrew its Rely brand tampons from the market.[16]

The number of cases reported by month of onset eventually reached a peak of 135 for August 1980.[17,18] The syndrome did not go away after Rely tampons were withdrawn from the market. Cases were associated with other tampon brands; about one-third of the cases in the two case-control studies had used other than Rely tampons.[10,14,19-21] After September 1980, the number of cases reported to CDC by month of onset decreased and leveled off at about 50.[18] How much of this decrease was due to differences in completeness of reporting and how much was real may never be resolved.

Women who became ill during menstruation have accounted for most of the reported cases. However, depending on the source of reports

and the time period considered, up to 16 percent of cases were reported in children, men, and women who were not menstruating.[18,22-24] The case fatality rate among reported cases was 5 percent in 1980 and 3 percent in 1981.[18,25] Further work also confirmed Todd's initial observation that Staphylococcus aureus is associated with the syndrome, although its etiologic role, if any, is unknown. However, recent studies also indicate that up to 6 percent of normal women of menstrual age may harbor the organism associated with the TSS cases. (See Appendix C.) If this organism is a cause of the syndrome, it is of major importance to understand why reported menstrual cases of the syndrome are so rare (probably fewer than 10/100,000 menstruating women per year).[26]

Emergence of TSS as a well-publicized health problem has focused attention on menstruation and products used by women to absorb the flow. Before September 1980, approximately 70 percent of menstruating women in the United States used tampons at least part of the time during their menstrual periods,[9,27] but surprisingly little information was available in early 1980 to the public about tampon composition and patterns of use. It also has become evident that much needs to be learned about normal vaginal physiology and flora, especially during menstruation. Toxic shock syndrome has encouraged a welter of research activity in the public and private sectors to improve information on these and related topics.

The Institute's Study

At a time of much publicity and public confusion about tampons and TSS, several groups from the public and private sectors asked the Institute of Medicine (IOM) to critically assess information related to TSS and to identify promising areas for future research. Major questions that existed in early 1981--and largely still exist--include the following:

- Etiology What are the causes of this syndrome and why is it only being recognized now?
- Clinical aspects What pathological processes and sequelae are associated with the syndrome, and what treatments and preventive measures are most effective?
- Epidemiology How complete is the case reporting and why are there apparent large variations in incidence rates among the states, and among different population groups? What risk factors are associated with the syndrome? How does the United States experience compare with that of other countries?
- Tampons Why are tampons overwhelmingly associated with the reported cases?
- Vaginal flora Why is the vagina, especially during menstruation, apparently a focal site for colonization with organisms associated with TSS? How is vaginal colonization by these strains related to TSS?

• Microbiology What are the characteristics and interactions of the organism or organisms involved and the toxins they produce, and how do they exert their effect? What studies need to be done to identify a causative agent?

• Host factors and susceptibility What other factors, such as variability in immune response, are associated with the syndrome? In particular, are there special risk factors for adolescents, who account for about one-third of cases?

To provide an objective and scientifically rigorous evaluation, the IOM selected committee members for the project who were not directly involved in TSS research, but who had the diverse expertise necessary to review the work being done. Major goals of the project were to:

a) critically review and analyze available data;
b) assess the feasibility of obtaining additional information;
c) stimulate research and suggest research strategies related to TSS.

In preparing this report, the IOM committee has not addressed policy and regulatory questions.

As a primary way of gathering information, the committee held a three-day conference at which researchers in the field of TSS and related areas presented papers and discussed their findings. The conferees included representatives of tampon manufacturers, federal agencies, public health officials, consumer groups, and academic researchers. The conference's emphasis on the unanswered questions and work in progress provided a current and broad base on which the IOM committee developed its research agenda. Appendix A contains the conference agenda and list of attendees.

Committee members recognized that the conference could serve an additional valuable function if the papers prepared for it were published in a single, widely available volume. By November 1981, the TSS technical literature consisted of more than 200 articles, scattered through many journals and newsletters with no one source providing an overview. To provide a central information source, the IOM and the Annals of Internal Medicine arranged to publish the conference papers as Part 2 of the June 1982 issue of the Annals.

The IOM arranged funding for this study from both public and private sources: the Centers for Disease Control, the Food and Drug Administration, the National Institute of Allergy and Infectious Diseases, the National Institute of Child Health and Human Development, the Procter & Gamble Company, and Johnson & Johnson, Inc. Separately, International Playtex Corporation, Kimberly-Clark Corporation, Personal Products Company (a division of Johnson & Johnson, Inc.), the Procter & Gamble Company, and Tampax, Inc., contributed to publication of the conference papers.

This report critically reviews research related to TSS. Study of this syndrome began intensively only in 1980, and knowledge about it is likely to change over short periods of time. This report refers

extensively to the published literature and to the papers prepared for the IOM conference on TSS. Unpublished data made available to the IOM committee also are cited as appropriate. The report begins with a description of the clinical features of TSS and then goes on to discuss surveillance and epidemiologic findings. The possible role of tampons, the vaginal environment, and toxins found in TSS-associated organisms are then addressed. The last chapter summarizes major findings of the committee and highlights research needs. A glossary (Appendix E) defines technical terms.

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2

CLINICAL AND PATHOLOGIC FEATURES OF TOXIC SHOCK SYNDROME

Case Definition

Until a reliable laboratory marker for toxic shock syndrome is found, the clinical definition for the syndrome presumably will remain descriptive. Table 2-1 contains the criteria originally used to define a case, and a footnote indicates the modifications introduced in 1981.[1,2] The original criteria were developed in 1980 by epidemiologists at the Centers for Disease Control (CDC) in consultation with outside researchers.

The original criteria for a "definite" case included fever, rash, hypotension, involvement of at least three organ systems, and desquamation one to two weeks after the onset of illness. If tests for bacteria in blood, throat, or cerebrospinal fluid were done, they had to be negative. More recently, orthostatic dizziness is accepted as evidence of hypotension, and patients with Staphylococcus aureus bacteremia can be included as cases. A "probable" case lacks one of the above criteria, except that desquamation is not a criterion in fatal cases. Implicit in these criteria is the assumption that there is no evidence to support an alternative diagnosis.

Restrictive criteria were intended to minimize confusion of TSS with other diseases whose signs and symptoms overlap. However, it is likely that toxic shock syndrome manifests itself in a variety of ways and appears in mild as well as severe forms. Current understanding of the syndrome is based on cases meeting the criteria in Table 2-1, which are presumably the more severe cases of the illness. With increasing numbers of case reports, a variety of additional clinical manifestations, such as a secondary maculopapular rash occurring one to two weeks after onset, are occasionally reported, but not with sufficient frequency to be part of the case criteria.[3,4]

The relationship of TSS to a variety of other diseases that have some of the same signs and symptoms must await a better diagnostic method. TSS shares clinical features with infection caused by group A streptococci (scarlet fever), with other diseases associated with exotoxin-producing S. aureus (toxic epidermal necrosis, staphylococcal scalded skin syndrome), and with endotoxin-related syndromes caused by gram negative bacilli (gram negative shock).[5-8] Endotoxin shock is characterized clinically by hypotension, fever (usually) or hypo-

TABLE 2-1. Criteria for Defining a Case of Toxic Shock Syndrome*

1. Fever (temperature $\geq$ 38.9 C (102 F).
2. Rash (diffuse macular erythroderma).
3. Desquamation, 1-2 weeks after onset of illness, particularly of palms and soles.
4. Hypotension (systolic blood pressure $\leq$ 90 mm Hg for adults or $<$ 5th percentile by age for children $<$ 16 years of age, or orthostatic syncope).
5. Involvement of three or more of the following organ systems:
   A. Gastrointestinal (vomiting or diarrhea at onset of illness).
   B. Muscular (severe myalgia or creatine phosphokinase level GE2 X ULN[a]).
   C. Mucous membrane (vaginal, oropharyngeal, or conjunctival hyperemia).
   D. Renal (BUN[b] or Cr[c] $\geq$ 2 X ULN or $\geq$ 5 white blood cells per high-power field--in the absence of a urinary tract infection).
   E. Hepatic (total bilirubin, SGOT[d] or SGPT[e] $\geq$ 2 X ULN).
   F. Hematologic (platelets $\leq$ 100,000/mm^3).
   G. Central nervous system (disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent).
6. Negative results on the following tests, if obtained:
   A. Blood, throat, or cerebrospinal fluid cultures.
   B. Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles.

[a] Twice upper limits of normal for laboratory
[b] Blood urea nitrogen level
[c] Creatinine level
[d] Serum glutamic oxaloacetic transaminase level
[e] Serum glutamic pyruvic transaminase level

From: Centers for Disease Control. Follow-up on toxic shock syndrome. Morbid Mortal Weekly Rep 29:441-5, 1980

*The above indicate the original case definition. These criteria were modified in the summer of 1981 so that orthostatic dizziness is accepted as evidence of hypotension, and patients with S. aureus bacteremia are included as cases if they otherwise meet the case definition.

A case is "definite" if it meets all the criteria, and "probable" if it is missing one of them. (Desquamation is unnecessary in fatal cases.)

thermia (rarely), rapid pulse and rapid respiration rate, lethargy, mental confusion, and sometimes kidney failure. A broad range of other diseases and illnesses that must be considered in the differential diagnosis of TSS include Kawasaki disease (mucocutaneous lymph node syndrome), Rocky Mountain spotted fever, leptospirosis, measles and other diseases caused by exanthem-producing viruses, and drug reactions.[9,10]

The diagnosis of patients who fulfill some, but not all, of the CDC case criteria for TSS is a difficult issue. Physicians and public

health authorities who screen reports can attempt to use further clinical, laboratory, and pathological examinations to rule out diseases that may mimic TSS. For a syndrome, in which no confirmatory laboratory test is available, the risk of diagnostic errors is greater in probable cases and may be especially high in mild cases.

Desquamation of the soles and palms during convalescence is one of the most distinctive signs of TSS, setting it aside from most other infectious diseases (except scarlet fever). In cases labeled "probable" because desquamation was not documented, present evidence suggests the diagnosis should be somewhat suspect. Among 304 probable cases with report forms available at CDC, the missing criteria were as follows: desquamation 117; hypotension 102; multisystem involvement 40; fever 23; rash 22.[11] Because desquamation may occur after the patient leaves the hospital, some probable cases likely could be reclassified as definite if an attempt were made to document desquamation.

The acceptance of orthostatic dizziness as evidence of hypotension enhances the possibility of including under the TSS rubric a variety of febrile, rash-associated diseases in which dizziness may occur, notably scarlet fever. Culture results (positive for coagulase-positive staphylococci; negative for group A streptococci) are not required for classifying a case as either definite or probable. If a suitable diagnostic test becomes available and can be performed on stored samples, the extent of misdiagnosis could be determined retrospectively. In addition, a wider variety of cases could be diagnosed during the initial illness.

A major challenge is the development of an objective, reproducible, sensitive, and accurate diagnostic test for the syndrome. Until such time it would seem advisable to adhere to the existing CDC criteria in classifying toxic shock syndrome cases, at least for epidemiologic analysis and other studies. Otherwise, patients with other diseases may be inadvertently reported and studied as TSS cases. However, physicians need to be aware that TSS cases are likely to exhibit a spectrum of signs and symptoms of varying severity, so that they can appropriately treat patients who show many features of TSS and in whom other causes seem to be reasonably excluded.

Comparison of Menstrual and Nonmenstrual Cases*

In various studies, up to 16 percent of TSS cases reported were not associated with menstruation, but were usually associated with a localized S. aureus infection.[12-15] Of 104 definite and 26 probable nonmenstrual cases reported to CDC by October 1981, 29 were in patients with cutaneous or subcutaneous nonsurgical infections, 26 were

*In this report, cases of TSS are definite cases unless otherwise indicated. However, some of this section discusses definite and probable cases.

associated with childbirth or abortion, and 17 were in patients with surgical wound infections. Typical signs of infection usually were not present in the surgical wound cases.[13] Postpartum women are a group known to have a relatively high prevalence of vaginal colonization with S. aureus.[13,16] Among the postpartum patients, onset occurred either within three days of delivery or more than two weeks after delivery; among those for whom tampon use information was available, 10 of 11 cases with onset two to eight weeks after delivery were associated with tampon use.[13] When cases involving postpartum and vaginal infections were excluded, the nonmenstrual cases were fairly evenly divided among males and females.[13] In Minnesota, which has carried out continuous active surveillance, of 19 definite nonmenstrual cases, four were male, three were postpartum, ten had vaginal colonization with S. aureus, and two other females had wound infections.[15]

The relatively small numbers of nonmenstrual cases reported to CDC present difficulty in analyzing the demography of these cases. However, nonmenstrual cases reported to CDC show a somewhat different age and race specificity than do menstrual cases. According to the CDC, among 154 definite nonmenstrual cases of known age reported by April 1982, 60 to 70 percent were between 10 and 29 years old, as compared with 80 percent in that age range for menstrual cases. Fifty-five cases were male. The ages for these nonmenstrual cases ranged from 1 to 75 years. Where race and ethnic background were known, non-whites and Hispanics accounted for about 10 percent of nonmenstrual cases and about 2 percent of menstrual cases.

The nonmenstrual cases, although relatively few in number, can provide important clues to the clinical and epidemiologic spectrum and immunology of toxic shock syndrome. The case definition is the same for menstrual and nonmenstrual cases, and the isolates of S. aureus from nonmenstrual cases appear similar to those associated with the menstrual cases.[14,17,18] The nonmenstrual cases show that initiation of TSS does not necessarily require the milieu of the vagina during menstruation, a tampon, or other local vaginal factors, although the vaginal area may be an especially susceptible environment.[13,15,16]

Pathology

Careful definition of the histologic changes in the multiple organs that are clinically involved in TSS is limited by the small amount of autopsy material studied.[19-22] Autopsy findings have been reported in fewer than 25 fatal cases, and in these the examination of tissues has often been incomplete. There is considerable overlap of the pathology observed in fatal TSS cases and fatalities from other septic causes associated with shock, including endotoxin and exotoxin bacteremic shock associated with gram negative and gram positive organisms. However, certain histologic findings at autopsy in TSS cases may be characteristic of the syndrome, in particular typical vaginal ulcerations due to separation of the mucosal epithelium at the basement membrane. Ulceration of other mucosal surfaces, particularly esophagus, mouth, and bladder mucosa, were common findings.[19,20]

The characteristic lesion found in staphylococcal scalded skin syndrome occurs above the basement membrane in the stratum granulosum,[6] and may thus be distinguished from the desquamation found in TSS.

Other characteristic autopsy findings include hemophagocytosis (ingestion of red blood cells by mononuclear cells), signs of adult respiratory distress syndrome, fatty metamorphosis of the liver, pulmonary, pancreatic, and cerebral edema, and occasionally focal myocardial damage. All are consistent with shock and pathology caused by bacterial toxins.[7,19-22] In menstrual cases, the lack of reports of peritonitis and the usual failure to recover S. aureus from blood or to demonstrate these bacteria in tissue sections is consistent with a non-invasive toxin-mediated illness.

When carefully evaluated in menstrual cases, vaginal pathology has been pronounced, with extensive mucosal ulcers and desquamation of vaginal epithelium. Definitive evidence relating tampons to these vaginal lesions does not exist at present. The characteristic vaginal pathology in TSS has been observed in a menstruating TSS patient who used only sanitary napkins, thus indicating that the TSS vaginal lesion is apparently not exclusively related to tampon use.[20] Furthermore, these TSS-associated lesions appear different from those apparently caused by tampons.[20,23]

Studies of the clinical course, pathology, epidemiology, and microbiology of toxic shock syndrome cases are consistent with a toxin-mediated syndrome. A better understanding of the pathophysiology of this illness should be possible when the toxin(s) are purified and their effects studied in a suitable animal model. More detailing of TSS pathology, including gross descriptions, histology, and ultrastructure electron microscope studies, should be done on human samples, including biopsies when available. Because autopsy material is scarce, banking of specimens and collaborative studies offer further opportunities for research.

Treatment

The life-threatening events associated with TSS have generated intense interest in therapeutic measures. The case fatality rate for reported definite cases was approximately 5 percent in 1980 and about 3 percent in 1981.[12] When death occurs in TSS cases, it is usually caused by irreversible hypotension, renal failure, or adult respiratory distress syndrome.[12,13,19,20]

Because TSS is a severe illness of relatively low frequency, controlled clinical evaluations of treatment methods have not been done and current treatment recommendations are based on a combination of testimonial evidence, logic, and speculation. General measures that have gained wide acceptance include vigorous volume support and vasopressors to treat hypotension, correction of electrolyte disorders and hypocalcemia, and correction of acid-base abnormalities.[24-27] The role of high dose glucocorticoids is unclear, but current data do not indicate proved benefit.[27]

Specific treatment with systemic beta-lactamase-resistant antibiotics,* which are effective against bacteria that can inactivate penicillin, is generally recommended. However, data are not available to indicate that such treatment ameliorates symptoms or shortens the course of the illness. These antibiotics appear to protect against recurrence by eliminating or suppressing a penicillin-resistant S. aureus organism usually associated with TSS.[28,29] Efforts to inactivate the putative TSS toxin by immunotherapy or measures to remove it by dialysis are considered investigational.

Sequelae

There is a paucity of information regarding sequelae of toxic shock syndrome, but some symptoms have been reported to persist for many months[3] or to appear as late sequelae.[30] Reported sequelae have included compromised renal function, cyanotic extremities, amenorrhea, and neuromuscular and neuropsychiatric abnormalities. Although the existing data are suggestive, larger numbers of patients must be evaluated in controlled studies to obtain systematic information about sequelae. Difficulty arises particularly in separating the effects of a severe illness with shock from specific TSS-related sequelae.

Preventing Recurrences

TSS has been reported to recur in about 30 percent of the menstrual cases.[29,31-33] No recurrences have been reported among nonmenstrual cases. Recurrences generally occur within the first few menstrual periods following the initial episode, and are characteristically milder than the first episode, a finding consistent with the possibility that partial immunity may develop. However, it is also possible that initial mild cases may fail to meet the case criteria for TSS.

In one study, 80 women with TSS were followed for five months to determine factors that influence recurrence rate.[31,32] Of the 29 women who had one or more definite or probable recurrences, 19 first recurrent episodes were milder than the initial episode. (The study used a modified set of criteria to define a recurrent case, particularly a probable recurrent case.)[2,31] Among the women who resumed tampon use and who had not received beta-lactamase-resistant antibiotics, the recurrence rate was 67 percent (12 of 18 patients); it was 35 percent (10 of 28 patients) for those who received the antibiotics and resumed tampon use; it was 50 percent (2 of 4 patients) for those who neither received the antibiotics nor resumed tampon use; and it was 17 percent (5 of 30 patients) for those who had received the antibiotics and did not resume tampon use. Thus, available

*See Glossary.

evidence, although limited, suggests that the risk of recurrence is reduced in patients who receive beta-lactamase-resistant antibiotics and who stop using tampons; the two effects appear to be independent.

Further study is required to better delineate factors associated with recurrences. In particular, since beta-lactamase-resistant penicillins given orally have been found relatively ineffective in eradicating nasal carriage of S. aureus,[34,35] the efficacy of currently used doses of these drugs in eradicating nasal and vaginal carriage of S. aureus associated with TSS cases requires study. Further studies could address the role of alternative antimicrobials for eradicating the carrier state and the role of household or other intimate contacts in causing recolonization of persons who have had TSS.

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3

EPIDEMIOLOGY

Epidemiologic methods have been used extensively in investigating risk factors associated with toxic shock syndrome. Use of active and passive surveillance to monitor the occurrence of TSS has enabled discovery of patterns of occurrence and estimations of incidence rates.* Several case-control studies have compared the characteristics of patients who have had menstrual TSS with characteristics of matched controls who have not had TSS. The illness also occurs outside the United States, and comparison of international and domestic cases shows some common features.

Surveillance

Surveillance systems for TSS, as for most other infectious diseases, are hampered by methodological problems that make interpretation of national data related to incidence rates difficult. This section will:

a) describe the general system of surveillance and reporting of infectious diseases in the United States
b) describe how surveillance for TSS was initiated and developed
c) describe patterns of occurrence of TSS in the United States, based on surveillance data

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*The incidence rate is defined as the number of new cases of disease in a population occurring in a specified time period divided by the population at risk. In this report, the numerator is based on reported cases. The population at risk (the denominator) is assumed to remain constant over the time periods being considered. Depending on the context, the denominator is often assumed to be the population of the United States or a particular state, but age and sex-specific incidence rates are given where indicated. Primarily because of difficulty in determining the full number of cases occurring, the estimated incidence rates for TSS generally are likely to understate the true incidence rate.

d) describe the temporal changes in reported TSS cases, with particular attention to whether the incidence rate increased suddenly in 1979 and 1980 and then dropped markedly in October 1980 after Rely tampons were removed from the market.

Surveillance of Infectious Diseases in the United States

In the United States, infectious disease surveillance is accomplished primarily through a passive system in which physicians send case reports to local and state health departments. In an active system, epidemiologists seek out cases. Gradations of intensity and consistency exist within each type of system.

Epidemiologists have long known that for most infectious diseases the cases reported to health departments usually represent a small fraction of the cases that occur. The degree of underreporting varies substantially by disease and geographic area but, in general, studies have shown that most cases of notifiable diseases are not reported, even where state regulations require such reporting.[1,2] Factors that contribute to poor reporting include inadequate medical training; inadequate medical awareness of the disease or syndrome, especially diagnostic criteria; lack of awareness of the need to report or how to report; concern over confidentiality; distrust of health authorities; and a belief that reporting is not worthwhile. Because these and other variables, such as the extent of active and passive surveillance and the extent of news media coverage, greatly influence the completeness and accuracy of data derived from reporting systems, such data must be interpreted carefully.

Infectious diseases <u>required</u> by state laws or regulations to be reported vary among the states. In most states, the list consists of 40 to 60 infectious diseases, which generally include those <u>requested</u> for national reporting by CDC.[3] Reporting by states is voluntary; CDC can request reports but cannot require states to report. In recent years, CDC has developed and promoted national surveillance for newly identified or emergent diseases such as Reye Syndrome (1977), Guillain-Barré Syndrome (1978), Legionnaires' Disease (1978), and Toxic Shock Syndrome (1980).[3,4] Notification of these diseases is not specifically required by law or regulations in most states, but voluntary reports by medical care providers have been encouraged. Whether the addition of these newer diseases or syndromes to state lists of notifiable diseases would significantly improve their reporting is debatable. In general, the extent of disease reporting depends more on the energy expended to obtain reports than on whether laws or regulations require disease reports.[2]

Surveillance of TSS

In late 1979, Minnesota and Wisconsin epidemiologists recognized the occurrence of TSS in young women during menstruation, and they began an immediate, active search for additional cases.[5] They

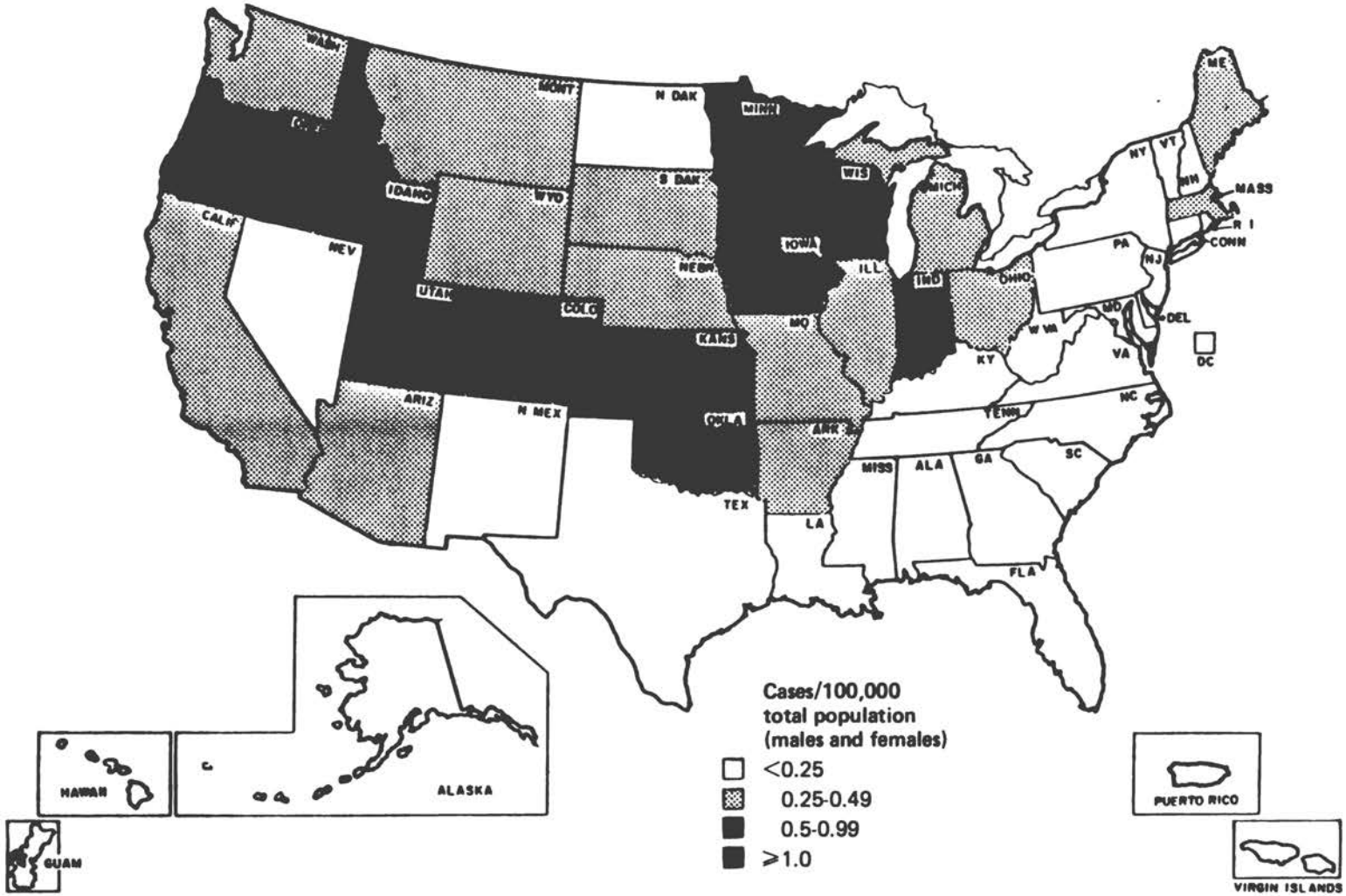

FIGURE 3-1. Incidence rates of cases of definite toxic shock syndrome for 1980, by state. Based on cases reported to CDC by October 18, 1981. Source: Reingold AL, Hargrett NT, Shands KN et al. Toxic shock syndrome surveillance in the United States 1980 to 1981. Ann Intern Med 96(6 Pt 2), 1982.

notified CDC of their findings in January 1980. CDC in turn published descriptive notes about TSS in Morbidity and Mortality Weekly Report (MMWR) in May and June 1980.[4,6] Subsequently, additional cases were reported to CDC either directly by individuals and/or their physicians, or indirectly through local and state health departments.

Regardless of the source of the report, CDC does not consider a case to be TSS unless it meets established diagnostic criteria (see Chapter 2). Therefore, it seems likely that few non-TSS cases are being misclassified as TSS, but cases that do meet the case criteria may fail to be recognized as TSS, resulting in underreporting. Awareness of the CDC criteria by the general public and medical care providers is variable.

Occurrence of TSS in the United States

By April 9, 1982, a total of 1,660 definite* cases of TSS had been reported to CDC, of which 154 were known to be not associated with menstruation; the earliest case had onset in 1960.[7,8,9] Among the definite cases for whom sufficient data were available, 96 percent were women, at least 92 percent of cases in women were associated with menstruation, and 98 percent of cases associated with menstruation occurred in tampon users. Among reported menstrual cases, about 2 percent occurred in non-white and Hispanic women. Of the menstrual cases, about 35 percent occurred in women of age 15 to 19, who accounted for about 17 percent of tampon users in 1980; about 60 percent of menstrual cases have occurred in women less than 25 years old, who accounted for about 40 percent of total tampon users in 1980.[7,8,10,11] The median age for menstrual cases was 20 years.[8] The illness apparently preferentially strikes young women using tampons. (Chapter 2 discusses nonmenstrual cases.)

Figure 3-1 depicts the reported pattern by state for definite TSS cases with onset in 1980. The large differences among states may be caused by variations in local distribution of the etiologic, host and/or environmental factors for TSS. (For instance, the eastern and southern states show very low rates of TSS.) However, the highest 1980 incidence rates, as of March 1982, expressed as cases with onset in 1980 per 100,000 population, were found in those states where active surveillance and case-control studies of TSS were conducted: Utah, 3.00; Minnesota, 2.28; and Wisconsin, 2.08.[8] In contrast, observed 1980 incidence rates in three large states where intensive efforts were not made to find cases were 1/15 to 1/30 the highest rate recorded: New York, 0.10; New Jersey, 0.16; and Pennsylvania, 0.18.[8] These results suggest that although actual geographic differences may

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*This report refers to definite cases, unless otherwise noted. As of April 9, 1982, 555 probable cases of TSS had been reported to CDC. Earlier data indicated the probable cases were approximately proportionately distributed among menstrual and nonmenstrual cases.[8]

exist, the marked differences among the states in reported TSS incidence rates probably are the consequence of variable reporting.

The 1980 national incidence rate, calculated from the number of TSS cases reported to CDC by April 1982, was about 0.38 per 100,000 population. For comparison, the 1980 national rates of legionellosis, rubella, and civilian primary and secondary syphilis were respectively 0.19, 1.7, and 12 per 100,000.[12]

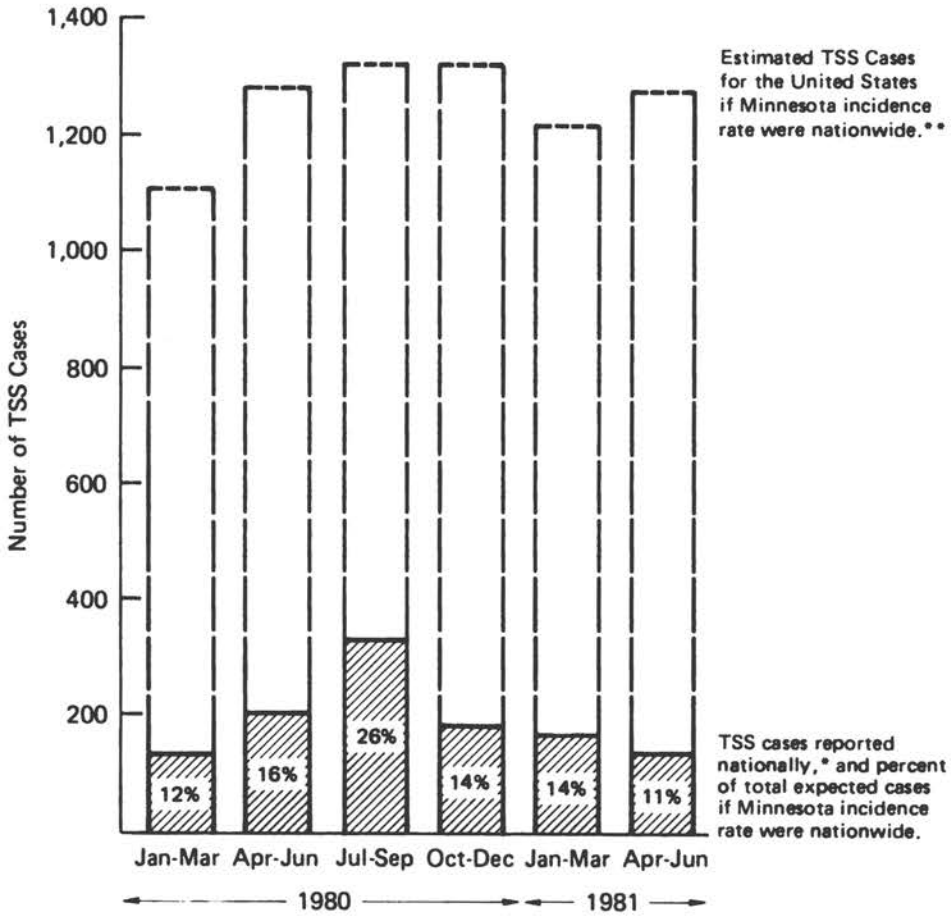
It is likely that the 492 TSS cases reported for 1981 understates the actual number of cases that occurred. Assuming the occurrence of TSS cases is not strongly influenced by local factors, such as prevalence of a causative organism or variations in tampon usage or host susceptibility, a loose estimate of the true number of cases occurring annually in the United States can be calculated from the incidence rate in Minnesota (Figure 3-2). From January 1980 to June 1981, active surveillance was maintained and the number of cases reported per three months was approximately constant in Minnesota.[13,14,15] The calculation yields a national total of approximately 5,000 cases per year, which is 5 to 10 times the number reported to CDC with onset in 1980 (867 cases) or 1981 (492 cases).[9]

However, 5,000 cases may be high, particularly if non-whites are less susceptible, because the nation's non-white population is underrepresented in Minnesota, and other possible but yet unidentified differences in that state may also exist. (Non-whites are 4 percent of Minnesota's population and 2 percent of its reported cases.)[13] Nevertheless, the data from states in which active surveillance has been conducted suggest that several thousand TSS cases occur annually in the United States.

It also is probable that national reports of TSS have been skewed toward menstruating women. Again, a more accurate estimate of the distribution of TSS by sex and menstrual status might be obtained from examining the Minnesota data, which are likely to be the most complete.[13,15,16] For the 18-month period January 1980 to June 1981, 84 percent of TSS cases in Minnesota were associated with menstruation, compared to 92 percent in all other states combined.[13,15] This indicates that total nonmenstrual cases may be underreported nationally to a greater extent than menstrual cases, although the relative underreporting may be less in 1981 than earlier; approximately 15 percent of cases reported to CDC with onset in 1981 were nonmenstrual compared with about 6 percent of cases before 1981.[7,9,17] The average number of nonmenstrual cases per month reported to CDC has remained approximately constant since mid-1980.

Temporal Changes in Reported TSS Cases

TSS apparently is not a new syndrome. Once the syndrome became recognized, cases with other diagnoses were reevaluated and reclassified as TSS.[18-20] Some illnesses that previously had been noted as adult Kawasaki disease or as atypical measles were retrospectively diagnosed as TSS. CDC has reports of 102 cases that occurred before 1979, the earliest in 1960.



*TSS cumulative case count compiled by CDC and reported as of January 18, 1982, by onset date.

**Minnesota cases: Osterholm M., Forfang J. Toxic-shock syndrome in Minnesota: results of an active-passive surveillance system. J Infect Dis 145:458-64, 1982.

Calculations of the potential number of TSS cases in the U.S. assumed that the population-based national incidence rate and the Minnesota incidence rate should be equal. Actual numbers of cases reported were obtained from CDC. Minnesota has 1.8 percent of the U.S. population, based on 1980 census data (U.S. population, 227 million; Minnesota, 4.08 million). Thus, the number of Minnesota cases divided by .018 gives the theoretical number of national cases. The estimated percent of cases reported is the ratio of the national incidence rate to the Minnesota incidence rate, multiplied by 100. Cases reported for Minnesota for each quarter, starting with Jan-Mar, 1980, were 20, 23, 24, 24, 22, and 23.

FIGURE 3-2. Estimated extent of underreporting of toxic shock syndrome in the United States, January 1980 to June 1981.

Although most reporting of earlier cases is sporadic, some systematic attempts are being made to determine the pre-1979 incidence rates and compare them to more recent rates. In one Colorado hospital where patient records for the years 1970-1978 were studied, approximately two cases per year were found, with approximately equal numbers of males and females affected;[21,22] in 1980 an increase in number of cases associated with menstruation occurred. The records were examined

using a screening procedure developed for detecting TSS. Thus, it appears that the predominance of tampon-using women among cases severe enough to be hospitalized was not present before 1979 in this study. Another study is attempting to identify TSS cases retrospectively from a Kaiser-Permanente group in California by using hospital discharge records starting in about 1977.[23]

The occurrence of TSS cases nationally by date of onset showed a gradual increase starting in late 1979, and this trend continued until the summer of 1980 (see Figure 3-3). There is little doubt that much of this increase in reported TSS cases can be attributed to the increasing awareness of TSS during this period. However, the true incidence rate of TSS also may have been increasing.

Coincident with a marked and well-documented increase in news media coverage of the syndrome and its association with tampons,[24,25,26] there was a sharp increase in reported cases of TSS with onset in August and September 1980. This was followed by a decrease of reported cases with onset in October 1980, immediately after Rely tampons had been voluntarily removed from the market by the manufacturer. (Nonmenstrual cases did not show an onset peak in August and September 1980.[8])

It should be noted that most of the reported cases with onset after May 1980 were reported after September 15, 1980, when publicity about TSS and tampons was most intense. Although the number of cases by month of onset eventually reported to CDC reached 135 for August 1980, relatively few of these had been reported by September 15, 1980. Some of the lag can be attributed to the usual delays from diagnosis to receipt of reports via public health channels. In addition, the increased publicity during autumn 1980 resulted in a heightened awareness of TSS, and this stimulated reports of cases that had occurred many weeks to months previously. (The date of reporting can be relevant for determining whether there is bias in the case mix for the case-control studies, as discussed in a later section.)

In regard to the relatively sharp decrease in reported TSS cases with onset after September 1980, CDC has concluded that it "was probably due in part to a true decline in the incidence of toxic shock syndrome brought about by a reduction in the total number of women using tampons; a change in the types of tampons they used, including a shift from Rely brand tampons to other brands; and possibly a change in the way tampons were used."[7] CDC notes that a decline in reporting also may have played a role.[7]

Although there is consensus that intensive publicity was a factor in the sharp increase of the nationally reported TSS cases in August and September 1980, there is no agreement that the October 1980 drop in reported cases reflected a true decrease in TSS occurrence. In Minnesota, where active surveillance was maintained throughout 1980, neither the sharp increase noted in August nor the sharp drop noted after September 1980 is apparent.[13,15] If we assume that the Minnesota data are relatively complete and extrapolate those data, we can derive some estimate of the degree of underreporting nationally for each of the time periods in question (Figure 3-2).

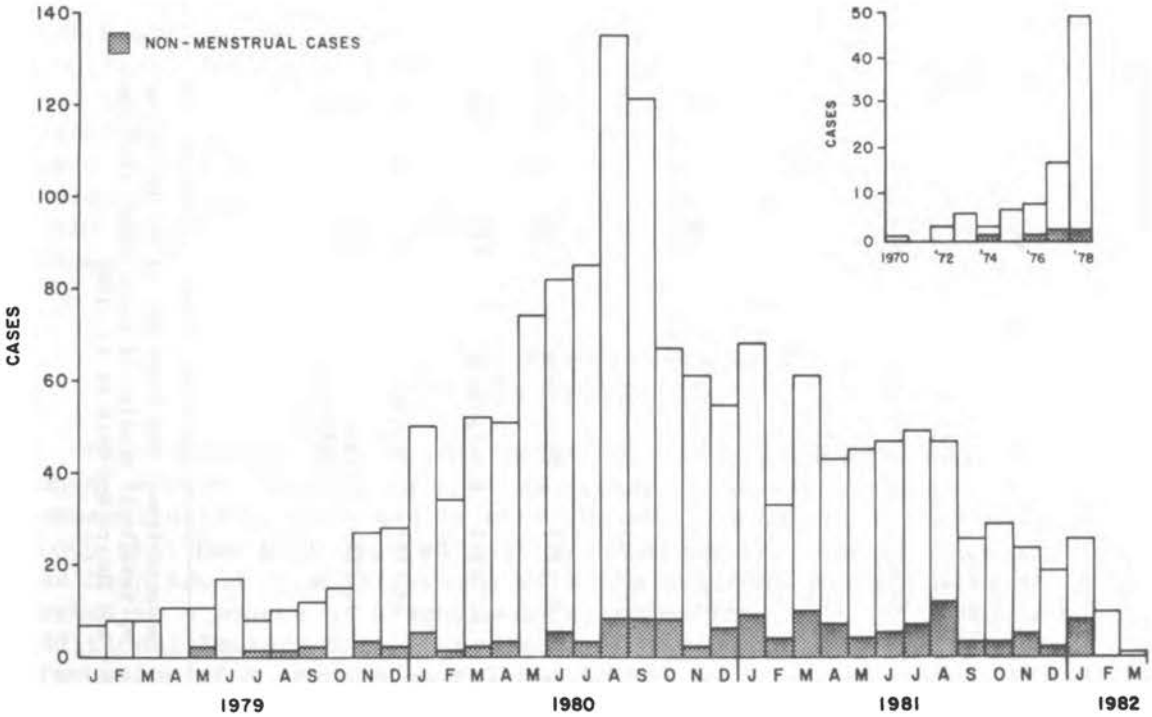


FIGURE 3-3. Definite cases of toxic shock syndrome in the United States by month of onset, January 1970 to March 1982. Reports received by CDC through April 9, 1982. Source: Centers for Disease Control. Morbid Mortal Wkly Rep 31:201-4, 1982.

A rise and fall of reported TSS cases was noted in a few states where some active surveillance was carried out in 1980. If surveillance in these states was uniformly active throughout 1980, their data support the changes observed during 1980 in the numbers of cases with onset each month. However, if their surveillance was not as uniformly active as in Minnesota, then the numbers of cases they reported could have been influenced by the noted changes in the intensity of TSS publicity.[24,25,27,28,29] Publicity about TSS since autumn 1980 has continued, but subsequent media coverage has not compared in intensity to the coverage given to this syndrome in August and September 1980. Data from Minnesota and national data for 1981 do not support seasonal variations as an explanation for the large number of cases reported nationally with onset in August and September 1980.

Additional data from Minnesota demonstrate how surveillance activities can affect the extent of TSS reporting. From July to December 1981, Minnesota dropped its active surveillance but maintained its passive surveillance program.[30] The number of cases reported fell to 30 to 35 percent of the previous levels, with preferential reporting of nonmenstrual cases. Preliminary review of hospital records indicates that the apparent decrease in cases was entirely due to incomplete reporting.[30]

TABLE 3-1. Summary of Methods and Some Results in Six Case-Control Studies of Menstrual Toxic Shock Syndrome

Study designation	Dates of onset of cases	Data collection		Cases associated with menstruation		Control subjects[a]			Significance of estimates of relative risk	
		Method	Dates	No.	Using tampons No. (%)	No.	Using tampons No. (%)	Source	Tampon use vs. no tampon use	Rely brand vs. other brands
Wisconsin[5]	Jan. 1979 - June 1980	Personal interview (cases); Self-admin. written questionnaire (controls)	March - May 1980	35	34 (97)	105	80 (76)	Gynecologic clinics; adolescent clinic	Sig	NS
CDC I[32,36]	Dec. 1976 - June 1980	Telephone interview	June 1980	52	52(100)	52	44 (85)	Friends	Sig	NS
CDC II[34,36]	July - Aug. 1980	Telephone interview	Sep. 1980	50	50(100)	150	124 (83)	Friends	Sig	Sig
Utah[29,33]	Jan. 1976 - Aug. 1980	Personal interview	May-Aug. 1980	29	29(100)	91	70 (77)	Neighbors	Sig	Sig
Tri-State[14,37]	Oct. 1979 - Sept. 1980[b]	Personal interview	Oct.-Nov. 1980	76	75 (99)	152	123 (81)	Neighbors	Sig	Sig
Oregon[27,38]	Dec. 1979 - Nov. 1980	Telephone interview (cases and friend controls); Personal interview (clinic controls)	Jan.-Mar. 1981	18	18(100)	18	14 (78)	Friends	NS	Sig
						18	16 (89)	Family planning clinic	NS	Sig

[a] All studies matched for sex; all but Utah matched for age
[b] Cases were all reported before September 19, 1980

Sig: Significant, $p < .05$
NS: Not significant

Adapted from: Stallones RA. A review of the epidemiologic studies of toxic shock syndrome. Ann Intern Med 96(6 Pt 2), 1982

It will not be possible to determine the national pattern of TSS occurrence for 1980 or 1981 with greater certainty until some measurement of TSS underreporting is obtained for several areas of the United States during a specified time period. Active surveillance in some areas besides Minnesota might also improve estimates of the national incidence rate. Identification of cases that occurred prior to 1980 would help to determine periods when patterns of TSS occurrence changed.

Risk Factors Associated with TSS: Case-Control Studies

The following discussion focuses on TSS cases in menstruating women, without minimizing the importance of studying the cases in nonmenstruating women and in men. However, menstruating women are the group that has been studied most systematically. One condition that has been found in most persons with the syndrome who are adequately tested is a source of staphylococcal infection.[5,17,31,32] However, additional factors must be necessary. (See Chapter 5 for further discussion of S. aureus as related to TSS.)

The sections below will evaluate the evidence associating TSS with

a) menstruation
b) tampons
c) a particular brand of tampon
d) specific tampon characteristics
e) other factors

The evidence is derived primarily from six reported case-control studies; two of these were based on national reports of TSS and four were based on regional reports.[5,14,27,29,32-38] Table 3-1 summarizes important methodologic features and results of the six studies, and Table 3-2 summarizes some of their additional findings.

Menstruation and TSS

Our presumption that TSS is more common among menstruating women than among other persons is based partly on the early cases reported from Wisconsin and to CDC.[4-7] Even before there was mass media publicity about the syndrome, the reported cases were overwhelmingly in menstruating women. For example, among the first 38 TSS cases reported in Wisconsin, 37 were in women and 35 were menstruating.[5] This would be a very unusual observation if the true distribution of cases in the population were equal among men and menstruating and nonmenstruating women. Thus, the presumption that TSS is most frequent among menstruating women is reasonable.

TABLE 3-2. Evaluation of Some Risk Factors for Toxic Shock Syndrome Among Menstruating Women

Study designation	Risk Factor											
	Continuous vs. not continuous tampon use	Frequency of tampon changing	Tampon absorbency	Sexual activity	Sexual activity during menses	Douching	History of vaginal infection	Similar illness in previous menses	Amount of exercise	Contraceptive use	Oral contraceptive use	Perceived menstrual flow
Wisconsin[5]				NS			NS		NS	-	NS	NS
CDC I[32,36]	+	NS		NS	NS					-	NS	NS
CDC II[34,36]			NS			NS						
Utah[29,33]				-	NS	NS	NS			NS	NS	
Tri-State[14,37]	NS	NS	+	NS	NS	NS	+	+	-	NS	-	NS
Oregon[27,38]												
Friend controls		NS			NS		NS			NS		
Gynecologic clinic controls		NS			NS		NS			-		

\+ Positive association; cases had factor more than controls

\- Negative association; cases had factor less than controls

All associations designated as + or - are significant at $p < .05$

NS Factor not significant

blank Not analyzed

General Features of Case-Control Studies

The case-control study is a useful epidemiologic method for exploring risk factors that may be associated with a particular disease or outcome.[39,40] In a case-control study, the frequency of various characteristics and prior experiences are compared between persons who have had the disease (cases) and in those who have not had the disease (controls). The cases and controls are matched for various characteristics, such as age, race, and other factors that might otherwise interfere with the interpretation of the results. While the method has potential pitfalls,[16,41,42] some of which are discussed below in the context of TSS, a well-conducted case-control study can provide a great deal of useful information. A single case-control study cannot prove a cause and effect relationship, but it can reveal associations and suggest avenues for future action and investigation. Results often are expressed as an odds ratio, which is an estimate of the relative risk, that is, the ratio of the risk of getting the disease if a factor is present to the risk of getting the disease if the factor is absent. Various types of mathematical analyses of case-control studies are used to identify associations and determine their statistical significance.[43,44]

Tampons and TSS

To explore the factors associated with menstruation and TSS, six case-control studies were conducted using only cases associated with menstruation. Among the menses-related features evaluated, tampon use was found to be more common among cases than among controls. This was a consistent finding, although tampon use among controls and in the population at large was very common. In the case-control studies, 97 percent or more of cases reported tampon use during the menstrual period in which they became ill as compared to tampon use by 76 to 89 percent of control women during a reference menstrual period. (See Table 3-1.)

By comparing the use of tampons among these control subjects and the population in general, sources of bias in the case-control study may be detected. Tampon use nationwide as determined by market surveys in early 1980 revealed that about 70 percent of menstruating women used tampons, a figure lower than the range reported by the control women in the case-control studies. The observation that control women were more likely to have used tampons than the population at large suggests that the method of selecting controls produced women more closely "matched" to the cases than to the general population of women.* This is likely to be the effect of choosing friend or

*The problem of "over-matching" in case-control studies is frequently of concern. If cases and controls are too well matched for some characteristics, the effect would generally be to enhance the validity

neighborhood controls (strategies used in these studies) although other factors, such as the age and race of the controls, may also have been important in determining their tampon use patterns. It is important that tampon non-users did not appear to be overrepresented among the controls, because an excess of tampon non-users among the controls would exaggerate the risk associated with tampons by producing a spuriously large odds ratio.

Other sources of error also could exaggerate the risks associated with tampons. Tampon use reported by cases in these studies could be higher than actual use if these women were aware of the publicity surrounding tampon use and TSS. However, the first two studies (Wisconsin and CDC I) completed subject interviews in June 1980, prior to the publicized association of TSS and tampon use.

Possible subject bias in reporting tampon use, and more specifically particular brands of tampons used (to be discussed later), is one of the weaknesses in these studies. Because cases and controls were asked to recall details about menstrual products used some months prior to interview, accurate information would be difficult to obtain. Women would know generally the types of products they preferred and most frequently used, but variations from usual use would be difficult to attribute to a particular period.

The major problem with subject recall is that accuracy is likely to differ for cases and controls, with recall bias likely to be most severe among the cases. Not only will publicity influence the cases' memory but the fact of having experienced a serious illness will have caused the cases to contemplate the details of events surrounding that illness. The controls will not have had such a stimulus. The issue of differential recall is one that plagues case-control studies in general but is particularly relevant in the studies of TSS.

It seems likely that the publicity about tampons would tend to increase the reported frequency of tampon use among cases. This effect then might exaggerate the size of the odds ratio derived from these studies. However, the TSS risks associated with tampon use compared with no tampon use were large; the relative risk estimate from the Tri-State study was 18, with a 95 percent confidence interval of 3.9 to 82.[13,37] To ascribe this 18-fold risk to bias one would have to postulate that 27 of the 29 controls who reported no tampon use actually did use tampons, or that 18 of 75 cases who reported tampon use actually did not use them, or some combination of these two variations in reporting.[35] This amount of error, all of which must operate in the same direction to have falsely produced the tampon-associated risk estimate, can be conjectured but is highly unlikely.

Notwithstanding different procedures, all but one of the six case-control studies showed a strong association between tampon use

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of any statistical associations detected. However, the study may fail to detect risk factors that would have appeared with controls chosen by different criteria.

and TSS. The one study (Oregon)[27,38] that did not demonstrate the association had too few subjects to provide adequate statistical power to demonstrate the association. Given the consistency of findings from different parts of the country, in studies employing a variety of methods, data collection techniques, and sources of controls, it is reasonable to conclude that tampons are associated with an increased risk of TSS among menstruating women.

Tampon Brand and TSS

Rely brand tampons were removed voluntarily from the market on September 22, 1980 by the manufacturer, the Procter & Gamble Company. At about that time, results of the findings of the CDC II and the Utah studies became available, associating Rely tampons with TSS.[33,45-48] The CDC II study was based on 50 TSS cases reported to the CDC with onsets in July and August 1980, and 150 friend control women.[34,36,48] All were interviewed by telephone during early September 1980. Cases were asked about menstrual products used during the menstrual period associated with their illness, and controls were asked about their menstrual period closest in time to that of the case's illness. Seventy-one percent of cases and 26 percent of controls had used Rely during the relevant menstrual period. The relative risk estimate for TSS in relation to Rely use was a highly significant 7.7 with a 95 percent confidence interval of 2.8 to 22.2. In the Utah study, 60 percent of cases and 23 percent of controls used Rely, a significant difference.

Data from the Tri-State study, the most detailed of these case-control studies, has been extensively analyzed in a variety of ways by different groups, and an excess risk associated with Rely has remained.[14,30,37,44]

Effect of Publicity In retrospect, one can ask whether the observed association between Rely brand tampons was real or a product of biases in the methods of these studies and of external events, specifically the publicity about the Rely-TSS association that was most intense in September and October 1980. Publicity leads to increased reporting, and the reported cases determine the composition of the case-control studies. Therefore, to the extent that cases may have reported themselves or were reported by physicians because they experienced TSS and used Rely, the case series will overrepresent Rely users as compared with the true distribution of Rely users among menstruating TSS cases in the population. (It must be reemphasized that regardless of the source of reports, cases were counted only if a physician confirmed that they met specific diagnostic criteria.)

The marked increase in TSS cases reported nationally with onset in August and September 1980 was undoubtedly related to the extensive media coverage of TSS and its association with tampons. However, most of those cases with TSS onset in August or September 1980 were actually reported after September 15, 1980, when most of the publicity occurred. The extent to which publicity may have biased TSS case reporting and caused a selective increase in TSS cases who reported

use of Rely tampons before September 15, 1980 is difficult to assess. However, Rely may be overrepresented among cases with earlier onset that were reported after that date. The available data that bear on potential reporting and recall bias is reviewed below.

The actual collection of tampon use data from cases and controls was carried out as follows: Utah, May to August 1980; CDC II, September 5 to September 8, 1980; Tri-State, October to November 1980; and Oregon, January to March 1981. (See Table 3-1.) Publicity about TSS and its possible association with tampons and specifically with Rely existed as early as July in some parts of the country (primarily in the West), but extensive coverage did not generally occur until mid-September 1980.[7,26] Thus, to some degree, selective reporting of TSS cases who were Rely users could have occurred starting in July 1980. Evidence for selective reporting was provided in Wisconsin,[24,25] where marked differences in Rely use were found between self-reported cases (60 percent Rely users) and physician-reported cases (26 percent Rely users). However, almost all of these self-reported cases were reported after mid-September 1980.

For three of the four case-control studies where an association with Rely was found, the cases were all reported before mid-September 1980. Therefore, although selective reporting bias related to publicity about Rely may have occurred to some extent, it should not have been a major factor in determining the case mix for these studies.

Nevertheless, the possibility existed that publicity associating TSS with Rely in July and August 1980 could have resulted in some selective recall of Rely use for those cases who were interviewed after July 1980. For example, Davis's group showed an increase in number of women who reported Rely use (from 7 to 11) among 22 women with TSS onset before July 1980 who were first interviewed prior to July and interviewed again after October 1980,[24,25] indicating a possible bias toward increased recall of Rely use.

Depending on the time period in which tampon use data were collected, recall bias could have affected several cases in the Utah study and possibly all cases in the CDC II, Tri-State, and Oregon studies, but some efforts were made to minimize or document recall bias. In the CDC II study, recall for no more than two months was required, and all participants were asked to get the tampon box that they had used during the menstrual period in question and to read the label to the investigator over the telephone.

In the Tri-State study, the authors compared data on tampon use collected during their study in October to November 1980 with data on tampon use obtained from the preliminary investigations carried out within a few weeks of TSS onset for cases reported before and after June 27, 1980.[15,37] (June 27, 1980 was the date of the first major publicity that associated occurrence of TSS with tampon use.[26]) The Tri-State researchers found no significant difference in reported use of Rely tampons for cases reported before June 27 compared with those cases reported after June 27. The two case groups also showed no significant differences in recall when the tampon use data that were collected months earlier were compared to the data collected from these same cases in October to November 1980.[37] These findings suggest that

the increased relative risk of Rely tampons found in the Tri-State study cannot be attributed to selective case reporting or to recall bias among cases promoted by publicity.

If Rely were responsible for the apparent increase in rate of occurrence of TSS, which peaked in August and September, its withdrawal from the market should have resulted in a marked reduction in the rate of occurrence of TSS during subsequent months. A reduction in the occurrence of nationally reported cases with onset after September 1980 did occur, as noted earlier, but this can reflect the extent of reporting as well as the effect of changes in tampon use and other relevant factors. In addition, as shown in Figure 3-2, the decrease was not observed in Minnesota, where active TSS surveillance continued throughout 1980. The unchanging incidence rate in Minnesota appears inconsistent with the Rely-TSS association noted in case-control studies. However, additional data related to tampon absorbency and composition may provide some explanation for this apparent anomaly.

Tampon-Associated Characteristics and TSS

The Tri-State study found that TSS risk was significantly greater for users of high absorbency tampons than for users of tampons of lower absorbency.[14,37,49] When CDC II data were analyzed for an absorbency effect, with Rely users included in the statistical model, no significant influence of absorbency was found that could be separated from the risk associated with using Rely brand tampons.[34] However, the effect could have been masked because there were only 12 non-Rely users among the 42 cases who exclusively used one tampon brand and absorbency.

Market studies suggest that long-term overall use of high absorbency tampons has not decreased substantially since Rely was withdrawn from the market.[49,50] (Also see Chapter 4.) If former Rely users have shifted to other high absorbency products, which appears possible, and if high absorbency tampon use is associated with an increased risk of TSS, this could explain the steady rate of reported TSS cases in Minnesota.[13,49] Furthermore, in the Tri-State study, several high absorbency tampon brand styles produced odds ratios of similar magnitude to those found for Rely.[14]

The Tri-State study also found that TSS risk varied by chemical composition of tampons, but absorbency and chemical composition were so closely correlated that independent effects of the two factors were difficult to disentangle. These data related to tampon characteristics need to be confirmed in other studies, and are important in suggesting avenues for future research.

Additional Risk Factors

The case-control studies examined many factors besides those related to tampon brand and absorbency for their possible association with TSS. Few other positive significant associations emerged.*

Table 3-2 shows some of these results. It should be remembered that the relatively small number of cases in these case-control studies limited the ability of researchers to obtain statistically significant differences between cases and controls.

Three studies indicated that cases used contraceptives to a lesser extent than did controls (although two of these studies used gynecologic or family planning clinic controls), and two other studies did not detect this difference. In the Tri-State study, cases used oral contraceptives significantly less often than did controls, but this factor did not reach significance at the 0.05 significance level in three other studies. CDC I found an association between continuous tampon use during menstruation and TSS, whereas the Tri-State study found that continuous tampon use (as opposed to intermittent use) was not a risk factor; the other studies did not evaluate this factor. The Tri-State study also found that cases exercised less than controls, were more likely to have had non-specific vaginitis during the past year, and were more likely to have had an illness with some TSS symptoms during the menstrual period preceding the index period. The Wisconsin, Utah, and Oregon studies found that a history of vaginal infection was not a significant risk factor.

Other factors that were found not to be significantly associated with TSS in more than one study included the average frequency of changing tampons, use of douches, having sexual intercourse during menstruation, and perceived amount of menstrual flow. The Tri-State study also found no significant differences between cases and controls for other characteristics, including drug use (prescription, over-the-counter, illicit), alcohol consumption, swimming or bathing habits with or without tampons in place, history of recent pelvic examination, length of usual menstrual cycle, and age at menarche.

International Perspective on TSS

More than 150 cases of TSS had been reported as of November 1981 from countries other than the United States, including Australia, France, Germany, Great Britain, the Netherlands, New Zealand, Scotland, and Sweden. The reported incidence rate usually is low compared with that in the United States, and, in general, active surveillance apparently is not being conducted. In Sweden the rate of occurrence approaches that found in the United States.[51]

Nonetheless, by comparing information on cases among the reporting countries, better understanding of risk factors associated with the syndrome may emerge. In general, the cases bear a striking similarity, having similar strains of S. aureus isolated in a number of

*Although studies of S. aureus carriage were not carried out as part of these case-control protocols, most menstrual TSS cases cultured before antibiotic therapy showed vaginal colonization with S. aureus.

instances.[52,53] As with interpreting geographic variations in United States incidence rates, it is unclear how much of the differences among other countries is due to reporting differences, differences in tampon use patterns, or differences in host susceptibility or in the presence of the TSS-associated S. aureus.

Use of menstrual products varies widely throughout the world.[54] In the most developed countries, market data suggest that each menstruating woman uses an average of about 200 tampons plus napkins per year. In some countries, however, such as India, home-made products apparently are used almost exclusively, and the market volume may represent only a tiny percentage of the usage. In such countries, the market ratio of tampon versus napkin use is, therefore, not very meaningful.

Among the countries where tampons represent 30 percent or more of the menstrual product market are Australia, Austria, Canada, Germany, Great Britain, Israel, Scandinavia, and New Zealand.[54] In most countries for which market information is available, napkin use exceeds tampon use in volume, based primarily on 1980 data. New Zealand is a notable exception with a napkin/tampon market ratio of about 6/7.[54] In Israel and Scandinavia, napkins outsell tampons by 2/1, whereas in Holland, Belgium, and Luxembourg (Benelux countries), the ratio is 5/1, and in Japan the napkin/tampon ratio is 13/1.[54]

Sources and types of tampons vary among countries. In Scandinavia and the Benelux countries, for example, two-thirds of tampons sold do not have applicators.[55] Tampons may be imported or manufactured locally. Tampax is sold in about 120 countries, and Playtex is also widely distributed. Superabsorbent tampons are available only in some countries, such as Belgium, Italy, France, Great Britain, Scandinavia, and New Zealand.[52,54,55] Rely brand tampons were not marketed outside the United States.[56]

Cases in Various Countries

The committee tried to learn about cases in the less developed parts of the world, as well as in the industrialized countries. According to the Pan American Health Organization, as of November 1981 no cases in the Americas were known outside of the United States and Canada, although all the countries were queried in late 1980 and again in the fall of 1981.[57] Approximately 25 other countries were contacted by the U.S. Food and Drug Administration in early 1981, and by the Institute of Medicine in the fall of 1981. Countries reporting no TSS cases by late 1981 were Ireland, Israel, Italy, Japan, Portugal, Switzerland, and Yugoslavia.

Table 3-3 summarizes the information available to the IOM about cases that have occurred in other countries. The information is unlikely to be complete but does show that cases are found in many countries. In general, the cases follow a pattern similar to that in the United States, with most reported cases associated with young, menstruating women using tampons. It is not possible to estimate how

TABLE 3-3. Characteristics of Some Toxic Shock Syndrome Cases Outside the United States

Country	Number of Cases (date)[a]	Number of Female Cases	Age of Cases	No. of Cases Menses-Assoc.	No. of Cases Tampon-Assoc.	Microbiologic Findings[b]
Australia[58,59]	10 (Nov 1981)	9	15-32 yrs; 5 F ≤ 20 yrs	8	≥ 6	S. aureus phage group 29/52/83A in 2 tampon-assoc. cases; SEF-producing S. aureus in 3/3 cases
Canada[60,61]	53 (Oct 31, 1981) 25 meet CDC def.	50	4-65 yrs; about half < 25 yrs	37	36	SEF in 14/15 cases
Denmark[62,63]	5 (Aug 1981)	5	16-24 yrs	4	4	S. aureus phage group 29/52 in 4 cases; 2/3 SEF
Finland[64]	1	1	17 yrs	1	1	
France[65,66]	4 (Nov 1981)	2	17-36 yrs	1	1	S. aureus phage type I or IV identified in 3 cases; 2/3 SEF
Netherlands[65,67]	12 (Nov 1981); at least 7 meet CDC criteria			≥ 4	≥ 4	11/12 SEF
New Zealand[68]	4 (Oct 81)	4	21-32 yrs	4	4	S. aureus isolated from 3 cases
Norway[69]	4 (Oct 1981)	4	15-20 yrs	3	3	
Scotland[70]	1	1	16 yrs	1	1	S. aureus phage group 29/52 isolated from anterior nares during convalescence
Sweden[51]	40 (Sept 1981)	36	24 F < 20 yrs; 9 F age 13-15 yrs	35	35	S. aureus isolated from at least 10 cases
United Kingdom[52]	15 (Nov 1981) (10 confirmed, 5 probable)	15	14 F age 15-25 yrs	15	15	S. aureus isolated from 13 vaginas. 7/15 TSS strains were type I, lysed by phage 29; 10 resistant to penicillin; 11 produced SEF
West Germany[65]	3 (Nov 1981)	3	21 yrs, 29 yrs, unknown	≥ 1	≥ 1	

[a] Date of last information received

[b] SEF: staphylococcus enterotoxin F, many from Bergdoll et al.[53,71] Fraction is number of strains positive for SEF over number tested.

F = Female

This table reflects the best information the IOM committee could obtain. The table may not be complete, and there may be additional cases in other countries.

complete the reporting is in the various countries, and it is difficult in some instances to know if the cases meet the strict CDC criteria.

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4

TAMPONS AND ADDITIONAL HOST FACTORS RELATED TO TSS

Introduction

The basis for the observed association between TSS and use of tampons remains to be elucidated. Only a small fraction of women who use tampons get TSS. Some characteristics of tampons or the way they are used by certain women may increase a user's risk of getting TSS. Tampons may act in concert with host factors related, for example, to age or race, so that certain tampon users are more--or less--likely to get TSS. Although there is not a sharp cutoff above age 19, girls age 15 to 19 seem particularly vulnerable, and the reason for their apparent susceptibility requires much further study.

Several potential factors have been suggested to relate tampons to the pathogenesis of TSS.[1-3] These include the composition and absorbency of tampons, the presence or absence of an applicator, the possibility that tampons block the vagina or traumatize it, and the possibility that tampons serve as vectors for the introduction of bacteria or as foreign bodies that enhance bacterial growth or toxin production. None of these yet provides a satisfactory explanation for the tampon-TSS association. After a brief history of tampon use and review of tampon usage patterns and characteristics, possible mechanisms for the tampon association with TSS are discussed in this chapter. Special attention is given to adolescents, who have accounted for more than one-third of TSS cases reported to CDC.

History of Tampon Use

Viewed in many societies as possessing supernatural powers for both good and evil, menstruating women have long dealt with the need to conceal the menstrual flow with ingenuity. A handful of grass, "rolls of papyrus, coconut fibers, moss, reeds, wood, cotton, horsehair, lambswool, lint, even the hollowed-out horns of animals,"[4] have all been utilized at one time or another. The bulky contraptions such as diapers and flannel squares wrapped around the perineum were associated with fashions such as the bustle, crinolines, and hoops. In those societies where body-revealing clothing was the fashion, internally placed absorbent material was utilized. "Ancient Greeks

TABLE 4-1. Summary of Some Characteristics of Tampons

Brand & Style	Absorbency Category *	Composition	Applicator
Kotex super	II **	Cotton and rayon with a polypropylene or rayon cover and polyester string. Cross-linked carboxymethyl cellulose was an ingredient in samples manufactured before September 1980, and therefore it was present in shelf samples prior to about March 1981.	Wound paper stick or polyethylene tube
Kotex regular	III		
o.b. super-plus	I	Cotton and rayon	None
o.b. super	II	" "	
o.b. regular	III	" "	
Playtex super-plus	I	Rayon polyacrylate fiber, cotton, and polysorbate 20. Styles come with or without deodorant. Fragrance is present in the deodorant versions.	Polyethylene tube
Playtex super	I		
Playtex regular	II		
Rely super [no longer sold]	I	Cross-linked carboxymethyl cellulose and polyester foam	Polyethylene tube
Rely regular " " "	III		
Tampax super-plus	I	Polyacrylate rayon fiber	Tube of spirally wound strips of paper held together with water-soluble glue
Tampax super	III	Cotton fiber and rayon fiber	
Tampax slender regular	IV	Cotton fiber, rayon fiber, and high absorbency cotton fiber (cross-linked carboxymethyl cellulose)	
Tampax original regular	IV	Cotton fiber	

* Tampon absorbency was based on measurements made by manufacturers using the syngyna ("synthetic vagina") method, as provided to Osterholm and colleagues who summarized the data and developed the categories used here.[6,18,20]

Category I: > 18.4 grams
II: 15.5 to 18.3 grams
III: 12.1 to 15.4 grams
IV: < 12 grams

** This product was in Category I before about March 1981 (see composition).

Dimensions: Tampons are approximately between 35 and 50 mm long and 10 to 18 mm in diameter.

Except for Rely, data reflect tampons available approximately October 1980 to June 1981.

and Romans, who wore robes of filmy fabrics, made internal devices out of compacted lint or soft wool, rolled and lightly greased for easy placement . . . aboriginal women on remote Pacific islands . . . insert tightly wrapped vegetable fibers."[4]

Following World War I, manufacturers of new, highly absorbent surgical dressings made from Cellucotton, needing a new market for their product, began what was later to become an $800 million industry, that of the manufacture of disposable sanitary products. By 1937, the year in which Consumers Union undertook to test menstrual products for absorbency, comfort, and "leak resistance," there were 20 different popular brands of disposable napkins in the United States. In the early 1930s, intravaginal cotton tampons were introduced, of which only Tampax survives today. Some advice to women at the time consisted of warnings from the medical profession about potential problems, such as irritation.[5] There were fears that tampon use would encourage masturbation and lead to loss of virginity. Between 1936 and 1966, numerous articles appeared in the medical literature discussing tampon use. (See Reference 6 for a bibliography.)

Trends in Tampon Use Before and After TSS Publicity

By 1980 approximately 70 percent of the approximately 50 million menstruating females in the United States used tampons.*[2,7-9] Table 4-1 summarizes some properties of the major brands and styles of tampons available in the United States between approximately October 1980 and June 1981. (Rely is listed for comparative purposes.) The tampons vary in fluid capacity (absorbency), composition, size, the presence or absence of an applicator, the presence or absence of deodorant, and undoubtedly other characteristics that may be relevant to TSS. More than 5 billion tampons were purchased each year in the United States in 1979 and in 1980, according to a national marketing company. Most women use about 15 to 20 tampons during a menstrual period, according to industry sources.

Most information about tampon use comes from surveys conducted by manufacturers or by marketing firms, or from various other types of studies. The data from different sources do not always agree in detail but do generally provide trend information.

Most adolescents use external sanitary napkins at their first menstrual period (12.5 years average in the United States) but adopt tampon use within about two years of menarche.[7,8,10,11] In one study, 14 percent of adolescents used tampons at menarche, and

*Users of menstrual products are conveniently classified as users of "tampons only," "tampons and napkins," or "napkins only." Unless otherwise specified, tampon users include the first two categories, that is, those who use tampons alone or tampons plus napkins. The number of menstruating women is estimated from census and survey data, counting only those who have menstruated in the past three months.

65 percent by 18 months later.[10] In another, 23 percent of menstruating girls in grades 5 and 6 used tampons, whereas 75 percent of those in grades 11 and 12 did.[11] One manufacturer's survey taken in September 1980 found that 55 percent of menstruating 14-year-olds and about 80 percent of menstruating 18-year-olds used tampons.[7] Figure 4-1 shows the pattern of tampon and napkin use by age from that survey.[7,12]

Overall tampon use dropped after September 1980. In July and August of 1980, the menstrual product market was about 47 percent tampons and 53 percent napkins, as determined from sales data. Four months after the adverse publicity in September 1980 linking tampons and TSS, tampons represented about 35 percent of the menstrual product market, a drop of about 25 percent.[9,13] However, tampon purchases increased during 1981 and in September and October 1981 were only about 7 percent below pre-TSS publicity levels. In 1981, slightly over 4.5 billion tampons were sold, down 10 percent from the level in 1979.[13]

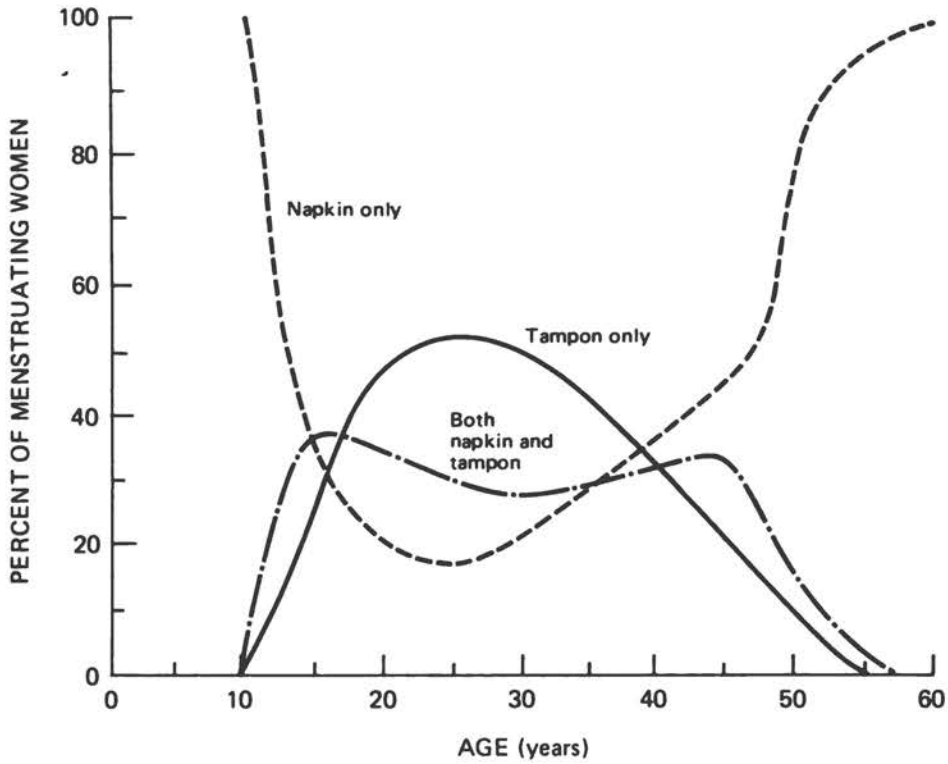

FIGURE 4-1. Use of menstrual products by menstruating women in the United States, by age. Data from a survey of approximately 2,000 women in September 1980. Source: Procter & Gamble Co. Figure provided to the IOM Committee on Toxic Shock Syndrome.

Changes in brands used and in patterns of use also occurred after September 1980. Table 4-2 compares the market share by brands of tampons during January to August 1980 and January to August 1981.

The total number of women using tampons apparently declined after September 1980, with fewer women using only tampons and more women using only napkins.[8,14] One survey involving more than 2,000 respondents found that the percentage of women using tampons decreased from 70 percent to 60 percent between September 1980 and September 1981.[8] In September 1980, 37 percent of poll respondents used tampons only, but a year later the figure had dropped to 20 percent, and the percentage of women who used tampons plus napkins increased from 32 to 39 percent. A survey by another manufacturer showed a decrease in percentage of women using tampons from about 70 percent in September 1980 to 50 percent in May 1981.[14]

Several studies found that total tampon use also decreased to some extent among younger women--those particularly susceptible to TSS.[6,10,14-16] In May 1981, in a national survey of 13- to 19-year-olds, representing a cross-section of the teenage market,[15] most respondents said they had modified their use of sanitary products in some way in response to TSS publicity. Among 168 adolescent tampon users in San Francisco studied immediately following the TSS publicity, one-third changed their tampon use as a result, including 27 percent who stopped using them entirely.[16] Adolescents who decreased or stopped their use of tampons were most likely to have used Rely brand tampons prior to publicity about TSS and to have felt they were especially susceptible to TSS. In a similar study in a northern California city, 14 percent of the adolescent population polled stopped using tampons following TSS publicity.[10]

Tampon use was also monitored through September 1981 among 132 controls in the Tri-State case-control study, of whom 80 percent had used tampons initially.[6] This population, mostly of the relatively young age of TSS victims, may be presumed to have had a heightened concern about TSS. There was a marked decrease in the number of exclusive tampon users, largely offset by an increase in those using tampons part-time, but more than 90 percent of initial users were using tampons to some extent in September 1981.

TABLE 4-2. Percent of Tampon Market Share by Brand

Dates	Tampax	Playtex	Rely	o.b.	Kotex
January - August 1980	44.5%	23.5%	15.1%	9.5%	5.9%
January - August 1981	57.8%	25.0%	Not sold	9.5%	6.0%

Totals do not equal 100 because of rounding and market share of other brands.

Source: A. C. Nielson. Tampon shares among food, drug, and mass merchandise stores.

A questionnaire sent to CDC II cases and controls five months after the study elicited responses indicating that about 10 percent of cases used tampons, but about 85 percent of initial control tampon users were still users.[1]

Changes in Styles of Tampons Used

Changes in composition and absorbencies of tampons used are usually more difficult to document that are changes in brand use. As noted in Table 4-1, fluid capacity is not consistently portrayed by the tampon label designation, although the super-plus tampons tend to have the higher absorbencies. Also, manufacturers can change the composition and absorbency of tampons without notifying the public. In Minnesota, a 7 percent decrease in sales of tampons of highest fluid capacity occurred between October 1980 and June 1981, but this change took place primarily because one manufacturer decreased tampon fluid capacity, rather than because women consciously changed their purchasing habits.[6]

Despite the association of higher absorbency tampons with TSS found in one study (see Chapter 3), the available data generally indicate that women have not preferentially decreased their use of high absorbency tampons since September 1980. On a national level, about 10 percent of women in one poll used super-plus (labeled) tampons before September 1980, while use of tampons labeled super somewhat exceeded use of tampons labeled regular.[14] According to the CDC, there was no detectable decrease in proportion of super-absorbent tampons sold following TSS publicity, although total tampon use was reduced. Also, one leading tampon manufacturer indicated that super-plus sales in July to November 1981 were about 17 percent of the brand's total sales, a proportion similar to that before the TSS publicity, and approximately reflecting the trend among all brands during 1979 and 1980 as well as 1981. A national survey of tampon sales in food stores indicated that about 15 percent of sales were super-plus in the 12 weeks ending September 19, 1980, and in the 12 weeks ending July 24, 1981.[17]

In order to better understand trends of tampon use and their association with TSS cases, it would be useful to have detailed marketing data by brand and absorbency for various age groups within the geographic region being studied, as has been done in Minnesota and Wisconsin. If a particular population used some products preferentially compared with the overall population, this information could be useful in interpreting surveillance data and planning case-control studies. For example, before September 1980, Rely super tampons had about half of the high absorbency tampon market among women age 12 to 17 in Minnesota and Wisconsin.[8] However, in Minnesota, the reported incidence rate of menstrual TSS cases has not decreased since Rely was taken off the market.[18]

Composition and Absorbency of Tampons

Before about 1977, all tampon products were made of cotton, rayon, or a blend of the two, according to manufacturers.[1] Beginning in about 1977, tampon manufacturers began to make more absorbent products and to vary the composition of tampons,[19] and these new products garnered a substantial share of the market.[1] The finding of an increased association between more highly absorbent tampons and TSS in one study has focused interest on the chemical composition of tampons, but the data relating composition to TSS are preliminary.

The Tri-State study researchers found that the risk of getting TSS was more closely associated with the fluid capacity of the tampon than with the use of any particular commercial brand of tampon and that composition may also be an important factor.[20] Also, for cases occurring in Minnesota between October 1980 and June 1981, the tampons with the highest absorbency had 28 percent of the Minnesota market share and were associated with 53 percent of the cases, whereas the lowest absorbency tampon group had 58 percent of the Minnesota market share and 35 percent of the cases,[18] suggesting that higher absorbency was associated with TSS. The absorbencies were categorized by fluid capacity rather than by box label, and only users of a single brand and style were included. The researchers suggest that tampon users have substituted other high absorbency tampons for Rely and note that the expected decrease in cases due to the slight decrease in tampon use would be too small to detect readily.

In the Tri-State study, Osterholm and his colleagues analyzed the risk of getting TSS associated with tampon chemical composition within each of three absorbency groups, but the limited amount of data and the inability to completely separate the effect of chemical composition from that of absorbency hinder interpretation of these data. Further epidemiologic and <u>in vitro</u> studies might lead to a better understanding of the role of tampon chemical composition as a risk factor associated with TSS.

Possible Role of Tampons in the Pathogenesis of TSS

Speculation for the reasons underlying the association of tampons with TSS has included the possibilities that tampons may 1) serve as a foreign body and, accordingly, promote or enhance the growth of bacterial pathogens; 2) serve as a vector for bacterial contamination acquired at manufacture; 3) traumatize the vaginal mucosa, by themselves or because of an applicator, and thus make the vagina more receptive to bacterial growth; 4) sensitize the vaginal mucosa through an allergic or contact mechanism with chemical additives; or 5) obstruct outflow, with a resulting reflux effect. Each of these potential mechanisms is briefly examined here; at present there is no compelling evidence favoring any of them.

Foreign Body

Tampon materials or other aspects of tampon construction could inhibit or enhance bacterial growth. Both in vivo and in vitro studies have addressed this question, but there is difficulty in relating in vitro data to the effect tampons may have in actual use during menstruation. The CDC has carried out in vitro studies on effects of tampons on S. aureus growth and survival. No enhanced growth of S. aureus was detected in nutrient broth or human blood, although growth was inhibited under some culture conditions.[21] In another study, toxin-producing strains survived longer on dry Rely tampons at room temperature (six weeks) than on the other three tampons tested,[21] but whether this characteristic relates to TSS is unknown.

The shape or other factors related to tampon structure may be involved in the pathogenesis of TSS. The way tampons expand in the vagina has not been explored. Further in vitro studies are under way to evaluate the possiblity that tampons, either because of composition or structure, may influence S. aureus growth or toxin production.

Effects of tampons on vaginal flora need further clarification. Several studies show no differences in genital S. aureus carriage with or without tampon use.[22-25] (See also Chapter 5 and Appendix C.) A CDC study found that the risk of S. aureus vaginal carriage was increased among women who inserted a tampon without an applicator or used Rely brand tampons, although the use of tampons (compared with no tampons) did not increase the risk.[25] Among the women who were S. aureus carriers, two toxin-producing strains were isolated among the 14 exclusive Rely users, and no toxin-producing strains were reported among the 86 exclusive users of other brands.[25] Other research groups have found a higher colonization rate with S. aureus among users of other tampon brands than among Rely users,[24] and no effect related to the presence or absence of an applicator.[22] With Rely no longer in use, these experiments cannot be repeated.

Vector

The possibility that tampons contaminated with S. aureus at manufacture are responsible for introducing the TSS organism was investigated; S. aureus contamination of tampons has not been documented in the United States.

The CDC cultured 504 tampons of various brands purchased between June 1980 and January 1981 to investigate intrinsic contamination.[21] S. aureus was not detected, suggesting that if such contamination occurred the rate would be no more than seven per thousand tampons.*

*If we assume a) the annual incidence rate of menstrual TSS is 10/100,000 menstruating women (or about 5,000 cases per year), b) each contaminated tampon leads to a case of TSS, and c) use of 5 billion

S. epidermidis and Bacillus species were detected to varying extents in all brands. The United States Food and Drug Administration tested tampon samples from 40 tampon boxes from each of five manufacturing plants in April 1981 and also failed to show any contamination with S. aureus.[26-28] Because the TSS-associated S. aureus apparently is found widely, there is no need to invoke tampon contamination at manufacture as the initial source of infection.

Another possibility is that the tampons become contaminated in the process of being handled and inserted.[25,29] Information consistent with this hypothesis is limited to the few cases in which the same organism has been recovered from both the tampon (or vaginal culture) and the nasopharynx of TSS patients,[30] or where the same strains were found in vaginal and nasal cultures of healthy women.[22,23]

Trauma

Tampons or their applicators might facilitate infection by traumatizing the vaginal mucosa, and cases of vaginal ulcerations apparently caused by tampons have been reported.[31-33] The relationship between tampon use and vaginal ulcerations was examined in two groups of 80 women through the use of colposcopy.[33,34] The women used tampons for five hours when they were not menstruating and used them during menstruation. Both during times of menstruation and times of non-menstruation, the tampons were associated with vaginal drying, epithelial layering, and micro-ulceration in more than 80 percent of the subjects. Biopsies of areas of mucosal alteration revealed disruption of intercellular bridges, widening of intercellular spaces, and loss of cell coherence, presumably secondary to fluid transfer and accumulation between individual epithelial cells and cell layers.

Tampon applicators might be responsible for mucosal damage, and FDA has received scattered reports of problems associated with applicators.[35] However, there is no indication from case-control studies that the presence or type of applicator affects the risk of getting TSS.

The possibility that mucosal alterations may predispose to TSS, and that more frequent changing of tampons may facilitate mucosal damage, has been responsible for the suggestion that tampons be changed less frequently.[36] However, other data and case reports suggest that leaving tampons in place for excessively long times may be associated with TSS.[20,37-39] More research is needed to discover whether vaginal ulcerations caused by tampons or by other factors increase the risk of getting TSS.

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tampons per year, then only one contaminated tampon in one million would be needed to account for the TSS cases. Assuming 500 cases per year, which is closer to the actual number reported to CDC, then the needed contamination rate would be one per 10 million tampons. Thus, cultures on a much larger number of tampons would be necessary to rule out tampon contamination as a factor.

Sensitization by Chemicals

Although no differences in use of deodorant vs. non-deodorant tampons have been found between TSS cases and controls, the potential for vaginal mucosal alteration secondary to sensitization by these chemicals is a possibility.[40] FDA analysis indicates that tampons may contain a wide variety of chemicals.[41]

Cause of Reflux

One researcher has proposed that tampons obstruct the flow of toxin-containing menstrual blood and cause reflux through the fallopian tubes into the peritoneal cavity where toxins are more rapidly absorbed.[42] Because various chemicals are readily absorbed through the vaginal mucosa,[43] it is not necessary to invoke additional mechanisms for toxin absorption. If reflux of infected menstrual blood did occur, it should result in evidence of peritonitis, which has not been observed in autopsies to date, although some symptoms of peritonitis have been noted.[44] Furthermore, TSS has occurred in a woman with a tubal ligation, where a reflux mechanism presumably could not operate.[45] A reflux mechanism is not necessary to explain tampon-associated cases and seems most unlikely.

Additional Host Factors

Additional factors may influence the disparate frequencies with which TSS is found in certain groups, such as adolescents and non-whites and Hispanics.

Adolescents

Data from Minnesota and from the CDC on reported cases indicate that women below age 25, and particularly those age 15 to 19, seem to be at increased risk for getting TSS compared with older menstruating women. In Minnesota, the incidence rate is twice as high for menstruating women ages 15 to 24 as for those 25 years of age or older.[18] Nationally, over one-third of menstrual cases reported to CDC by April 1982 occurred in women age 15 to 19.[46] The median age for menstrual cases reported to CDC is 20 years and for total female cases is 21 years.[46,47] There is no adequate explanation for this increased susceptibility among younger women. Although it might be related to immunologic competence (see Chapter 6), other factors of hormonal status or habits may contribute, especially among the adolescents. If the data for adolescents in case-control studies were analyzed separately from the rest of the study populations, any special risk factors might become evident. A few possibilities will be discussed below, but further research is needed to understand the susceptibility of adolescents.

Hormonal status In contrast to menstrual cycles in adult women, which are almost all ovulatory, those during adolescence may be anovulatory with accompanying specific hormone characteristics.[48] Within the first post-menarchal year, fewer than 20 percent of cycles are associated with ovulation. By the third post-menarchal year, this percentage has risen to more than 50 percent, and by the seventh year post-menarche, fewer than 15 percent of cycles are anovulatory. These data suggest that the adult level of ovulatory cycles is reached in most women by 19.5 years.[49]

Anovulatory cycles are characterized by low levels of serum progesterone, due to absence of the post-ovulatory corpus luteum, which is the major source of progesterone production, and by relatively constant levels of serum estrogen.[48] Patterns of glycogen in the vaginal mucosal cells and in the endometrium differ in ovulatory and anovulatory cycles, but it is not known whether these changes would influence factors relevant to TSS susceptibility or growth of TSS-associated organisms.

Another presumed manifestation of the adolescent's unique hormonal status is the difference in vaginal and cervical histology between adolescent and adult women. During adolescence, columnar epithelium covers the endocervical canal and with advancing age changes in large part to squamous epithelium.[50] Columnar epithelium is believed to be more susceptible to bacterial infection than is squamous epithelium.

If either of these factors were largely responsible for enhancing TSS incidence in this age group, one might expect the highest incidence of TSS to occur in the youngest adolescents. However, the available data on cases reported nationally have shown 16 to be the peak age for menstrual TSS.[46] Nonetheless, hormonal factors could act in conjunction with other factors, such as the increasing use of tampons with age, to enhance adolescent susceptibility to TSS.

Personal hygiene and contraception Various habits of personal hygiene and sexual habits have been found not to be significant as risk factors in TSS case-control studies. (See Chapter 3.) Nonetheless, there may be effects that relate specifically to adolescents, because they differ from older women in several habits. Adolescents douche to a lesser extent than older women,[8] a practice that might be expected to modify the bacterial flora in the vagina, and also tend to practice contraception less than adult women.[51]

Contraceptive and sexual practices might be relevant to TSS in several ways, although further study would be needed to evaluate these possibilities. The use of oral contraceptives might exert a hormonal effect that decreases susceptibility to TSS. Also, contraceptive foams and jellies containing 9-nonoxynol might exert a bactericidal effect and alter the vaginal environment; 9-nonoxynol has been reported to be bactericidal against gonorrhea.[52] Lastly, if personal transmission of staphylococci among sexual partners is implicated in the pathogenesis of TSS,[53] sexual and contraceptive practices might play a role.

Racial and Ethnic Factors

Non-whites and Hispanics have accounted for about 2 percent of nationally reported menstrual TSS cases where race was known,[46,47] and about 10 percent of nonmenstrual cases. However, only a small number of non-white and Hispanic cases were reported to CDC by April 1982. These included 18 blacks, 8 Hispanics, and 9 persons of Asian descent.[46] Non-whites and Hispanics make up more than 15 percent of the United States population based on the 1980 census. The low incidence rate of reported menstrual TSS cases found in non-whites and Hispanics compared with whites may be partially related to less common use of tampons among women in minority groups.

Although sparse, some data are available about tampon use among non-whites in the United States. National surveys during 1980 and 1981, each polling about 8,000 women 18 years of age and older, including almost 1,000 blacks, found that approximately the same percent of blacks and whites used tampons.[54] Among approximately 175 black women and 1,600 white women questioned in a national survey in mid-September 1980, 56 percent of blacks and 70 percent of whites used tampons.[8]

Approximately 700 post-menarchal northern California adolescents of ages 12 to 19 of various racial and ethnic backgrounds were questioned about their use of tampons during the summer of 1980.[55] In that study, tampons were used by about 65 percent of whites, 30 percent of blacks, and 10 to 15 percent of Hispanics, Asians, and other groups. Statistical analyses indicated a significant association between race or ethnicity and tampon use. If these data reflected national practice, they might help explain the relative paucity of menstrual TSS cases among minority groups. Various explanations have been offered.[56]

In Minnesota, where non-whites make up about 4 percent of the population, they have accounted for 2 percent of TSS cases; the 4 non-white cases were all associated with tampon use.[18] Nationally, less than 1 percent of reported menstrual TSS cases have occurred in blacks,[46] although blacks make up more than 10 percent of the national population. The available data on tampon use suggest that less common tampon use among black menstruating women might explain some but not all of the difference between blacks and whites in reported rates of occurrence of menstrual TSS.

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5

VAGINAL PHYSIOLOGY AND MICROBIOLOGY

Introduction

Most reported cases of toxic shock syndrome occur during the menstrual period in young women using tampons. In almost all menstrual cases adequately investigated, a local vaginal colonization or infection with an S. aureus strain with particular characteristics has been found. Therefore, efforts are underway to achieve better understanding of vaginal factors that might encourage growth of this organism. Although associated with the syndrome, the organism has not been proved to cause TSS. There are questions about the extent to which the organism is present in normal women, and the conditions during menstruation that might encourage its growth. Is it found in association with other organisms, and in TSS cases are other organisms found as well? Information also is needed about how the organism is introduced into the vagina and the effect of tampon use on its prevalence.

The emergence of TSS has indicated how much remains to be learned about the vagina during menstruation, and about changes that occur during the menstrual cycle, particularly in adolescents around the time of menarche. Recent research relevant to TSS has entailed:

- descriptive analysis of the normal vaginal physiology and microbiology in adult women during various phases of the menstrual cycle
- observations on sequential changes in vaginal microbiology in the same women studied during several cycles
- comparison of staphylococcal colonization in the vagina and other body surfaces, particularly the nares.

The studies so far have serious limitations. TSS cases in general have not been followed after the acute episode to determine changes in vaginal physiology and flora. Also, there have been no systematic, well-controlled studies of the effect of tampon use on vaginal physiology and flora. Adolescents have not been adequately studied. And finally, none of the studies of the physiology and microbiology of the vagina adequately address the clinical status of the vagina on pelvic

examination, thus precluding clinical-microbiological and clinical-physiological correlations.

Normal Vaginal Physiology and Flora

The vagina provides a specific environment for microorganisms.[1,2,3] However, its characteristics change during the menstrual cycle, and the number and type of organisms may also change. Study of vaginal flora is made more difficult because the flora among different women may vary greatly, and a given woman may have organisms one month that are undetectable the following month.[4,5,6] In women who menstruate the vagina is normally somewhat acid, with a pH of 4.5 or less during non-menstruating days of the cycle.[7] A recent study of 18 women found that the pH at the surface of the vaginal mucosa averaged 4.2.[8] During menstruation, the pH becomes more nearly neutral, increasing to about 6.5 in the presence of menstrual blood, and then falling again.[8] Changes in the mucosa and in the concentration of oxygen, carbon dioxide, or various substrates may also occur.[8]

Many studies have indicated that lactobacilli predominate in the vaginal flora of nearly all normal women during all phases of the cycle.[1,3,9] Most, but not all, studies have suggested that facultative lactobacilli outnumber obligate anaerobic lactobacilli throughout the cycle.[3,4,6] Measurement of organic acid metabolites in vaginal fluid shows predominantly lactate, which is the major metabolite of lactobacilli.[10] Many other bacterial species are found in the normal vagina, including S. epidermidis, various species of hemolytic and non-hemolytic streptococci, various poorly characterized species of corynebacteria, Gardnerella vaginalis, Ureaplasma urealyticum, and Mycoplasma hominis.[1,3,6]

Several investigators have studied the vaginal flora during menstruation and at other times in the cycle, although data concerning changes in the number of organisms and types of species vary.[3,6,11] A study of endocervical flora (which have a similar composition to vaginal flora) found the aerobic flora more varied during menses and the lactobacilli more prevalent and dominant during the second and third weeks of the cycle.[12] Several investigators have found an increase in the prevalence of S. epidermidis and coagulase-positive S. aureus during menses (see below).[3,13] Enteric gram negative rods, most commonly Escherichia coli, have generally been found in about 10 to 15 percent of normal women in low concentration during nonmenstrual phases of the cycle and, although data are scanty, they suggest that these organisms may increase during menstruation.[3,12,13] One investigator has noted a marked increase in the prevalence and concentration of coliforms on days 2 and 3 of menses.[14] Further investigation is needed to learn about changes in microbial species during the menstrual cycle.

A large proportion of otherwise normal women (20 percent of college students) and a higher proportion of women attending certain clinics have clinical manifestations of non-specific vaginitis (NSV).[7] In NSV, a facultative gram variable rod (G. vaginalis) replaces lacto-

bacilli as the predominant vaginal microbe, and other anaerobic organisms also increase.[10] This condition changes the milieu of the vagina, and is important in TSS for two reasons: 1) in choosing normal women for study, persons with NSV should be excluded or studied separately, but researchers have not generally made a special effort to detect persons with asymptomatic NSV, and 2) it is unclear if there is a relationship between NSV and TSS. However, a history of vaginal discharge or a vaginal infection was more common in TSS cases than in controls in one study.[15]

Studies of S. aureus Carriage in Normal Subjects

To better understand the possible relationship between S. aureus and TSS, studies have been undertaken in normal women to determine factors associated with vaginal carriage of the organism, and to relate these to carriage at other body sites. For other kinds of staphyloccocal infections, such as those acquired in a hospital, transmission is often by contaminated hands, and it would be of interest to know whether that kind of transmission might apply to TSS.[16,17]

Vaginal Carriage of S. aureus

Appendix C summarizes results of S. aureus carriage in a number of studies, many of which were not specifically seeking S. aureus. The reported prevalence of vaginal S. aureus ranges from 0 to about 17 percent. The proportion of women with detectable genital (vaginal, labial, or cervical) S. aureus is often higher during menstruation than at other times in the cycle. This finding applies to instances of women being cultured once, or being followed through several cycles.[3,13] For example, 3 of 31 women had positive vaginal S. aureus cultures the second or third day of menstruation, but none was positive a week later.[3] Another study of 54 women found cervical S. aureus both in midcycle and menses in 3 women, during menses alone in 6 women, and during midcycle alone in none.[13] Another study of 600 women found that S. aureus was recovered from vaginal cultures in 5 percent of women, and from labial cultures in an additional 4 percent, for a genital colonization rate of 9 percent; the authors state that overall frequency of S. aureus recovery was the same throughout the menstrual cycle. An important finding in studies of women tested repeatedly is that some can apparently be characterized as persistent vaginal carriers of S. aureus, some as intermittent carriers, and some as persistent non-carriers.[18,19]

One or more recent studies have shown that the prevalence of coagulase-positive S. aureus was:

1) higher in the nares than in the genital tract[6]
2) higher on the labia than in the vagina[18]

3) higher in the nares, labia, or vagina than on the hand[6]
4) higher in postpartum patients than in prenatal patients or those seen for routine examination or for other complaints.[3,18]

Additional factors also were considered for correlation with S. aureus carriage, and results from various studies often are contradictory.

Age[11,16,18] Guinan found that rates of vaginal colonization with S. aureus were essentially the same for women of ages 14 to 19, 20 to 29, and 30 to 39. Linnemann states that his study of colonization rates by age showed no significant differences. A greater rate of colonization among younger women was noted in one preliminary report.[11]

Race In one study, blacks had a higher rate of S. aureus carriage than whites.[18] Of 225 blacks, 14 percent had positive labial or vaginal cultures, whereas 6 percent of 373 whites had positive cultures. Comparable figures for vaginal cultures were 8 percent for blacks and 4 percent for whites.

Socioeconomic status S. aureus was more prevalent in the genital area in women of lower SES under some conditions in at least two studies,[13,18] but was unrelated to SES in another.

Vaginal discharge or history of genital herpes The evidence here is also inconsistent,[13,16,18] with one group reporting no association with S. aureus colonization[18], another reporting a weak association in one of two studies,[16] and a third group finding a significant association.[13]

Contraceptive method At least two studies found no significant relationship between oral contraceptive use and S. aureus vaginal carriage.[16,18] However, one study reports that use of a diaphragm or IUD (intrauterine device) was associated with a 16 to 18 percent prevalence of vaginal S. aureus carriage, compared with an overall 9 percent rate.[16]

Menstrual product use At least four studies found that the use of tampons or napkins was not correlated with S. aureus carriage.[13,16,18,19] However, CDC studies involving relatively small numbers of subjects suggested there was a significantly higher prevalence of S. aureus carriage among Rely tampon users than among users of other brands.[16] Another study, also with small numbers, found a lower incidence of colonization among Rely users (2/16, 12 percent) than among users of other tampons (5/24, 21 percent).[13] Insertion of a tampon with fingers rather than an applicator was associated with increased S. aureus carriage in one study,[16] but not in others.[13,18,19] A study that compared tampon and sea sponge use found a higher rate of isolation of S. aureus, E. coli, and Klebsiella-Enterobacteriaceae sp. from sponge users compared with users of other internal products, suggesting that sea sponge use does not protect against colonization with S. aureus, and may increase the risk of such colonization.[13] No extensive study has yet prospectively studied the prevalence or concentration of S. aureus in the vagina during menstruation in relation to tampon use vs. napkin use.

Non-Vaginal Carriage of S. aureus

The presence of S. aureus in the vagina was correlated with the presence of the organism on the labia and with nasal S. aureus carriage in several studies.[6,16,18,19] In addition, the phage types of S. aureus isolated from the vagina were usually the same as those from the other sites. The majority of vaginal carriers were also nasal carriers. In Guinan's study, 9/13 or 70 percent of vaginal carriers also had positive nasal cultures, whereas 19/114 or 15 percent of vaginal non-carriers were nasal carriers. Where vaginal and labial cultures were both analyzed, they were the same phage type about 60 percent of the time. In another study of 39 women with positive genital cultures, 15 (38 percent) had positive nares cultures, and, when the S. aureus were typable, the same phage type was always found.[18]

Toxin-Producing S. aureus Carriage

The prevalence of S. aureus containing the putative TSS toxin(s) was investigated in some studies. In Cincinnati, strains that produced staphylococcal enterotoxin F (SEF) were isolated from the genitalia of 3 of 275 healthy women.[18] In another study, approximately 5 percent of women carried a strain of S. aureus producing pyrogenic exotoxin C (PEC); 4 of 11 S. aureus strains isolated from anterior nares and 12 of 36 vaginal isolates produced PEC, compared with only 5 percent (1 of 20) of isolates from wounds or abscesses, suggesting a predilection for such toxin-producing strains to the nares and vagina.[20] In three families in which a woman carried SEF-producing S. aureus in the vagina (but not in the nares), an SEF-producing S. aureus was isolated from the nares of a child in the household, suggesting the possibility of intrafamilial transmission.[18] A few reports of TSS cases suggest that person-to-person transmission may occur.[21,22] Studies of sexual partners of SEF carriers and of recovered TSS patients are needed to learn if sexual transmission of the organism occurs.

S. aureus Interactions with Other Microorganisms

Microbial growth on mucosal surfaces is greatly influenced and regulated by the presence of other organisms. Interference or enhancement of growth may be particularly relevant for organisms such as the TSS-associated S. aureus, which may not usually provoke specific host defense responses.[12,23,24] Little research, either in vivo or in vitro, has been conducted to clarify the relationship between vaginal S. aureus and the other vaginal microbes. Some studies in vivo have suggested that lactobacilli may act to prevent growth of other organisms in the vagina.[12] In vitro experiments suggest that certain strains of lactobacilli inhibit growth of S. aureus, but further study is needed.[9] A preliminary study of 95 women using tampons during menstruation suggests a possible positive correlation between vaginal

colonization with S. aureus and beta-hemolytic streptococci (presumably Group B).[25]

Microorganisms in TSS Cases

Where adequate cultures have been taken, S. aureus has been recovered from a high percentage (up to 100 percent) of patients with menstrual or nonmenstrual TSS (see Appendix D). However, quantitative cultures for S. aureus have not been performed in TSS cases, and there has been no attempt to compare the prevalence or quantity of S. aureus in the vagina or nares of menstrual TSS cases and matched controls during menstruation. Therefore, interpretation of differences in S. aureus carriage between normal populations that have been studied and TSS cases should be done cautiously. Data related to S. aureus in TSS cases will be reviewed below. Chapter 6 discusses the characteristics of TSS-associated S. aureus.

According to CDC reports, of 1390 menstrual definite cases of toxic shock syndrome, only 415 had a known culture result; 384 (93 percent) of these were reported as positive for S. aureus.[26] This high percent of reported recovery has been constant over the periods of time that the CDC has been receiving reports (pre-1980 to the present). Of 104 nonmenstrual definite TSS cases, 67 had a known culture result for the site of infection. Sixty-four were positive for S. aureus, and the three negative samples were taken after administration of antibiotics.[26] Among probable cases reported to CDC with known culture results, over 90 percent were positive for S. aureus.[27]

S. aureus data are also available for some of the cases in the case-control studies described in Chapter 3 (see Appendix D). The CDC I and CDC II data are also included in the total CDC data above. In the Wisconsin study, 17 of 23 cultures (74 percent), were positive for S. aureus.[28] In CDC I, 16/16 cultures were positive.[29] In CDC II, 43 of 44, or 98 percent, of cultures were positive.[30]

In the Tri-State Study, among 80 cases seen from October 1979 to September 1980, the rate of recovery of S. aureus from patients with a known culture result before initiation of antibiotic therapy was as follows: cervix/vagina 44/54 (81 percent); rectum 6/31; throat 4/45; nose 11/24; other sites (conjunctival, axillary, etc.) 16/50; overall (at least one site) 51/67 (76 percent).[31]

Although the association of S. aureus with toxic shock syndrome appears to be strong, results of cultures are not included in most of the cases reported to the CDC. It also is not clear how much bias there may be in reporting positive (and not negative) culture results and in excluding the diagnosis in patients with negative culture results.

There is a need for more complete culture data, including quantitative studies on S. aureus and other genital flora in TSS cases. Because it is possible that other organisms, including possibly viruses, may play an accessory role in TSS (or a primary role in cases without S. aureus), quantitative information on vaginal flora and gram

stains of vaginal secretions are especially needed. Reports on a few TSS cases suggest that other vaginal organisms are not completely replaced by S. aureus in many instances. For example, among a limited number of cases reviewed, a substantial proportion had gram-negative coliform bacteria isolated on primary culture along with S. aureus.[32,33] Therefore, cultures performed with inhibitors of S. aureus in the media would be useful, since S. aureus may overgrow other organisms of possible pathogenic significance. For example, it is well known that staphylococci may overgrow and obscure group A streptococci in wounds or burns and in pyoderma or impetigo where S. aureus is a frequent secondary invader.[34,35]

Some of the needed information could be obtained if physicians seeing patients with suspected toxic shock syndrome obtained cultures from multiple sites before antibiotics are initiated, and reported these results to the CDC. In addition, longitudinal follow-up studies in patients with TSS, taking cultures from multiple sites at frequent intervals, would provide information about the possible temporal association of recurrence with reappearance of positive cultures for toxin-producing S. aureus. Other physiologic variables should be monitored at the same time.

Additional Studies Needed

Although the available studies reveal a great deal about S. aureus carriage in apparently normal women, some critical experiments remain to be done. Women have not been adequately systematically followed in an experimental design that includes random assignment to napkin or tampon usage. Furthermore, vaginal physiology and flora have not been adequately studied, especially in women who are intermittent S. aureus carriers. Little is known about the changing flora during adolescence. The available data show that S. aureus colonization of nares is common among women who are vaginal carriers, but further study is needed to determine how the S. aureus is introduced into the vagina.

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6

TSS-ASSOCIATED STRAINS OF *STAPHYLOCOCCUS AUREUS*: THEIR TOXINS AND OTHER CHARACTERISTICS

The apparent nature of the host-parasite interaction in TSS suggests that the syndrome is mediated by a bacterial toxin or toxins elaborated by particular strains of *S. aureus*.[1] The toxin might act directly or might enhance the effect of other toxins. The clinical picture has many features in common with bacterial endotoxin shock.[2] (See Chapter 2.) Although many of the studies have concentrated on two toxins found in these TSS-associated strains of *S. aureus*, the possibility that other toxins or other organisms are involved has not been adequately explored. This chapter reviews the studies that have been done related to TSS-associated *S. aureus* strains.

The mechanism by which the infective organism is introduced is not yet known. However, for menstrual cases, a possible sequence of events in the host-parasite interaction would involve nasal or skin colonization by a TSS-associated strain of *S. aureus* followed by the organism's introduction into the vagina and its establishment in this local environment in competition with the normal vaginal flora. It can be further postulated that multiplication of the implanted organism then occurs most readily during menstruation in association with tampon usage, although the reasons for the enhanced multiplication are not yet understood. (For nonmenstrual cases, the *S. aureus* could also be introduced from the skin or the nares of the individual or from other sources.) Toxin(s) apparently are produced, released, and absorbed across the mucous membrane of the host, affecting multiple target organs, and finally producing the systemic signs and symptoms of TSS. A schematic diagram of this possible sequence of events is presented in Figure 6-1.

Several questions must be answered to confirm or refute this sequence, define the etiology and pathogenesis of the disease, delineate the determinants of host susceptibility or resistance, and develop more effective methods of prevention, diagnosis, and treatment:

- What toxin(s) do TSS-associated strains produce and what roles, if any, do the toxins play in the pathogenesis of the illness?
- What other characteristics identify TSS-associated strains of *S. aureus*, and how may these be used for epidemiologic studies, diagnostic tests, and elucidation of how these strains spread, colonize, and infect the human host? What factors influence toxin production

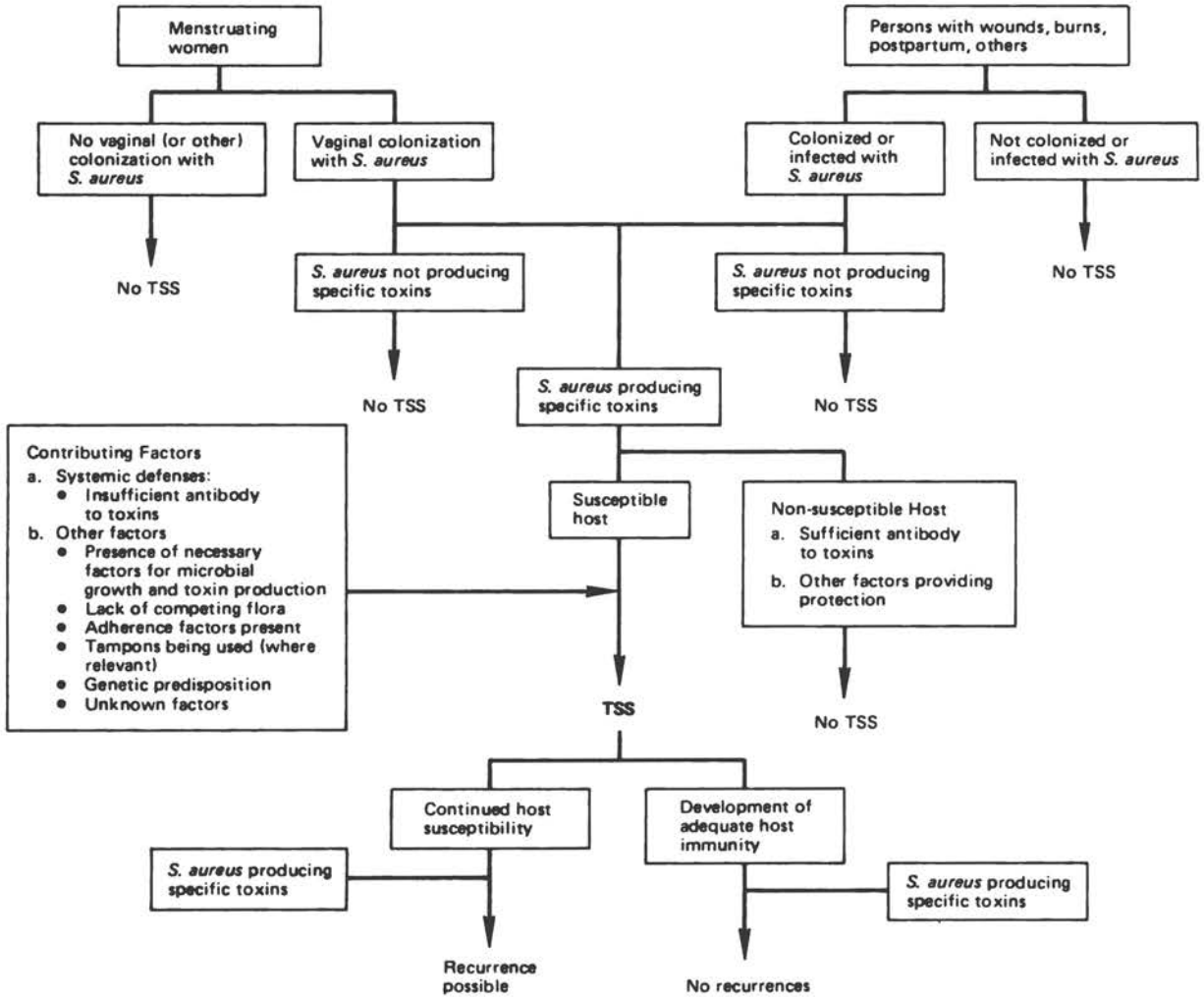

FIGURE 6-1. Possible sequence of events in the development of toxic shock syndrome, assuming a Staphylococcus aureus toxin model.

in vitro and *in vivo*, including both the mechanism of genetic control in the organism and the physiologic, biochemical, and microbiological host environment?

- What factors determine host susceptibility and resistance? If TSS-associated *S. aureus* strains are common and many people are colonized and at risk, what determines the relatively small number of individuals who develop the syndrome?
- Can researchers develop an animal model that will permit study of the syndrome's pathogenesis and the host response under controlled experimental conditions?

In studies to detect differences in various characteristics between TSS-associated and non-TSS-associated strains, a potential weakness is in the choice of control strains. They ideally should be from the same population groups, body sites, and stage of menstrual cycle (where applicable) as TSS-associated strains, but such matching is rarely achieved.

Toxin Production and Role in the Pathogenesis of TSS

S. aureus strains produce many toxins that have roles in illnesses associated with these organisms.[3,4] TSS-associated strains of *S. aureus* produce several distinct toxins.[5-8] Attention has been focused primarily on two such toxins, which may be the same or related proteins, described by Bergdoll and by Schlievert.[6-8]

Schlievert and coworkers have isolated an exotoxin that they have designated pyrogenic exotoxin C (PEC). It was present in culture supernates of 93 percent of 259 *S. aureus* isolates from patients with TSS but was detected in only 26 percent of 609 non-TSS strains.[8] Partially purified preparations of PEC are pyrogenic in experimental animals, enhance susceptibility to bacterial endotoxin, have immunoregulatory activity, and are mitogenic for T lymphocytes.[7,8] These properties are similar to those reported for staphylococcal exotoxins A and B[9,10] and streptococcal pyrogenic exotoxins A, B, and C.[11]

Another toxin, described by Bergdoll and coworkers,[6,12] was produced by 91 percent of 142 TSS-associated strains of *S. aureus* tested but by only 10 percent of 284 *S. aureus* strains from other sources, including patients with food poisonings, furuncles, staphylococcal scalded skin syndrome, and women with vaginal colonization. These workers have characterized the toxin as an enterotoxin, staphylococcal enterotoxin F (SEF). SEF is antigenically distinct from previously identified staphylococcal enterotoxins A through E.[3,6,12]

Critical issues now concern whether SEF and PEC are the same or different toxins and whether they represent only markers for TSS-associated bacterial strains or are the major mechanism through which the signs and symptoms of the syndrome are produced. If the latter, the unique characteristics of PEC and/or SEF that are determinants for TSS must be identified and distinguished from the toxins or other properties of non-TSS strains of *S. aureus*.

Although most TSS-associated strains tested were positive for both SEF and PEC,[13,14] biological and physico-chemical differences are reported to exist between currently available preparations of these toxins. Bergdoll's group reports that SEF has a molecular weight of 27,000, an isoelectric point of 6.8, and contains about 7 percent tyrosine.[6,12,15] Schlievert's group finds that PEC has a molecular weight of about 22,000, an isoelectric point of 7.2, little tyrosine, and a pale yellow color as isolated.[8] It has been claimed that lines of identity occur when antibody against SEF or PEC is run against both SEF and PEC preparations in an immunodiffusion assay.[15,16] The results of the immunodiffusion assays suggest that the substances are structurally related.

Other Characteristics and Markers of TSS-Associated S. aureus

Various characteristics of TSS-associated staphylococci other than production of PEC or SEF may serve as useful markers for initial screening and recognition of these strains and may also relate to the organism's possible pathogenicity.

Phage Typing and its Relationship to Toxin Production

Phage typing, a method of grouping S. aureus strains according to their susceptibility to different bacteriophages, has placed most of the TSS strains in group I. Within group I, phage types 29 and 52, alone or in combination, predominate.[13,14] About 65 percent of 159 TSS-associated strains in one study were type 29/52, while 25 percent were non-typeable, suggesting that other unknown phage types may also be associated with TSS. Over 80 percent of the non-typeable TSS strains, and over 90 percent of the type 29 and/or 52 TSS strains, produced PEC.

Studies suggest that type 29/52 has increased in frequency in recent years and that within that phage type the ability to make PEC and SEF has also increased. Studies in Ohio of S. aureus strains isolated from infections over many years have indicated that phage types 29 and 52 existed as long ago as 1960. Their prevalence increased to about 20 percent of strains isolated in the late 1960s and early 1970s, and decreased to about 10 percent in frequency during the late 1970s.[14]

PEC and SEF have also apparently become more prevalent in recent years. The Centers for Disease Control report that PEC was present in 17 percent of 35 tested strains of phage type 29/52 isolated between 1956 and 1964 and in 2 percent of other phage types tested (one of 40 strains).[17] For isolates obtained in 1979, PEC was detected in about 40 percent of phage types 29/52 tested (12 of 29 strains) and in a similar percentage of other phage types (5 of 13 tested).

In the Ohio collection a progressive increase of PEC-producing strains was found among the phage type 29/52 isolates during the

1970s, with an especially high prevalence (60 to 85 percent) of toxin production in these strains during 1974 to 1979.[14] The frequency of PEC production by phage type 29/52 strains apparently declined somewhat during 1980 and 1981. Many of the 29/52 strains also produced SEF, and a few were positive for staphylococcal enterotoxin A.

Additional Proteins

Another TSS-associated toxin was originally described by Todd and coworkers.[1] They reported that TSS S. aureus isolates produced an exotoxin that caused exfoliation in mice, but was distinct from the epidermolytic toxin responsible for the staphylococcal scalded skin syndrome. Approximately 73 percent of 52 TSS-associated strains of S. aureus tested produced this new epidermal toxin compared with 18 percent of 106 control strains tested.[5] In contrast to the epidermolytic toxin associated with the scalded skin syndrome, the epidermal toxin produces extensive cellular destruction beneath the germinal layer, leaving the granular layer intact. This epidermal toxin has not been extensively studied, and its role in the pathogenesis of the disease remains uncertain.

Two additional proteins have been identified in whole cell preparations of TSS-associated strains of S. aureus.[18] The molecular weights for these proteins (30,000 and 33,000) are greater than those of PEC and SEF, and the relationship, if any, of these higher molecular weight proteins to PEC, SEF, or other known staphylococcal substances is not clear.

Phenotypic and Genetic Studies

Traits more frequently found in TSS-associated S. aureus strains than in non-TSS isolates include resistance to penicillin, cadmium, and arsenate, increased proteolysis of hemoglobin, reduced hemolysis of sheep red blood cells in agar medium, and lack of lethality of culture filtrates for chicken embryos and rabbits.[19,20] In particular, the narrow zone of hemolysis of TSS-associated strains on sheep blood agar is often a striking feature of these TSS strains.[19,21] In addition, TSS-associated strains have been shown to produce low amounts of hemolysin for rabbit erythrocytes and low amounts of lipase and nuclease compared with non-TSS strains of S. aureus from wounds, nares, or the vagina.[8] Also, most TSS strains appear to lack a protein with isoelectric point 8.6 found in most other S. aureus strains tested.[19] It has been suggested that the patterns of enzymes noted above may prevent TSS-associated S. aureus from readily invading host tissues.

Preliminary studies have indicated that TSS-associated strains of S. aureus lack plasmids, and that the characteristic cadmium, arsenate, and penicillin resistance are chromosomal traits.[22,23] This is unusual for S. aureus; earlier studies of 30 strains showed that penicillin resistance usually was plasmid determined, and cadmium resis-

tance always was.[24] Present evidence suggests that the gene for TSS-associated toxin is a variable and mobile genetic element in the general category of a heterologous chromosomal insertion (i.e., an extra segment of chromosomal DNA), but further study is needed.[22]

Factors Related to Toxin Production

Studies gradually are elucidating the factors favoring production of the TSS-associated toxin(s) *in vitro*.[25] Various substances present in the *in vivo* environment during menstruation may be useful to the TSS-associated organisms for growth and toxin production. For example, iron is known to be critical in production of diphtheria and other toxins, but its effect on TSS-associated organisms has not been explored.[26,27] Whether the increased ability to hydrolyze hemoglobin would be an advantage for growth or toxin production in menstrual fluid is also not known.

In view of the association of TSS with tampons, and apparently more specifically with high absorbency tampons, the effect of the materials and structure of tampons on the growth of TSS-associated strains and on toxin production need to be carefully considered. Preliminary results from *in vitro* studies indicate that aeration enhances the rate of growth and PEC production of TSS-associated *S. aureus*,[25,28] and it has been hypothesized that tampons may provide oxygen for vaginal *S. aureus*. Further studies are needed to verify or refute the hypothesis.

Host Defense Mechanisms

To cause infection and illness, according to the model in Figure 6-1, the TSS-associated bacteria presumably must enter the host, grow and make toxin, and the toxin must be dispersed and act.[29] Any of the local and systemic host defense mechanisms could play a role in preventing the full sequence from occurring and causing TSS.[27,29] For most aspects of host defense mechanisms, few data are available that can be critically evaluated. For example, local antibody (secretory IgA) might interfere with adherence of staphylococci to the vaginal wall, but this possibility has not been tested. (One study sought and failed to find adherence differences among control strains and TSS-associated *S. aureus*.[30]) Evidence of an antibody response to staphylococcal teichoic acid usually is not found in patients with TSS, a finding consistent with the generally non-invasive nature of the infectious process.[31] A toxin or toxins may influence the host's immune response. Finally, the susceptibility of the host and the host's ability to produce antibody against TSS-associated *S. aureus* antigens may be important.

Antibody to SEF may be a measure of resistance to TSS, although direct evidence on this point is lacking at present. TSS patients appear to have lower levels of antibody to SEF than normal subjects.[6,12] Using a radioimmune assay for antibody to SEF, only 7 percent of acute

sera from 92 TSS patients had antibody titers of 1:100 or greater, whereas 81 percent of 111 controls had antibody at that level.[12] This finding implies that most, if not all, TSS patients might have been susceptible to this toxin because they lacked SEF antibody before becoming ill. Since antibody levels did not increase during convalescence in most patients, most TSS patients may be unable to respond to this toxin, or the toxin may suppress the immune response.[27] Alternatively, antibiotic therapy during treatment may have interfered with antibody production or, as in patients with tetanus or botulism, little or no antibody response may occur, possibly due to the small amount of toxin needed to produce disease.[32] However, antibody titers do increase in some patients, and one patient developed antibodies to SEF after two TSS recurrences.[15]

Preliminary studies of more than 700 serum samples from Wisconsin suggest that the prevalence of antibody to SEF in the general population increases with age, reaching 85 percent of tested individuals by age 20 and 95 percent by age 30.[33] Sera were obtained from healthy individuals and from patients being tested for viruses, but no differences in antibody titer were detected between the two groups. Antibody prevalence was about the same in sera obtained in 1970 as in sera from 1980. These antibodies are apparently present at one year of age in 30 to 40 percent of infants tested; by this age the maternally derived antibodies present earlier are depleted and infants make their own antibodies. A prevalence of 30 to 40 percent in one-year-olds is surprising since it implies that by this age one out of three infants may have encountered this toxin or some cross-reacting antigen and responded immunologically to it. On the other hand, SEF or cross-reacting antigen may be not uncommon, so early exposure may be possible.

Further studies on host immunity related to TSS are needed. The immune response during menstruation, especially in regard to leukocyte function, should be studied in women of various ages. Another obvious lack of data concerns the *in vivo* production and distribution of the putative staphylococcal toxin(s) in the human host. The presumed toxins have not been directly identified in vaginal samples or in blood or urine from cases or healthy carriers, although SEF apparently has been detected by immune assay in breast milk of a patient.[34]

The immunological data and the studies on prevalence of PEC and SEF in pre-1980 samples of *S. aureus* appear inconsistent with the hypothesis that the emergence of TSS in the past few years is related solely to the appearance of these toxins as new agents of disease. It seems likely that some factor other than production of these toxins, or in addition to toxin production, contributed to the emergence of TSS as a notable medical problem in 1980.

Development of Animal Models

The development of an animal model of TSS will be an important step in further defining the pathogenesis of the syndrome and the determinants of host resistance and susceptibility. No well-developed

experimental model reproducing all of the manifestations of TSS in humans is currently available, but several are being sought. Although relatively large doses of other enterotoxins produce some of the signs and symptoms of TSS in monkeys[6], this model does not appear to be a good one for SEF. Attempts are being made to develop models using rabbits,[7,35] mice,[36] monkeys,[6] and the baboon.[37]

In rabbits, PEC has biological activity which is manifested by fever and up to 50,000-fold enhancement of the lethal effects of bacterial endotoxin.[7,20] This work has suggested the possibility that enhancement of endotoxin activity may contribute to the pathogenesis of TSS in humans. Based on present evidence, however, this interpretation remains speculative and emphasizes the need for an experimental model that would more clearly and fully mimic the human syndrome.

A localized infection with S. aureus has been established in a whiffleball chamber implanted in rabbits. A lethal infection was observed only with TSS-associated strains that produced PEC.[35] Further work is necessary to determine whether the effect is specifically due to toxin(s) and whether the pathologic findings simulate the systemic effects of TSS in humans.

Another model of a localized staphylococcal infection with systemic manifestations is being developed.[36] A lethal infection in the absence of septicemia results when S. aureus is inoculated into mice by implantation on a surgical suture placed in the kidney of leukopenic mice. IgE antibody is associated with enhanced lethality. The relationship of this outcome to TSS remains to be defined.

At present none of these animal models reproduce all of the clinical features of TSS and further development of experimental models is clearly needed.

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7

FINDINGS AND RECOMMENDATIONS

Much is lacking in our knowledge of the etiology, pathogenesis, and risk factors associated with toxic shock syndrome (TSS). Our major findings are highlighted below, followed by recommendations about needed research and ways of facilitating such research. Finally, measures are suggested to enhance recognition of the syndrome and minimize its occurrence, although it is recognized that more effective preventive measures will be possible only when the illness is better understood.

We emphasize that toxic shock syndrome, an illness that predominates in young menstruating women using tampons, is associated with toxin-producing strains of Staphylococccus aureus, and that cases of the syndrome are still occurring.

Findings

Case Definition

Approximately 500 TSS cases have been reported in the United States with onset in 1981; thus, it appears that TSS, as defined by the CDC criteria, is a relatively rare illness. It is defined by a constellation of clinical signs and symptoms that include acute onset of fever, rash and subsequent desquamation, hypotension, and multi-system involvement. The specific CDC criteria for a case appear reasonably sufficient to distinguish TSS from other conditions. As with most illnesses, TSS seems to show a range of clinical manifestations and severity, but more systematic study of less severe cases awaits a specific laboratory marker for the illness.

Treatment and Sequelae

Published case reports emphasize the value of treating TSS symptoms with general supportive measures, including vigorous volume support and vasopressors to treat hypotension, and correction of hypocalcemia and of electrolyte and acid-base abnormalities. A penicillin-resistant S. aureus is usually present in TSS cases; use of beta-lactamase-

resistant antimicrobial agents to inhibit or eradicate this organism seems to have value in preventing recurrence. However, evidence is not available to indicate that such treatment ameliorates symptoms or shortens the course of the acute illness. Existing information is not sufficient to provide certainty that the reported neuropsychologic sequelae are attributable to TSS.

Pathology

Autopsy results have been reported for approximately 25 TSS cases. Pathologic findings show considerable overlap with those seen in cases of shock caused by other conditions, such as gram negative rod bacteremia. Two types of histologic findings found predominantly in TSS cases are of interest: 1) ulcerations of mucosal surfaces, especially of the vagina, mouth, bladder, and esophagus, caused by separation at the basement membrane, and 2) ingestion of red blood cells by mononuclear cells (hemophagocytosis). Death in TSS cases is generally attributed to hypotension, renal failure, or adult respiratory distress syndrome.

Patterns of Occurrence and Risk Factors

Cases of TSS are still occurring, but the number of new cases occurring per month in the United States is not known with certainty because many variables influence reporting of cases. From a high of 135 reported cases with onset in August 1980, the number of cases reported nationally fell to about 70 with onset in October 1980, and remained at about 50 cases per month throughout 1981. The case fatality rate among reported cases was about 3 percent in 1981. Approximately 150 cases had been reported by the end of 1981 from a dozen countries other than the United States.

Based on reported cases, large variations in the apparent incidence rates of TSS exist among the states. The number of new cases of TSS per month reported to CDC declined after Rely tampons were removed from the market by the manufacturer in September 1980, although the decline was not seen in Minnesota, which has conducted active surveillance for TSS. The highest 18-month reported incidence rate (from Minnesota between January 1980 and June 1981) was about 2.3 cases per year per 100,000 population; by age and menstrual status, there were 8.9 menstrual cases per year per 100,000 menstruating women in Minnesota, or 13.7 menstrual cases per year per 100,000 menstruating women of ages 15 to 24. It is not known if the observed differences in incidence rates among the states reflect reporting differences, actual differences, or a combination of various factors.

TSS is reported to occur most commonly during menstruation. Fifteen percent of cases reported to CDC with onset in 1981 occurred in males or in females who were not menstruating when they became ill.

Use of tampons during menstruation is associated with an increased risk of developing TSS, but the mechanism by which tampons enhance this risk remains unknown. Cases have been reported with all major tampon brands and absorbency ranges. The absorbency of the tampon has been implicated in one study as a risk factor for TSS, but confirmative studies are needed. Furthermore, it is not known whether the risk of acquiring TSS is lessened if tampons are used intermittently rather than continuously during a menstrual period. Although there were many potential biases that could have resulted in the finding of an increased relative risk for TSS associated with Rely tampons compared with other tampon brands, the consistency of the data from several case-control studies conducted at varying times in several states suggests that this increased relative risk was real.

The rate of reported menstrual TSS cases among United States blacks is less than 10 percent of that of whites. It is unknown if the lower incidence rate is due to poorer recognition and reporting of TSS, to less frequent use of tampons among blacks, to lower susceptibility among black women using tampons, or to a combination of these or other factors. It seems unlikely that less frequent use of tampons among blacks accounts for the entire difference in reported incidence rates.

TSS-Associated S. aureus and Toxins

Most of the TSS cases that are adequately cultured at the site of suspected infection show strains of S. aureus with distinctive characteristics. However, the possibility that other associated bacteria or factors are required for expression of the syndrome has not been eliminated. Furthermore, some apparently healthy people carry S. aureus strains that are similar or identical to those associated with TSS cases. TSS-associated strains of S. aureus have been found to be predominantly group I, 29/52 phage type, although about one-quarter have been non-typeable.

The lack of bacteremia noted in most cases suggests that TSS is a toxin-mediated syndrome. Two proteins, pyrogenic exotoxin C (PEC) and staphylococcal enterotoxin F (SEF), are produced in vitro by over 90 percent of TSS-associated S. aureus strains tested. Currently available preparations of these toxins have some biological and physicochemical similarities. They are apparently immunologically related, and it is possible that they may be the same toxin. However, the role of these toxins in the pathogenesis of the syndrome is not known. They may represent markers for TSS-associated S. aureus strains. Although animal models have been developed in which systemic effects have some resemblance to those of TSS, none of these models reproduces the syndrome as it appears in humans.

Prevention

Minnesota and national data indicate that 80 to 85 percent of reported TSS cases are associated with tampon use during menstruation; it is likely that the number of reported cases would be markedly reduced in the absence of tampons.

Research Recommendations

The following research recommendations reflect the shortcomings in available information about TSS that have been identified earlier in this report. Some recommendations are quite general, whereas others are more specific about types of research needed.

Case Definition

1. For studies of the epidemiology, pathology, and natural history of TSS, CDC's criteria for definite cases (see Chapter 2) should be maintained to exclude most illnesses with overlapping clinical features and to allow for better comparison among studies. However, clinicians should be notified that TSS apparently manifests itself in mild as well as severe forms, so that they can provide appropriate reporting and treatment for patients who may have only some of the features of the syndrome.

2. Clinicians and other health workers should be reminded that the CDC case definition does not require the presence of menstruation, tampons, or S. aureus.

Multi-Institutional Collaboration and Specimen Banking

1. Because TSS is an illness of low frequency, many of the unanswered clinical and etiologic questions can best be approached by multi-institutional collaborative studies that share clinical and pathological samples and data, and undertake treatment in a systematic way. We strongly recommend and encourage the establishment of such collaboration. With about 500 cases reported for 1981, collaborative study is essential for collection of data over a wide geographic area.

2. Several areas recommended for priority investigation of cases include (1) evaluation of treatment and prevention modalities, (2) definition of sequelae of TSS, (3) comparison of menstrual and non-menstrual cases with regard to host factors that might be TSS determinants, (4) collection of comprehensive and quantitative microbiologic data from multiple body sites and from tampons, and 5) developing evidence for presence of toxins in vivo. More detailed pathological description, including gross, microscopic, and ultrastructural studies, should receive high priority. Because autopsy material is scarce, pathology is an area in which specimen banking for collaborative studies has great promise.

3. Physicians should be encouraged to obtain detailed clinical information and laboratory specimens on all definite and probable cases of TSS, as well as on suspected cases (i.e., those who have some features of TSS and in whom other diagnoses appear to be excluded). Cultures should be taken before initiation of antibiotic therapy. Information should be reported and shared appropriately among researchers.

Epidemiology

1. A standardized, uniform hospital chart review study to identify TSS cases retrospectively should be developed and conducted in several areas of the United States. Such a review should include illnesses in males and females that could have been TSS but were diagnosed as something else. The review should go back at least to 1977-1978. Such a study would provide objective data regarding the incidence rates for TSS before and after its recognition as a distinct clinical entity. Such a review might provide a more accurate assessment of the extent of underreporting and overreporting of TSS.

2. Active surveillance of TSS should be undertaken in several different areas of the United States, in conjunction with the hospital chart review mentioned above. At least one such area should have a substantial population of non-white and Hispanic females of menstruating age. Such a study might indicate the extent to which incomplete reporting explains apparent geographic and racial variations in occurrence of TSS.

3. A prospective follow-up study of a population-based sample of women, including those who are carriers of TSS-associated strains of S. aureus and those who are not, should be undertaken. The purpose of such a study would be to indicate the feasibility of identifying microbiologic and immunologic markers that may place some women at high risk of TSS; the study would not be seeking an outcome of TSS. The number of women should be large enough and their follow-up long enough to document the extent of within-person and between-person variation in colonization patterns. The level of antibodies to staphylococcal components and products should be correlated with colonization patterns and both of these related to types and characteristics of menstrual products used.

4. A comprehensive TSS case-control study should be developed. It should address risk factors associated with patterns and types of menstrual product use, especially as related to absorbency and chemical composition. Microbiological and immunologic evaluation of cases and controls should be included.

Tampons

1. Characteristics of tampons that may be related to TSS should be studied. Such characteristics could include tampon ability to affect growth and toxin production by microorganisms in vitro and in the

vagina. These investigations could help establish a rational basis for recommendations concerning tampon characteristics and use patterns. Furthermore, such studies might lead to *in vitro* methods for premarket testing of new types of tampons for various properties.

2. Ways that tampons modify the vagina as an environment for microorganisms should be evaluated. These investigations should include longitudinal studies of individuals through a number of menstrual cycles.

Vaginal Characteristics of Normal and TSS Cases

1. Any studies of the microbiology, physiology, and biochemistry of the vagina and surrounding genital area should consider the subject's menstrual history, stage in menstrual cycle, previous and recent use of tampons and antibiotics, and history of non-specific vaginitis. Information on douching, sexual habits, and related habits should be available. The clinical status of the vaginal area must be assessed, including microscopic and biochemical investigations of vaginal fluid.

2. Studies are needed to compare vaginal characteristics among normal women, those who have had TSS, those who carry *S. aureus*, and those who carry the TSS-associated strains of *S. aureus.* More detailed physiological and biochemical information is needed on cyclic changes in the vagina and cervix, such as variations in pH, glycogen concentration, oxygen and carbon dioxide content, and redox potential. Such alterations should be correlated with changes in vaginal flora, and with menstrual product usage. Other body sites, for example the anterior nares, should be cultured for *S. aureus*. These studies should include women of minority groups, so that differences among population groups may be discovered. In addition, specific efforts should be directed towards studying adolescents.

3. Careful quantitative studies of the aerobic and anaerobic flora of the vaginal area and other body sites of TSS patients are needed to learn about the various organisms that may be present and the factors (age, menstruation, tampon use, and contraceptive use) that may affect their prevalence.

4. In follow-up studies of women who have had TSS, those who are culture positive for TSS-associated *S. aureus* could be treated with beta-lactamase-resistant antibiotics and the effect on carrier status and recurrence rate studied.

Microbiology and Toxins

1. Mechanisms by which the TSS-associated *S. aureus* gains access and establishes itself need to be studied, including studies of sexual partners as possible carriers. Growth characteristics of the TSS-associated *S. aureus* should be determined *in vitro* and in a suitable animal model, especially in relation to its interaction with other organisms that may be found in the vagina, wounds, and other sites.

2. Further microbiologic characterization of TSS-associated strains of S. aureus should be attempted in order to facilitate their identification in routine clinical laboratories, and to enhance knowledge of the possible variants of strains that may be associated with TSS. Careful choice of control S. aureus strains is required in these and related studies.

3. Pyrogenic exotoxin C and staphylococcal enterotoxin F, found in TSS-associated strains of S. aureus, should be further characterized and evidence about their relationship obtained.

4. Monoclonal antibodies to these TSS-associated S. aureus toxins should be prepared. Antibodies to the toxins should be used to test for the presence of toxin in clinical samples and body fluids. In addition, such antibodies might aid in the development of a much-needed specific diagnostic test for the syndrome.

5. Similarly, studying the levels of antibody to toxins of TSS-associated S. aureus in normal persons and those who have had TSS, including non-menstrual cases, may provide further information regarding susceptibility. Variations in the immune response during the menstrual cycle also should be investigated.

6. Suitable animal models should be developed to further define the pathogenesis of TSS and the nature of host resistance mechanisms under controlled conditions. The role of particular toxins in production of the syndrome should be elucidated and the need for additional factors investigated.

Prevention and Recognition of TSS

Although the etiology and epidemiology of TSS are not completely understood, some preventive efforts can be taken. Most cases are associated with tampon use and a marked reduction in the number of cases would be expected in the absence of tampon use. In the future, it may be possible to manufacture tampons that do not enhance the user's risk of getting TSS, or to identify susceptible persons who might benefit from specific preventive measures, such as tampon avoidance or immunization. The syndrome is rare, but the consequences can include death; the case fatality rate in 1981 was about 3 percent of reported cases.

Because TSS occurs at a relatively low rate--an annual incidence rate of less than 10 menstrual cases per 100,000 menstruating women, according to Minnesota data--we believe that individual women can best make decisions about use of tampons. Consequently, education efforts, both of the public and of health professionals, are necessary to enhance informed individual decision making. The public, especially younger menstruating women, should be made aware of the increased risk of TSS associated with tampon use and of the possible severe consequences. The following recommendations seem prudent, based on current information:

1. Women who have already had TSS should be advised not to use tampons. Postpartum women should be informed that use of tampons may increase TSS risk.

2. Women, especially adolescents, should be advised to minimize their use of high absorbency tampons.

3. Physicians and other health professionals should be informed about the variations in presentation of non-tampon associated cases that have occurred, should be alerted to the symptoms of TSS, and should be encouraged to report all definite and probable cases, as well as suspected cases. Physicians also should be advised that treatment of TSS patients with beta-lactamase-resistant antibiotics apparently decreases the chance of recurrence.

APPENDIX A

AGENDA AND PARTICIPANTS

INSTITUTE OF MEDICINE
CONFERENCE ON TOXIC SHOCK SYNDROME

November 20-22, 1981 Leesburg, Virginia

Friday Evening, November 20

6:00 p.m.	RECEPTION
7:00	DINNER (cafeteria style)

Saturday Morning, November 21

8:00 a.m.	Welcoming Remarks - Frederick C. Robbins, President, Institute of Medicine Charles H. Rammelkamp, Chair, IOM Committee on Toxic Shock Syndrome
8:15	Keynote Address - James Todd History, case definition, major unanswered questions

CLINICAL ISSUES

Chairs: Pierce Gardner, Sheldon Wolff

8:45	Comparison of recurrent/mild cases with "classical" cases - Robert Tofte
9:00	Non-menstruating cases - Arthur Reingold
9:15	Treatment and sequelae - Joan Chesney
9:30	Discussion (Jeffrey Davis, others)
	BREAK
10:30	Pathology and correlates with clinical aspects - Allen Paris, Steven Larkin
11:00	Discussion (Karen Rosene, others)
12:00 noon	LUNCH

Saturday Afternoon

EPIDEMIOLOGY

Chairs: James Chin, Barbara Hulka

1:30 p.m. Introduction - Barbara Hulka

A. Surveillance and Reporting Issues Associated with TSS

Chair: James Chin

1:35 The national picture - Arthur Reingold

1:50 International comparisons - A. J. Clayton (Canada)

2:00 Publicity and TSS reporting - Jeffrey Davis

2:15 Minnesota surveillance - Michael Osterholm

2:30 Discussant - Donald Peterson

2:45 General Discussion

BREAK

B. Risk Factors for TSS: Case-Control Studies

Chair: Barbara Hulka

3:20 Wisconsin - Jeffrey Davis

3:30 CDC I & II - Kathryn Shands

3:45 Tristate - Michael Osterholm

4:00 Utah - Robert Latham
Oregon - Steven Helgerson

4:15 Critique - Mary Harvey

4:30 Statistical methods used in analyzing the studies - Lloyd Chambless

4:45 Discussant (Reuel Stallones)

5:00 Discussion and summary

6:30 RECEPTION

7:30 DINNER (served)

Sunday Morning, November 22

CERVICAL-VAGINAL PHYSIOLOGY AND MICROBIOLOGY AND TAMPONS

Chairs: Ezra Davidson, King Holmes, Iris Litt

A. Cervical-vaginal Physiology and Microbiology

Chairs: Ezra Davidson, King Holmes

8:00 a.m.	Physiology of the normal vagina - Gorm Wagner
8:15	Cervical-vaginal physiology and infection in the adolescent - Thomas Bell
8:20	Discussion
8:25	Normal vaginal flora - Rudolph Galask
8:40	Dynamic changes in the vaginal flora - William Brown
8:55	Discussion
9:00	Transmission of *S. aureus* - Edward Mortimer
	S. aureus carriage in females:
9:10	Patrick Schlievert
9:25	Calvin Linnemann, Jr.
9:35	Mary Guinan
9:45	Invited discussion (Charles Smith, R. Russell Martin, others)
10:00	Summary: Vaginal flora in normal women and TSS cases - King Holmes
10:15	Open Discussion
10:30	BREAK

B. Tampons

Chair: Iris Litt

10:45	Characteristics of tampon use and composition - Michael Osterholm
11:00	Growth of bacteria on tampons - Claire Broome
11:15	Panel: Habits and practices of adolescents that may relate to TSS - Jeanne Brooks-Gunn, Charles Irwin, Michael Osterholm
11:45	Discussion and summary
12:00 noon	LUNCH

Sunday Afternoon

TSS-ASSOCIATED S. AUREUS; HOST FACTORS

Chairs: Lowell Glasgow, Lewis Wannamaker

1:30 p.m. Statement of objectives - Lowell Glasgow

A. Toxins of TSS-associated S. aureus

1:40 Association of staphylococcal enterotoxin F with TSS - Merlin Bergdoll

2:10 Purification and characterization of staphylococcal pyrogenic exotoxin type C - Patrick Schlievert

2:40 Epidermal toxin production - Frank Kapral

2:55 Discussion

B. Characteristics of TSS-associated S. aureus

3:35 Genetics - Richard Novick

3:45 Correlating phage-typing and toxin production - William Altemeier

3:55 Other characteristics - Patrick Schlievert

4:05 Discussion

C. Immunology, Host Factors, Animal Models

4:20 Host defense mechanisms - Jeffrey Davis

4:40 Role of hypersensitivity in staphylococcal infections - J. Gabriel Michael

4:50 Animal models - Gary Best, Fred Quimby, others

5:15 D. Discussion and Summary

5:50 CLOSING COMMENTS

NATIONAL ACADEMY OF SCIENCES

INSTITUTE OF MEDICINE

Conference on Toxic Shock Syndrome

November 20-22, 1981 Leesburg, Virginia

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APPENDIX B

Committee on Toxic Shock Syndrome

Biographical Sketches

JAMES CHIN is Chief of the Infectious Disease Section of the California Department of Health Services. He received a B.S. in 1954 from the University of Michigan, his M.D. in 1958 from the State University of New York, Downstate, and an M.P.H. in 1961 from the University of California, School of Public Health, Berkeley. His specialization in the epidemiology and control of infectious diseases began with the Hooper Foundation in San Francisco, and with the Institute for Medical Research in Kuala Lumpur, Malaysia. Dr. Chin has served on many national committees related to infectious disease control, including the American Public Health Association Committee on Infectious Diseases, the National Advisory Committee on Immunization Practices, and the Armed Forces Epidemiology Board.

EZRA C. DAVIDSON, JR., is Professor and Chairman of the Department of Obstetrics and Gynecology of the Charles R. Drew Postgraduate Medical School; Professor of Obstetrics-Gynecology at the University of California at Los Angeles Health Sciences Center; and Chief-of-Service in the Department of Obstetrics and Gynecology at Martin Luther King, Jr., General Hospital, all in Los Angeles. He received a B.S. from Morehouse College in Atlanta, Georgia in 1954, and an M.D. in 1958 from Meharry Medical College in Nashville, Tennessee. Dr. Davidson's major interests concern management of pelvic infections, development of fetoscopy for fetal blood samples, and delivery of comprehensive perinatal care to low income communities. Among many professional activities, he was chairman of the 1980 Surgeon General's Workshop on Maternal and Infant Health, and chaired the Task Force on Prevention of Adolescent Pregnancy of the American College of Obstetricians and Gynecologists. He was awarded a Robert Wood Johnson Foundation Health Policy Fellowship of the Institute of Medicine for 1979-80.

PIERCE GARDNER is Professor of Medicine and Pediatrics and Director of the Training Program in Infectious Diseases, University of Chicago Pritzker School of Medicine. He received his B.A. degree at Amherst College in 1957 and his M.D. from Harvard University in

1961. He trained in Internal Medicine at the University of Washington and Case Western Reserve and was an Infectious Disease Fellow at the Massachusetts General Hospital. Dr. Gardner was on the Harvard faculty for five years prior to assuming his position in Chicago in 1974. His research interests include clinical epidemiology and antiobiotic resistance in bacteria. Dr. Gardner is an Associate Editor of the Journal of Infectious Diseases and has served as a consultant to the World Health Organization. He is currently the Chairman of the Division of Nosocomial Infections of the American Society for Microbiology.

LOWELL A. GLASGOW was Professor and Chairman of the Department of Pediatrics at the University of Utah Medical Center and Medical Director at Primary Children's Medical Center, Salt Lake City, Utah, before his death in February 1982 at age 49. He received his B.A. in 1954 from the University of Rochester and his M.D. in 1958 from the University of Rochester Medical School. Further training was in microbiology and pediatrics. He did extensive research on the staphylococcal scalded skin syndrome, the macrophage response to viral infection, and the use of interferon in treating viral infections. Among his many other activities, he was president of the Western Society for Pediatric Research and organizing chairman for an NIH Workshop on Genital Herpes.

KING K. HOLMES is Professor of Medicine and Adjunct Professor in the Department of Epidemiology and the Department of Microbiology and Immunology at the University of Washington, Seattle. He received his B.A. degree at Harvard University in 1959, his M.D. degree from Cornell University Medical School in 1963, and a Ph.D. in microbiology from the University of Hawaii in 1967. He did an internship in internal medicine at Vanderbilt University, and completed training in internal medicine and infectious diseases at the University of Washington in 1970. From 1964-1967, he was an epidemiologist with the U.S. Navy. Dr. Holmes' major research interests concern sexually transmitted diseases and genital infections. He has chaired the NIH Microbiology and Infectious Diseases Advisory Committee and serves on the NIH Recombinant DNA Advisory Committee.

BARBARA S. HULKA is a Professor of Epidemiology in the School of Public Health and a Clinical Associate Professor in the Department of Family Medicine, School of Medicine at the University of North Carolina in Chapel Hill, North Carolina, and a Clinical Associate Professor of Community and Family Medicine at Duke University Medical Center, Durham, North Carolina. She received a B.S. from Radcliffe College in 1952, an M.S. from the Juilliard School of Music in 1954, an M.D. from Columbia College of Physicians and Surgeons in 1959, and an M.P.H. from Columbia School of Public Health and Administrative Medicine in 1961. She specializes in health services research and cancer epidemiology. Dr. Hulka has served as a consultant to various governmental agencies and

private institutions, such as the National Institutes of Health, the National Academy of Sciences, and the National Center for Health Services Research. She currently chairs the Epidemiology and Disease Control study section of the NIH.

IRIS F. LITT is Associate Professor of Pediatrics and Director of the Division of Adolescent Medicine at the Stanford University School of Medicine and is currently president of the Society for Adolescent Medicine. She received an A.B. from Cornell University in 1961 and an M.D. from the State University of New York, Downstate Medical Center in 1965. She has had extensive clinical and research experience in the fields of adolescent drug abuse, contraception, and medication compliance.

CHARLES H. RAMMELKAMP was Emeritus Professor of Medicine and Preventive Medicine at Case Western Reserve University School of Medicine before his death in December 1981 at age 70. He had been director of the Department of Medicine at Cleveland Metropolitan General Hospital from 1957 until his retirement in 1980. He received an A.B. degree from Illinois College in 1933 and an M.D. from the University of Chicago in 1937. He did internships in medicine at Barnes Hospital in St. Louis and in surgery at Billings Memorial Hospital in Chicago. His major research concerned infectious diseases caused by streptococci and staphylococci. He was a member of the National Academy of Sciences and of the Institute of Medicine. The Streptococcal Diseases Laboratory of which he was director received the Lasker Award in 1954. His contributions were also recognized by the first American Heart Association Research Achievement Award in 1961. He was active in many professional groups, including the American Heart Association, and served as president-elect, president, and past-president of the Infectious Diseases Society of America during 1965-68. He also served as member or director of several commissions of the Armed Forces Epidemiological Board and as a member of the Central Board.

LEWIS W. WANNAMAKER is a Professor of Pediatrics and of Microbiology at the University of Minnesota. Since 1958 he has been a Career Investigator of the American Heart Association. Dr. Wannamaker received his pre-medical education at Emory University and his M.D. degree from Duke University in 1946. He is a specialist in infectious diseases. His research activities have focused mainly on the biology of streptococci and on streptococcal infections and their complications, using epidemiologic, microbiologic and immunologic approaches, and to a lesser extent on the biology of staphylococci. He has served as a member, assistant director, and director of the Commission on Streptococcal and Staphylococcal Diseases, Armed Forces Epidemiological Board, and on a number of advisory committees of the National Institutes of Health and non-governmental agencies, notably the American Heart Association and the World Health Organization.

SHELDON M. WOLFF is Endicott Professor and Chairman, Department of Medicine, Tufts University School of Medicine, and Physician-in-Chief, New England Medical Center Hospital. In addition, he is Adjunct Professor of International Health at the Fletcher School of Law and Diplomacy, Tufts University, Medford, Massachusetts. Dr. Wolff received his B.S. degree from the University of Georgia in 1952, his M.D. degree from Vanderbilt University School of Medicine in 1957, and an honorary doctorate from the Federal University, Rio de Janeiro, Brazil, in 1976. He received his clinical training at Vanderbilt University Hospital and the Albert Einstein College of Medicine, and training in infectious diseases and immunology at the National Institutes of Health. From 1960 through 1977, Dr. Wolff worked at the National Institute of Allergy and Infectious Diseases (NIAID), and for the last ten years of his stay there he was Clinical Director of NIAID and Chief of the Laboratory of Clinical Investigation. Dr. Wolff's research has dealt with biological properties of bacterial endotoxins and, in particular, with the pathogenesis of fever. In addition, he has published widely on host defenses and response to infectious diseases. He is past-president of the Infectious Diseases Society of America, and chairman-elect of the Subspeciality Board of Infectious Diseases of the American Board of Internal Medicine.

APPENDIX C

STAPHYLOCOCCUS AUREUS CARRIAGE IN NON-TSS SUBJECTS

Year	First Author	n	% subjects with S. aureus: Cervical/Vaginal non-menstrual	Cervical/Vaginal menstrual	Nasal	In vitro production of PEC and/or SEF
1958	Hunter[9]	48	0			
1963	Williams[23]	review			40.-44.	
1967	Morris[15]*	269		2.7**		
1969	Calia[3]	268			19.	
1972	Keith[10]	80	1.			
1973	Gorbach[6]	30	0			
1975	Ohm[16]	100	0			
1975	deLouvois[5]	83	4.			
1976	Tashjian[22]	100	7.			
1977	Osborne[17]	50	16.			
1977	Bartlett[1]	22	2.-5.			
1977	Corbishley[4]	70[a]		17.[f]**		
1978	Grossman[7]	98	3.			
1978	Lindner[13]	42		0[b]		
1980	Shands[20]	71		10.	18.	
1980	Sautter[18]	7	[c]			
1982	Brown[2]	14		64.[d]**	57[d]	
1982	Guinan[8]*	71		9.9		Of 119 viable strains isolated and tested, 3 were positive for PEC
		545	8.1		20.7[e]	

(continued)

Non-TSS S. aureus carriage, cont.

Year	First author	n	% subjects with S. aureus: Cervical/Vaginal non-menstrual	Cervical/Vaginal menstrual	Nasal	In vitro production of PEC and/or SEF
1982	Larsen[11]	31	0	9.7		6% of women had strains with PEC
1982	Linnemann[12]*	600	5.	5.		1% of women had strains with SEF
	blacks	225	8.	8.		
	whites	373	4.	4.		
1982	Martin[14]*	145	10.3		26.9	
1982	Schlievert[19]	205	10.7			3% of women had strains with PEC
		95		14.7		5% of women had strains with PEC
	children	22			50	18% of children had strains with PEC
1982	Smith[21]*	83	1.2	10.8		

* No correlation between S. aureus carriage and tampon use, except Guinan[8] found a higher percentage positive with non-applicator tampons or with Rely.

** Menstrual status unknown or unspecified.

a 70 sets of vaginal and cervical swabs were taken for culture from 40 patients.

b Staphylococcus aureus present, but not in sufficient quantity to be reported.

c 3 percent of 65 serial vaginal cultures from 7 subjects (nurses) were positive for S. aureus.

d Total of 9 samples/person over 3 months. Percentage is of women positive at some time during the 3 months.

e Based on 296 women.

f Authors state that menstrual and non-menstrual data are the same.

n: number of subjects or cultures tested

PEC: Staphylococcal pyrogenic exotoxin C

SEF: Staphylococcal enterotoxin F

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APPENDIX D

STAPHYLOCOCCUS AUREUS CARRIAGE IN TSS CASES

First author	n	Vaginal/Cervical # pos./# cultured (% pos.)	All sites (including vaginal/cervical) # pos./#cultured (% pos.)	# Penicillin resis./ # strains tested	# Toxin pos./ # strains tested in vitro
Davis[1]	38	17/23 (74%)		11/15[d]	7/13 (SEA OR SEC)[d] (Not tested for PEC or SEF)
Shands[2]	52[a]	16/16 (100%)	33/45 (73%)	33/36	
Todd[3]	7	≥ 1/1	6/6 (100%)		5/5 (positive Nikolsky sign in mice)
Tofte[4,5]	15	8/13 (62%)	11/15 (73%)		11/11 (PEA) (Not tested for PEC or SEF)
de Saxe[6]	10	8/9 (89%)		5/8	2/2 (PEC); 6/8 (SEF)
McKenna[7]	11	4/6 (67%)	5/11 (45%)		
Tanner[8]	8	4/6 (67%)		4/4	
Helms[9]	14	7/8 (87%)			Of 25 definite and probable cases, 14/15 (SEF)[9,10]
Saadah[11]	10	8/8 (100%)		7/8	
Davis[12]	80	44/54 (81%)	51/67 (76%)		
Schlech[13]	50[b]	43/44 (98%)			
Reingold[14] [c]					
Menstrual cases	1,390		384/415 (93%)		
Nonmenst. cases	104		64/64 (100%)		

[a] CDC I cases

[b] CDC II cases

[c] Culture results reported to CDC include CDC I, CDC II, and possibly other cases from this table.

[d] Includes all sites.

n: Number of subjects

SEA, SEC, SEF: Staphylococcal enterotoxin A, C, or F

PEA, PEC: Staphylococcal pyrogenic exotoxin A or C

Cases where cultures were known to be taken after antibiotic therapy were excluded.

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APPENDIX E

GLOSSARY

ADULT RESPIRATORY DISTRESS SYNDROME
A syndrome characterized by acute respiratory failure because of diffuse lung injury.

AMENORRHEA
Absence or abnormal cessation of menstruation.

ANAEROBIC
Without air. Usually refers to the metabolism of a tissue in the absence of adequate oxygen or to organisms that live in the absence of oxygen. A facultative anaerobe can grow with or without oxygen; an obligate anaerobe grows only in the absence of oxygen. The latter are difficult to culture.

ANOVULATORY
Lack of discharge of an egg cell (ovum).

ANTERIOR NARES
The front part of the nostrils.

ANTIBODY
A type of protein that is made by human beings and other animals in response to foreign substances in the body. Each foreign substance usually evokes a unique antibody. The formation of antibodies is part of the immune response and is usually protective to the host.

ANTIGEN
A protein or other substance that induces antibody formation.

BACTEREMIA
The presence of bacteria in the circulating blood. (Bacteria are not normally present in blood.)

BASEMENT MEMBRANE
The thin noncellular layer that separates the lowest layer of epithelial cells from the underlying connective tissue.

BETA-LACTAMASE
An enzyme that degrades susceptible beta-lactam compounds such as certain penicillins. Bacterial strains with this enzyme are resistant to penicillin.

BETA-LACTAMASE-RESISTANT ANTIBIOTIC
Any of a number of antibiotics, such as methicillin and cephalosporin, that are not degraded by beta-lactamase. Such antibiotics can therefore prevent the growth of penicillin-resistant bacteria.

BUN (BLOOD UREA NITROGEN)
A measure of the amount of urea in the blood. Because urea is a waste product of metabolism and is excreted by the kidneys, BUN usually is an indication of kidney function, i.e., BUN increases when kidneys are not functioning well.

CASE-CONTROL STUDY
An epidemiologic study in which a group of persons who have had a disease (cases) are compared with a group who did not have the diesease (controls) in order to discover risk factors that may be associated with the disease. The frequency of occurrence of various characteristics and prior exposures is compared between the two groups.

CATAMENIAL
Relating to menstruation, usually in the context of "catamenial products," which are tampons, napkins, etc. that are used to absorb the menstrual flow.

COAGULASE
An enzyme that clots plasma and is produced by strains of staphylococci that cause disease. Its presence in Staphylococcus aureus is used to differentiate that organism from other types of staphylococci.

COAGULASE POSITIVE
Refers to organisms that have coagulase.

COLIFORMS
A group of gram-negative bacilli commonly found in the lower intestine in human beings and belonging to the Enterobacteriaceae family. Escherichia coli is a typical coliform.

COLPOSCOPY
Visual examination of vagina and cervix by means of an endoscope, a long tube with a magnifying glass and cold light on the end.

COLUMNAR EPITHELIUM
A kind of epithelium cell that is taller than it is wide.

CUTANEOUS
Relating to the skin.

DESQUAMATION
The shedding of the outer layers of skin (cuticle or epidermis).

DIALYSIS
The method of separating smaller molecules from larger molecules or other material mixed in a solution by putting the mixture on one side of a semipermeable membrane that allows the smaller molecules to pass through but retains the larger materials. Hemodialysis is a method of selectively removing some substances from blood by the process of dialysis.

EDEMA
The swelling that results from the presence of abnormally large amounts of fluid outside of cells; usually applies to excess fluid in tissues just below the skin surface.

ENDOCERVICAL CANAL
The narrow passage through the cervix of the uterus, connecting the upper vagina with the interior of the uterus.

ENDOTOXIN
A bacterial toxin that is a heat-stable lipopolysaccharide forming an integral part of the cell wall of gram-negative bacteria. In contrast to exotoxins, endotoxins are not usually freely liberated into the surrounding media.

ENDOTOXIN SHOCK
Shock caused by endotoxin. Symptoms include hypotension, rapid pulse and respiration rate, lethargy, kidney failure, and usually fever.

ENTEROTOXINS
A class of bacterial proteins that act on the intestinal mucous membrane to produce symptoms such as diarrhea and vomiting.

EPIDERMIS
The outermost layer of the skin, also called the cuticle. It contains no blood vessels and consists of up to 5 layers. Starting from the innermost layer are 1) a basal layer, composed of columnar cells arranged perpendicularly; 2) a spinous layer, composed of rounded or polygonal pigmented cells; 3) a granular layer, composed of flattened granular cells; 4) a clear layer consisting of several layers of transparent cells with indistinct or absent nuclei; 5) a horny layer, composed of flattened keratinized, non-nucleated cells. The granular and clear layers are sometimes absent.

EPIDERMOLYTIC
Able to cause lysis or destruction of the epidermis.

EPITHELIUM
The covering of internal and external surfaces of the body, including the lining of vessels and small body cavities.

ERYTHRODERMA (ERYTHEMA)
Red skin color, often caused by an inflammatory reaction.

ETIOLOGY
The cause of disease.

EXOTOXINS
Protein toxins (poisons) released from bacterial cells. Examples are toxins associated with diphtheria, botulism, and scarlet fever.

FACULTATIVE ANAEROBE
(See ANAEROBIC.)

FLORA
Plant life found in a particular location. In this report, refers to bacteria and related organisms found in particular body sites, for example, vaginal flora.

GERMINAL EPIDERMAL LAYER
The lowest layers of the epidermis, comprising the basal and spinous layers, but sometimes referring only to the basal layer. The basal layer, from which the other layers are derived, rests on the basement membrane. (See also EPIDERMIS.)

GLUCOCORTICOIDS
Steroids made by the adrenal cortex. In addition to promoting glucose synthesis, they are potent anti-inflammatory agents. Examples are cortisol and corticosterone.

GLYCOGEN

A high molecular weight derivative of glucose found in most tissues of the body, especially liver and muscle. It is the principal carbohydrate reserve and is readily converted into glucose.

GRAM NEGATIVE BACILLI

A group of bacteria that do not retain a gram stain. Gram staining is a useful way of classifying bacteria, as either gram negative (e.g., Enterobacteriaceae such as E. coli) or gram positive (e.g., staphylococci, lactobacilli).

GRANULAR EPIDERMAL LAYER

The third of the five layers of the epidermis. It consists of only two or three layers of cells, which contain keratohyalin and seem to be in the process of being transformed into keratin.

GYNECOLOGIC AGE

Number of years since first menstrual period.

HEMODIALYSIS

(See DIALYSIS.)

HEMOLYSIS

The dissolution or destruction of red blood cell membranes with the consequent release of the red pigment of blood.

HEMOPHAGOCYTOSIS

A process in which certain types of cells (phagocytes) ingest and destroy red blood cells.

HISTOLOGY

The branch of anatomy that deals with the minute structure, composition, and function of tissues.

HYPEREMIA

An increased amount of blood in a part of the body.

HYPOCALCEMIA

Abnormally low concentration of calcium in the blood.

HYPOTENSION

Below-normal arterial blood pressure. It is often defined as less than 90/60 mm mercury for an adult but varies with age, previous blood pressure, and other factors. 90/60 mm mercury means a pressure of 90 mm mercury on heart contraction (systole) and 60 mm mercury between contractions (diastole), measured as the height of a column of mercury that could be supported in an appropriate measuring device.

IMMUNOTHERAPY

Treatment of disease by administration of substances, such as antibodies, intended to increase the immune response for therapeutic purposes. (More broadly, the term is sometimes applied to measures taken to increase the immune response in order to prevent disease.)

INCIDENCE RATE

In epidemiology, the ratio of the number of new cases of a disease in the population during a specified period of time to the number of persons exposed to the risk of developing the disease during that period of time.

ISOELECTRIC POINT
One of the properties that characterize proteins. It is the pH (numerical value on an acid-base scale) at which a given protein is electrically neutral and therefore does not migrate in an electric field under suitable experimental conditions.

LACTOBACILLUS
A genus of non-spore-forming, nonmotile bacteria that produce lactic acid. They can survive under slightly acidic conditions and are the major bacteria found in the normal vaginal flora.

LEPTOSPIROSIS
A disease caused by infection with a species of Leptospira and partly characterized by fever, rash, and malaise.

LYMPHOCYTE
A variety of white blood cell important in the immune response.

LYMPHOCYTOPENIA
A reduction in the number of lymphocytes in the circulating blood.

LYSOZYME
An enzyme that destroys the cell walls of certain bacteria. It is present in tears and some other body fluids, in egg white, and in some bacteria.

MACULOPAPULAR RASH
A rash made up of both flat and raised lesions.

MENARCHE
A female's first menstrual period.

MITOGEN
Any substance that stimulates cell division.

NECROSIS
Death of cells, usually in a localized region of tissue.

ODDS RATIO
In a case-control epidemiologic study, the odds ratio is an estimate of the relative risk associated with a particular exposure. (See RELATIVE RISK.)

ORTHOSTATIC DIZZINESS
Dizziness that occurs when moving from a reclining or sitting position to a vertical position, usually caused by a sudden decrease in blood pressure.

ORTHOSTATIC SYNCOPE
Fainting that occurs when moving to a vertical position from a reclining or sitting position, usually caused by a sudden drop in blood pressure and resulting inadequate oxygen supply to the brain.

OSTEOMYELITIS
Inflammation of the bone, usually caused by bacteria that result in production of pus. Osteomyelitis may be localized or may spread to the marrow, adjacent bone, and cartilage.

PATHOGENESIS
The mechanism of origin or development of any disease.

PEC
(See PYROGENIC EXOTOXIN C.)

PERITONITIS
Inflammation of the lining of the abdominal cavity (peritoneum), for example, as a result of infection.

PHAGE
A virus that "infects" bacteria. (Also known as bacteriophage.)

PHENOTYPE
The external visible characteristics of an organism resulting from its hereditary endowment (genotype) and its environment.

PLASMID
A piece of double-stranded DNA sometimes present in bacteria and usually not attached to the bacterial chromosome. Plasmids can replicate independently of the bacterial chromosomal DNA. Except under special conditions, plasmids are not necessary for bacterial survival.

PLATELETS
Disk-shaped structures in the blood that function early in the clotting process.

POSTPARTUM
Refers to the time following childbirth or delivery, usually about eight weeks.

PYROGENIC EXOTOXIN C (PEC)
A protein isolated from S. aureus strains associated with TSS. It produces fever when given to rabbits and may be related to Staphylococcal enterotoxin F.

RELATIVE RISK
In an epidemiologic study, the ratio of the rate of occurrence of disease among two different groups, for example, a group that has been exposed to a particular factor and a group that has not been exposed to that factor.

RETICULOENDOTHELIAL SYSTEM
A functional (rather than an anatomical) system that is an important defense mechanism of the body. It is composed of highly phagocytic cells (cells that ingest other cells or particles) and is present primarily in liver, spleen, lung and lymph nodes.

SEF
(See STAPHYLOCOCCAL ENTEROTOXIN F.)

SEQUELAE
Signs or symptoms of ill health following as a consequence of a disease.

SHOCK
A physiologic state characterized by low blood pressure and inadequate blood supply to the brain and other essential organs. It may arise from excessive bleeding, physical injury, infection, or other causes and may lead to death.

SQUAMOUS CELLS
Irregularly shaped flattened cells that line the skin and entry to the body openings, such as the mouth and vagina. They are protective in nature.

STAPHYLOCOCCAL ENTEROTOXIN A (SEA)
One of a group of proteins made by strains of S. aureus, that cause gastrointestinal symptoms (vomiting, diarrhea) when given to monkeys. Related toxins are SEB, SEC, SED, SEE.

STAPHYLOCOCCAL ENTEROTOXIN F (SEF)
: A protein isolated from TSS-associated strains of S. aureus, that shares some properties with the other enterotoxins and may be related to pyrogenic exotoxin C.

STRATUM GRANULOSUM
: (See GRANULAR LAYER.)

SURVEILLANCE
: In epidemiology, the continuing scrutiny of all aspects of occurrence and spread of disease that are pertinent to effective control.

SYNDROME
: A set of signs and symptoms that occur together and in aggregate provide a picture of a particular disease condition.

SYNGYNA METHOD
: A laboratory method for determining the fluid capacity (absorbency) of tampons by using a synthetic vagina.

TELANGIECTASIA
: Abnormal dilation of small blood vessels.

THROMBI
: Blood clots (singular is thrombus).

TOXIC SHOCK SYNDROME
: A syndrome reported in 1978 and characterized by fever; hypotension; rash and subsequent peeling of skin, especially on palms and soles; and involvement of various organ systems. A localized S. aureus infection is often present in patients.

TOXINS
: Poisonous substances, usually referring to substances produced by living organisms, such as some microorganisms and some higher plants and animals, that are harmful to other organisms.

TYROSINE
: One of the amino acids found in proteins.

ULCER
: Erosion of skin or mucous surfaces, with loss of surface tissue, disintegration and localized death of tissue, and often inflammation and pus.

VASOPRESSORS
: Substances that cause blood vessels to constrict, leading to a subsequent increase in blood pressure.

APPENDIX F

WORK OF THE COMMITTEE

The Institute of Medicine (IOM) of the National Academy of Sciences (NAS) undertook a project to assess critically the information related to toxic shock syndrome and to suggest research strategies to improve understanding of the illness. The IOM formed a Committee on Toxic Shock Syndrome to achieve these goals. (Brief biographical sketches of the committee members are in Appendix B.) As its major activity, the committee organized a three-day Conference on Toxic Shock Syndrome. The conference brought together researchers working directly in the field of toxic shock syndrome and persons with related expertise or interests, including government and industry representatives. In a program of prepared papers and discussion, the conference provided a forum for critical analysis of research completed, work in progress, and promising areas for future research. Committee members served as reviewers for the papers prepared for the conference, which appear as Part 2 of the June 1982 issue of Annals of Internal Medicine.

Throughout the project, the committee and staff made every effort to obtain views and information from public health and academic researchers, government agency representatives, and manufacturers concerned about toxic shock syndrome. To encourage communication among these groups and the committee, representatives of the various groups participated in discussions at the first two committee meetings, where the project and the conference were planned. The groups also had opportunities to make presentations to the committee and to speak informally with committee members at these meetings and at the conference.

Two full committee meetings and two smaller meetings were held to plan for the conference. In addition, the committee met immediately following the conference and again six weeks later to coordinate drafting of its report. A final subcommittee meeting resolved remaining questions. Further details of the committee's activities follow.

A preliminary meeting was held June 16, 1981, in Washington, D.C., to give members of the Toxic Shock Syndrome Task Force from Johnson & Johnson, Inc., an opportunity to meet with committee chairman Charles Rammelkamp and the IOM staff. The purpose was to discuss approaches to the major questions that the planning committee and the conference should address and to coordinate use of information that Johnson & Johnson might provide pertaining to toxic shock syndrome. In attend-

ance were Dr. Rammelkamp; Johnson & Johnson representatives Thomas Gerding, W. C. Hamilton, Ruth Edelson, Kenneth Kraskin, and Harvey Dickstein; and IOM staff members Enriqueta Bond, Barbara Mandula, and Victoria Weisfeld.

The full committee met first on July 7, 1981, in Washington, D.C., to begin planning for the conference. Kathryn Shands of the Centers for Disease Control and Michael Osterholm of the Minnesota Department of Health summarized current information and unresolved questions relating to TSS. All committee members were present. Guests included representatives of the Procter & Gamble Company, Johnson & Johnson, Inc., the Food and Drug Administration (FDA), the Centers for Disease Control (CDC), the National Institute of Child Health and Human Development (NICHD), and the National Institute of Allergy and Infectious Diseases (NIAID).

On July 20, 1981, a planning subcommittee met in Washington, D.C., to continue detailed drafting of the TSS conference agenda and to make recommendations about additional speakers to be invited. Committee members Charles Rammelkamp, Pierce Gardner, Barbara Hulka, and Lewis Wannamaker attended.

The second meeting of the full committee took place on September 11-12, 1981, in Washington, D.C., to complete arrangements for the conference and to hear presentations prepared by Johnson & Johnson, Inc. and by Procter & Gamble Company. All committee members attended. Additional attendees included Thomas Gerding, W. C. Hamilton, Kenneth Kraskin, Ruth Edelson, and Anthony Rudy (Johnson & Johnson, Inc.); Royce Wilson, J. S. Widder, and Geoffrey Place (Procter & Gamble Company); Michael Osterholm (Minnesota Department of Health); Maria Donawa and Alan Andersen (FDA); Claire Broome (CDC); and Milton Puziss (NIAID).

Following this meeting, committee members contacted speakers for the conference and planned the sessions of the conference in detail. The IOM Conference on Toxic Shock Syndrome was held November 20-22, 1981, in Leesburg, Virginia. Approximately 110 participants from the United States and four other countries met to give and hear presentations and to discuss current information and further research needed on toxic shock syndrome. The conference agenda and list of participants are in Appendix A. Committee members remained in Leesburg on November 23 to meet and draft sections of the report.

After the death of Dr. Rammelkamp in December 1981, IOM president Frederick Robbins asked Sheldon Wolff to serve as chairman of the committee.

On January 5 and 6, 1982, the committee met in Palo Alto, California, to review the first draft of its report and to discuss conclusions and recommendations related to research on toxic shock syndrome. A final subcommittee meeting was held in Washington, D.C., on March 22, 1982, to resolve the remaining questions related to the report.

The committee and the IOM staff wish to thank all those who participated in the conference, attended planning meetings, and provided background information for the committee. Special thanks are due Michael Osterholm, Minnesota Department of Health; Jeffrey Davis,

Wisconsin Department of Health & Social Services; Patrick Schlievert, University of Minnesota Medical School; Kathryn Shands, Arthur Reingold, and Claire Broome, CDC; Maria Donawa, FDA; W. C. Hamilton and Kenneth Kraskin, Johnson & Johnson, Inc.; and Royce Wilson, the Procter & Gamble Company.