CLINICAL MICROBIOLOGY REVIEWS, Oct. 1988, p. 432–446
0893-8512/88/040432-15$02.00/0

Vol. 1, No. 4

Toxic Shock Syndrome

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INTRODUCTION

Toxic shock syndrome (TSS) was originally described 10 years ago, in 1978 (167). At that time, seven children (three males and four females) who had similar clinical and laboratory findings of acute fever, hypotension, multisystem involvement, and a rash which progressed to peeling of the hands and feet in the six survivors were reported. Extensive laboratory evaluation failed to identify any conventional microbial etiology other than the isolation of *Staphylococcus aureus* from focal infections in two patients and other colonized sites in three others. These staphylococcal strains all reacted with group I bacteriophages and produced an apparently new epidermal toxin. After laboratory exclusion of other potential microbial etiologies, this apparently unique group of clinical findings was described as "toxic shock syndrome associated with phage group I staphylococci." At that time it was apparent from a review of the literature that similar cases associated with staphylococcal infection had been reported as far back as 1927 (167, 169).

In 1980, TSS was recognized with increasing frequency in the United States and was epidemiologically associated initially with menstruation in young women and soon thereafter with tampon usage (47, 153). In September 1980, an epidemiologic report of the association of TSS specifically with one brand of tampon (Rely) (141) resulted in its removal from the market and a general public impression (albeit erroneous) that TSS was solely a tampon-related disease (56, 141, 168). In 1981, an exoprotein purified from *S. aureus* strains from patients with TSS was described independently by Bergdoll et al. (enterotoxin F) and Schlievert et al. (pyrogenic exotoxin C) (12, 149); subsequently, these proteins were confirmed to be one and the same and thereafter have been called toxic shock syndrome toxin 1 (TSST-1) (23, 42, 136).

Extensive investigations of the epidemiology of TSS and the chemical and biological features of TSST-1 resulted in the general impression that the pathogenesis of TSS was straightforward (13, 14, 53, 136, 142, 143, 145, 147). However, recent studies suggest a more complex microbe-host relationship. Further epidemiologic investigations have shown that the incidence of TSS did not diminish in some states after the Rely tampon was removed from the market (114, 115, 177) and, in fact, increased in another (123). In addition, many nonmenstrual cases of TSS were described in increasing numbers in males as well as females (8, 110, 132, 133, 177, 185), and not all of the *S. aureus* strains isolated from these patients produced TSST-1 (45, 84, 132). Animal model studies suggested that under some circumstances TSST-1 was not particularly toxic (127); subsequently, other exoproteins have been described (including the previously described epidermal toxin) which may also play roles in the pathophysiology of TSS (41, 65, 145, 151, 170, 173, 192; D. Lawellin, A. Franco-Buff, C. Smith, and J. K. Todd, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 18, p. 18; P. M. Schlievert, Letter, Lancet i:1149–1150, 1986).

Thus, after 10 years, TSS is still an important disease with many interesting clinical, epidemiologic, and microbiologic features. Concepts are evolving which may explain the apparent discrepancies between past assumptions and current observations.

CLINICAL FEATURES

Signs and Symptoms

TSS can occur in patients of any age, but it is commonly seen in young adults and children who are otherwise healthy (177). The typical patient presents with fever, rash, and toxicity often progressing to hypotension (31, 36, 47, 48, 61, 62, 107, 153, 167, 169, 178, 180). These presenting symptoms have usually been preceded by a several-day history of watery diarrhea, nausea and vomiting, sore throat, and myalgia. At the time of presentation, the patients may have orthostatic hypotension or overt shock; hypotension may also be manifested by a decreased urine output and poor capillary refill.

On physical examination there may be signs of dehydration, especially if fever, vomiting, and diarrhea have persisted for a number of days without adequate fluid intake. In extreme cases when the patient has severe hypotension, the rash may not be apparent until the blood pressure is appropriately reestablished (186). It usually presents as an erythema over the total body, is more prominent on the trunk, and has many features similar to that of scarlet fever, although it tends not to be as intense and does not ordinarily feel rough. The rash is usually not painful or pruritic and rarely (compared with scalded skin syndrome) forms bullous lesions. A Nikolsky sign is rarely present. If the patient survives, a unique peeling is noted to occur in week 2 to 4 on the finger and toe tips, progressing to the palms and soles.

Most patients present with conjunctival hyperemia (without purulent exudate) and pharyngeal hyperemia with a strawberry (or raspberry) tongue. Some may be jaundiced. Patients may be semicomatose without focal neurologic signs and may have other signs and symptoms related to a generalized, toxic (or hypotensive) effect on other organ systems (48).

Laboratory Findings

Laboratory examinations are consistent with an acutely ill, febrile patient with poor organ perfusion. The leukocyte count is usually elevated, and the differential count shows a shift to the left with increased band forms and metamyelocytes. The platelet count may be decreased with additional signs of disseminated intravascular coagulation, although overt bleeding is uncommon. Liver enzymes may be elevated. The bilirubin may be increased, and often the direct (conjugated) component is predominant. Serum creatinine phosphokinase levels are often dramatically elevated, consistent with the symptom of myalgia. The urine analysis is usually abnormal with a cellular sediment; creatinine and blood urea nitrogen are often increased. These findings may represent a prerenal effect of dehydration and hypotension but may progress to acute tubular necrosis unless the blood pressure is re-established quickly. Serum electrolytes may be variously affected depending on the amount and type of prior fluid intake; however, serum calcium and phosphate are often abnormally low (33; M. A. Wagner, D. H. Batts, J. M. Colville, and C. B. Lauter, Letter, Lancet i:1208, 1981). Blood cultures are usually (but not always) negative for *S. aureus*; however, focal sites of infection usually yield the causative organism (98).

Definition and Differential Diagnosis

A strict definition for severe TSS was jointly created by the Centers for Disease Control and several investigators in 1980 (153), although various other definitions have been used (169). The collaborative definition has been most widely utilized and more recently shown to be quite specific in excluding other illnesses which might fit into the differential diagnosis (189). To have a confirmed case of TSS, a patient must have all major criteria and three or more minor criteria, besides exclusionary evidence that no other disease is present. Major criteria (must have all) are a fever, with temperature of $\geq$102°F (38.8°C); a rash (diffuse, macular erythroderma); skin desquamation, usually 1 to 2 weeks after onset of illness and particularly of the palms of the hands and the soles of the feet; and hypotension, with systolic blood pressure of <90 mm Hg for adults or below the fifth percentile by age for children of <16 years of age, or orthostatic syncope. Minor criteria (involvement of three or more of the following organ systems) include gastrointestinal involvement (vomiting or diarrhea at onset of illness); muscular involvement (severe myalgia or creatinine phosphokinase level more than twice the upper limit of normal); mucous membrane involvement (vaginal, oropharyngeal, or conjunctival hyperemia); renal (blood urea nitrogen and creatinine levels more than twice the upper limit of normal, or >5 per high-power field in the absence of a urinary tract infection); hepatic leukocytes (total bilirubin, serum glutamic oxaloacetic transaminase, and serum glutamic pyruvic transaminase more than twice the upper limit of normal); hematologic involvement (platelets, <100,000/mm^3); and/or central nervous system involvement (disorientation or alterations in consciousness without focal neurological signs when fever and hypotension are absent). Excluding data (negative results on the following tests, if obtained) are cultures of the throat (for group A streptococcus), blood, or cerebrospinal fluid (except *S. aureus*) and serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles. Menstruation does not play a role in the diagnosis. A focus of staphylococcal infection is not required, nor is *S. aureus* isolation from any site required.

There is no question that TSS of lesser severity likely occurs often (10, 61, 155, 161, 179, 189). Probable cases include those patients who are missing one of the major or minor criteria without any other explanation for their illness. The severity of multisystem involvement seems to correlate with the degree of hypotension (48). Nonetheless, the strict definition identifies patients who need hospitalization and are most likely to benefit from aggressive therapy. Cases of less severe TSS may respond to early therapy and never require hospital admission. To make accurate observations about the epidemiology, microbiology, and clinical treatment of TSS, the strict definition has been very important in ensuring that most cases so identified truly have a single syndrome.

The differential diagnosis of TSS includes other febrile illnesses associated with rash or hypotension or both (167, 189). These include bacterial sepsis, meningococcemia, streptococcal scarlet fever (9, 43), staphylococcal scalded skin syndrome, leptospirosis, measles, enterovirus infection with myocarditis, Rocky Mountain spotted fever, and severe drug eruption (16) (e.g., Stevens-Johnson syndrome or toxic epidermal necrolysis [172]). The strict case definition for TSS usually excludes these other illnesses when applied rigidly (189); however, a thorough history and thorough physical examination should be performed to identify epidemiologic and clinical clues which might point to a different etiology, as well as appropriate laboratory tests (cultures and serology) to add additional exclusionary information. In the end, the diagnosis of any syndrome requires the inclusion of appropriate signs and symptoms with the exclusion of other diseases based on history, clinical findings, and appropriate selected laboratory tests.

Therapy and Hospital Course

The pathophysiology of TSS, as determined by histopathologic examination and physiologic monitoring, suggests high-output, low-peripheral-resistance hypotension associated with capillary leakage and poor venous return (48, 60). Thus, patients with TSS require large volumes of fluid and electrolytes to counteract the vascular volume loss to the interstitial space (171). These volumes may far exceed the amount of fluid calculated to be needed on the basis of normal replacement and deficit fluid therapy (175). Because of the continued loss of fluid into the interstitial space of the peripheral tissues, severe edema may develop. This is not necessarily a sign of vascular volume overload, which should be independently assessed. Generally, adequate vascular volume can be estimated by a normal central venous pressure, blood pressure, capillary refill, and urine output (assuming no diuretics have been given and overt renal failure is not present).

A thorough examination of the patient should be conducted to identify any potential focus of staphylococcal growth. It is imperative to identify and adequately drain any focally infected site (e.g., abscess, sinusitis, or arthritis) as even small amounts of undrained infection may lead to severe clinical consequences. Appropriate antistaphylococcal antibiotics should be prescribed, taking into consideration typical *S. aureus* susceptibility patterns after appropriate cultures (blood, urine, and any focus) have been taken (156). Gram stains of material from a focally infected site may assist in the differential diagnosis as well as in the choice of antimicrobial therapy.

There is good clinical evidence and some laboratory support for the idea that corticosteroid therapy may be effective if given to patients with severe illness early in their disease (175). This is consistent with other evidence relating to the effects of steroids on the staphylococcal pathogenesis and epidemiology of TSS (see subsection "Host Defenses").

In spite of the administration of appropriate amounts of fluids and management of the infected site, some patients may require more invasive monitoring and therapy for adult respiratory distress syndrome and myocardial failure, which often develops in day 2 or 3 of hospitalization (60). Adult respiratory distress syndrome usually responds well to positive airway pressure, and myocardial failure often requires additional inotropic support (60). Because capillary leakage plays an important role in the pathophysiology of TSS, significant subcutaneous edema often develops early. It is usually an error to assume that edema, adult respiratory distress syndrome, or myocardial failure is a sign of fluid overload in TSS. Vascular volume status should be followed carefully, but continued administration of crystalloid (or colloid) may be very important to maintain adequate venous return and blood pressure.

Antistaphylococcal therapy is usually continued for 10 days; if the patient improves sufficiently (afebrile, fluids being taken orally), an appropriate oral drug may be given. It is important to emphasize that the cutaneous sites of infection in patients with TSS associated with surgical wound infections or other *S. aureus* surgical wound infections (e.g., cellulitis, septic arthritis, etc.) or other *S. aureus* cutaneous infections do not usually show much inflammatory response. This probably is related to the phenotypic characteristics of these *S. aureus* strains, which differ significantly from characteristics of other *S. aureus* strains (173). When the clinical diagnosis of TSS is suspected, it is very important to surgically explore all wounds thoroughly to make sure any focus of infection has been thoroughly drained, successful therapy of TSS being often dependent on complete drainage.

Outcome and Sequelae

Approximately 2 to 5% of patients with TSS may die, but most patients respond to appropriate therapy (171, 180). A few will suffer from poor arterial perfusion, especially of the distal extremities, and may develop dry gangrene and loss of digits or even distal parts of extremities. Most patients will develop the typical desquamation of the fingers and toes beginning 2 to 3 weeks after onset of the illness and subsequently will experience creasing of the fingernails and hair loss, both of which resolve in time. Persistent neuropsychological sequelae have been reported (140) but are probably rare. There is no question that TSS is a frightening illness for any patient; a certain degree of intensive care neurosis is to be expected in the convalescent phase. A recent study by Davis et al. reports that, in contrast to controls, women with TSS were more likely to have diplopia, joint stiffness, weakness, frequent urination, chest pain or rapid pulse, vaginal discharge, difficulties with memory or maintaining concentration or reading, emotional changes, fatigue, more prolonged delay in return to usual activity or health, changes in attitude about menses, changes in menstrual flow, cycle duration and regularity, and dysmenorrhea (J. P. Davis, L. Vergeront, L. Amsterdam, J. Hayward, and S. J. Stolz-LaVerriere, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 1, p. 1). Some of these reported sequelae were more common in patients who sought legal counsel than in those who did not. Nonetheless, most patients with TSS ultimately recover completely and are able to resume normal lives.

Recurrence and Prevention

Early studies of TSS in menstruating women showed a recurrence rate as high as 60% over the ensuing 6-month period (48, 75). It has been shown that this risk of recurrence can be markedly reduced by initial treatment with antistaphylococcal therapy and avoidance of tampon use (48). It is hypothesized that women who use low-absorbancy tampons and change them frequently and women who alternate the use of tampons with pads (especially at night) may, at least in theory, reduce their risk of TSS. In spite of the changes in tampon formulation as well as whatever changes in use have occurred since 1980, it is apparent that TSS still occurs in menstruating women and that the issue of prevention is still of importance (123, 177; S. Gaventa, A. L. Reingold, A. Hightower, C. V. Broome, and B. Schwartz, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 4, p. 4; D. P. Petitti, A. L. Reingold, and J. Chin, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 3, p. 3).

PATHOLOGY

Skin biopsies have been performed in a number of patients with TSS (79, 80, 186). In a few there has been evidence of epidermal separation (58), but more commonly, there is a mild lymphocytic dermal perivasculitis (5, 79, 80, 99, 116), and some think that the skin pathology is typical and diagnostic of TSS (79). In most cases, evidence of inflammation is uncommon. Although TSS behaves like a vasculitic disease, there is very little evidence of intravascular inflammation, and, in spite of the high leukocyte count and shift to the left, the mild perivascular inflammation tends to be lymphocytic rather than mediated by polymorphonuclear neutrophils. The typical signs of shock, in the lung, kidney, and liver, are not accompanied by significant inflammatory lesions except on the mucous membranes of the esophagus and vagina (1, 19, 99, 116, 188). Although vaginal ulcerations have been seen in TSS patients who were using tampons, they also have been found in patients who were not using tampons, suggesting that the ulceration may be the result of the disease rather than its cause (99).

EPIDEMIOLOGY

Association with Menstruation and Tampon Use

In January 1980, prior to the association of TSS with menstruation and subsequently with tampon use, a summary of all cases prospectively reported by investigators in and around Colorado was made (168). There were 35 cases, of which 10 were male and 25 were female. The females were significantly older than the males, with an average age of 20.2 years. Seven of 10 of the males had clear-cut evidence of focal staphylococcal infection as compared with 2 of 22 females. The 20 remaining females gave a history of a vaginal discharge that grew *S. aureus*. Two-thirds of the isolated staphylococci reacted with group I staphylococcal bacteriophages and produced the epidermal toxin originally described in 1978 (167). These data clearly demonstrated a female predominance (although males were also affected) and suggested that affected females were more likely to be older than males with TSS. In males, there was a strong association with focal staphylococcal infections, while in females the data suggested a vaginal association. These data are important because they reflected a selection of cases which occurred prior to any public suggestion of a relationship with menstruation and tampon use, which may have biased subsequent reports.

In the spring of 1980, several investigators noted an apparently increased incidence of TSS predominantly in young menstruating women. Subsequently, significant associations with tampon usage were reported (47, 62, 69, 112, 153). Initially, no particular tampon was implicated; however, a second case control epidemiologic study performed at the Centers for Disease Control demonstrated an association with a particular brand of tampon (Rely) which was thereafter removed from the market (141). Other epidemiologic studies supported these early associations (56, 74, 89, 100). Subsequently, cases reported passively (i.e., voluntarily) to the Centers for Disease Control seemed to diminish (134) with increasing reports of nonmenstrual cases (postpartum, focal staphylococcal infection, surgical wound infection, and infections associated with nasal surgery and packing). Subsequent epidemiologic studies demonstrated a continued association between menstruation and tampon use in TSS, but suggested that the association with tampon brand, or chemical composition, is less predictive of risk than absorbancy: women using the high-absorbancy tampons seem to have the highest risk of TSS (15, 113). It is not clear whether this increased risk results from leaving tampons in the vagina longer or from some as yet undetermined factor (see "Pathogenic Model" below). There is also clear evidence of an increased TSS risk associated with various methods of barrier contraception (6, 28, 55, 59, 81, 96, 191).

Nonmenstrual Cases

Since 1980 many investigators have reported the recognition of nonmenstrual cases (8, 63, 132, 133), often with increased frequency (122, 177) compared with the early epidemiologic reports which may have selectively focused on females who were menstruating (47, 153). High-risk groups appear to be postpartum women (24, 30, 35, 67, 68, 187) and patients with surgical wound infections (8, 25, 57, 187), focal staphylococcal infections (175), and nasal surgery (78, 85, 162, 166). These cases confirm an association with *S. aureus* and also suggest the importance of focal infection in the pathogenesis of TSS, a finding further substantiated by a more recent survey comparing patients with TSS and patients with another staphylococcal toxin disease, scalded skin syndrome (176). The TSS patients were more likely to be older and female compared with scalded skin patients, who were uniformly young with an equal sex distribution. The TSS patients were far more likely to have a clear-cut focus of staphylococcal infection whereas most of the patients with scalded skin syndrome seemed to be colonized in the respiratory tract; this finding suggests that colonization alone is not sufficient to permit toxin production and absorption, whereas something more invasive (i.e., a focal infection) is required in patients with TSS. Several studies have suggested that about 1% of all patients hospitalized with *S. aureus* infections are at risk of developing TSS (J. A. Jacobson, E. M. Kasworm, and J. A. Daly, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 2, p. 2; A. M. Wiesenthal, M. Ressman, S. A. Caston, and J. K. Todd, Letter, Infection **14**:86, 1986). Recently, TSS has been reported associated with influenza outbreaks (104, 158). It has been suggested that this association may be due to an occult *S. aureus* infection in the sinuses following influenza (J. K. Todd, Letter, J. Am. Med. Assoc. **257**:3070–3071, 1987), and TSS has now been associated with *S. aureus* sinus infection (J. K. Todd, unpublished observation).

Incidence

It is difficult to determine the true incidence of TSS in populations for which reliance is placed on passive reporting (29, 120, 159). Davis and Vergeront demonstrated that self-reporting of TSS cases was encouraged by frequent newspaper coverage of the topic and seemed to diminish when articles on the subject were infrequent (49). A number of the early studies on the epidemiology of TSS relied on passive case reporting (47, 153) and came to the conclusion that its incidence decreased after removal of Rely tampons from the market (134). The biases introduced by such studies and their effect on the ultimate interpretation of the data

TABLE 1. Individuals at risk for TSS

Risk factor	Sex	Symptoms
Menstruation with tampon or other inserted vaginal foreign body	F	Any[a]
Barrier contraception	F	Any
Postpartum	F	Any
Surgical wound	M or F	Any
S. aureus infection	M or F	Any
Fever, rash	M or F	Others[a]
Hypotension	M or F	Others

[a] Symptoms include fever, rash, hypotension, conjunctival hyperemia, strawberry tongue, vomiting, diarrhea, and myalgia.

have been amply discussed without definitive resolution (70, 71, 77, 131). Several retrospective case studies surveying broad hospital populations have been performed to avoid some of these biases (73, 102, 105, 123, 177). In Minnesota, using an active case-finding technique, Osterholm and Forfang found no significant decrease in incidence of TSS after the removal of Rely tampons from the market (115).

TSS did not decrease in incidence in Colorado in 1981 and 1982 (177) and, in fact, increased in California when the same case ascertainment techniques were applied in a Health Maintenance Organization population (123). In several studies, TSS incidence was actually found to rise in the late 1970s prior to the introduction of Rely tampons (102, 123, 177).

In Colorado, the maximal incidence of TSS was reported to be 15.8 cases per 100,000 woman years and 9.1 per 100,000 per year for the total population (177), whereas in California, as recently as 1985, rates were in the range of 1.4 per 100,000, similar to those seen in 1981 and 1982 (Petitti et al., Abstr. Int. Symp. T.S.S. 1987).

Current estimates suggest that approximately 60 to 80% of cases of TSS nationwide occur in menstruating females and the remainder can be associated with focal or surgical wound infection, postpartum women, or various methods of barrier contraception (59; B. Schwartz, S. Gaventa, A. L. Reingold, A. Hightower, C. V. Broome, P. Wolf, and J. Perlman, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 6, p. 6). Considerable evidence from several studies indicates that, besides biases introduced by self-reporting and passive case ascertainment, many cases of TSS are still not clinically recognized (177). There may also be a bias in diagnosis and reporting of TSS cases when they occur in male patients or women who are menstruating and not using tampons (177). Clinicians may continue to inappropriately use menstruation and tampon use as a marker for TSS, while the case definition clearly avoids such an association.

High-Risk Groups

It is important to recognize TSS as an illness which affects a population that is not limited to menstruating young women. TSS has been confirmed in patients from newborns and children (26, 32, 35, 64, 67, 190) to geriatrics. The highest risk is still in children and young adults (177), presumably because they are more likely to represent individuals who have not previously encountered or developed immunity to the involved toxin(s). Table 1 summarizes the individuals who should be considered at risk of TSS based on epidemiologic and clinical experience. There is no question that a menstruating woman who is using a tampon or other inserted vaginal foreign body is at some increased risk for TSS. The risk just for menstruation ranges from 1 to 16 cases per 100,000 woman years. Certainly for any menstruating woman presenting with a fever along with associated symptoms of hypotension, rash, or conjunctival hyperemia, TSS should be included in the differential diagnosis. The same is true for women who are using barrier contraception or are postpartum.

It is important to emphasize, however, that females are not the only individuals at risk of TSS and that males as well as females are in the high-risk groups associated with surgical wound infections or known *S. aureus* infections. Individuals of either sex in these groups who have any symptoms of fever, hypotension, or rash should be considered at risk of TSS. Finally, for patients of either sex with no known risk factor, TSS should still be considered in the differential diagnosis if patients present with fever and rash or hypotension with or without fever. A fascinating hypothesis suggested by Langmuir et al. is that the great fatal plague of Athens (430 to 420 B.C., the so-called Thycydides syndrome) might have been due to an epidemic of TSS (97). Goodman, reflecting on the apparent potency of the toxin(s) causing TSS, has suggested that it may have been the cause of the Bundaberg vaccine disaster in Australia (J. S. Goodman, Letter, N. Engl. J. Med. **303**:1417, 1980).

MICROBIOLOGY

Association with *S. aureus*

A number of lines of evidence have strongly associated *S. aureus* with most cases of TSS. In the original description of TSS (167), this supportive evidence included the presence of documented *S. aureus* infection in two of the seven patients, isolation of phenotypically similar *S. aureus* strains from three other patients, further characterization of these strains which demonstrated the production of an apparently new epidermal toxin, the exclusion of other illnesses of different etiologies in the differential diagnosis by use of extensive laboratory testing, and the preexistence of other case reports of similar illness in patients with *S. aureus* infection.

Subsequent data have confirmed the association of clinical TSS with certain strains of *S. aureus* (3, 7, 47, 54, 153). The majority of cases reported since 1978 have been associated with focal *S. aureus* wound infections or menstruation and tampon usage with *S. aureus* isolated from the patients' vaginal cultures. These *S. aureus* strains have characteristic phenotypes which differ from those of *S. aureus* strains in the general population (7, 173). Further microbiologic evaluations of these strains have demonstrated at least one (and probably more) toxin (12, 23, 53, 149) which in certain (but not all) animal models reproduces many of the symptoms of TSS (127, 129, 151, 152, 165). Most patients acquiring TSS do not have antibody against TSST-1 (21, 160) compared with the majority of individuals in the general population who have immunity and appear to be at lower risk of developing TSS (111, 138, 182).

Finally, some patients have had multiple episodes of TSS associated with recurrent focal *S. aureus* infections (Todd, unpublished observations.) Such recurrences are well known in menstruating women who use tampons, and the use of antistaphylococcal antimicrobial therapy significantly reduces the risk of that recurrence (48). All of the above evidence strongly supports the contention that TSS is caused by certain *S. aureus* strains.

Strain Characteristics

S. aureus strains isolated from patients with TSS were originally reported to have a unique phenotype, reacting with group I bacteriophages and producing an apparently new epidermal toxin in the newborn mouse animal model (167). Several studies have compared the phenotype of TSS-associated strains with those of other *S. aureus* strains, supporting the general conclusion that most TSS organisms represent a unique subset of the overall *S. aureus* population (3, 7, 148, 149, 173). Besides reacting commonly with group I bacteriophages (2, 3, 167, 173), TSS strains are less likely to contain plasmids (173) and more likely to produce the epidermal toxin (88) as well as other exoproteins, including enterotoxins and TSST-1 (173). They are more likely to be resistant to heavy metals and susceptible to a particular *S. aureus* bacteriocin and are more proteolytic (7, 173). TSS-associated strains are less hemolytic (27, 40, 173) and more likely to be pigmented (173). Interestingly, TSS strains tend to be less toxic than other *S. aureus* strains when given parenterally in certain animal models (chicken, embryo or rabbit) (7, 52).

Other Microflora

Although most cases of TSS have been directly associated only with *S. aureus* infection or colonization, a few cases with similar clinical features have been associated with group A streptococci (e.g., severe streptococcal scarlet fever and sepsis) and *Streptococcus pneumoniae* (9, 43; Todd, unpublished observations) and with *Pseudomonas aeruginosa* (C. E. Daman Willems, B. Jones, and D. J. Matthew, Letter, Lancet **ii**:1218–1219, 1986). Although two studies have suggested that TSS can be caused by toxin-producing coagulase-negative staphylococci (46, 87), others have not confirmed this observation (93, 118).

One theory of the pathogenesis of TSS suggests that the presence of *S. aureus* strains along with endotoxin-producing organisms might result in an interaction of toxins (e.g., TSST-1 and endotoxin) to achieve a synergistic toxic effect in the host (149). These effects are seen primarily in rabbits and chicken embryos (52) pretreated with endotoxin. Therapeutic studies in rabbits with just TSST-1 have shown a beneficial effect of polymyxin in one study (50) but not of polymyxin or anti-endotoxin J5 antiserum in another (M. E. Melish, S. Murata, C. Fukunaga, C. Wong, K. Frogner, and S. Hirata, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 36, p. 36). Chow and co-workers have shown increased vaginal colonization with *Escherichia coli* in women with TSS (34) but, from most cases of TSS associated with wound infection, it is clear that *S. aureus* alone is usually sufficient to cause disease. Although the signs and symptoms of TSS may be associated with infection by some other organisms, it appears likely that most cases of the syndrome are strictly related to *S. aureus* infection.

TOXINS

TSST-1

In 1981, Bergdoll et al. (enterotoxin F) and Schlievert et al. (pyrogenic exotoxin C) independently described extracellular proteins associated with *S. aureus* strains in patients with TSS (12, 149). Enterotoxin F was purified by using its biologic activity, emesis in monkeys, as a marker (12), and pyrogenic exotoxin C was purified based on its ability (synergistically with endotoxin) to cause fever and death in a rabbit model (149). Both putative toxins were purified independently and, when compared by amino acid profile and immunologic cross-reactivity, appeared to be the same protein, which is now called TSST-1 (23, 42).

Based on studies with purified protein, TSST-1 has a molecular weight of 22,000 to 24,000 and an isoelectric point of 7.2 (12, 23, 42, 130, 149). It is commonly purified by initial ethanol precipitation, followed by isoelectric focusing (147) or ion-exchange and size exclusion column chromatography (12, 23, 149). By common protein-staining techniques (e.g., Coomassie blue), it appears as a single band on denaturing polyacrylamide gels. Ouchterlony immunodiffusion with monospecific antisera to TSST-1 shows a single line of identity. In some preparations, however, more sensitive staining techniques (e.g., a silver stain) show higher-molecular-weight bands in addition to the primary band; and when Coomassie blue followed by silver staining is used (or Western blot [immunoblot] analysis with pooled normal human sera), multiple additional bands are seen (A. W. Chow, N. E. Reiner, P. M. Rosten, and K. H. Bartlett, Abstr. Int. Symp. T.S.S. 1983, abstr. no. 17, p. 17). Preparations of TSST-1 similar to the ones described above have been used in the preparation of antisera (both polyclonal and monoclonal) and for widespread toxin characterization in various tissue culture and animal models. The presence of possible impurities in these antigen preparations raises some questions about directly attributing observed effects to TSST-1 or complete reliance on test results obtained with polyclonal antisera.

TSST-1 is assayed by a number of different immunological techniques. Originally, agar diffusion with Ouchterlony plates and various extract dilutions (12) or isoelectric focusing (149) methods were used. The isoelectric focusing technique has since proven to be less specific (72). More recently, radioimmune assays, latex agglutination tests (82), and enzyme-linked immunosorbent assay techniques (109, 176) have been developed with antigen detection sensitivity as low as 1 ng/ml. A rapid immunoblot assay has been described (184). Many of the latter techniques use monoclonal antibodies to TSST-1 which presumably permit the detection of a single specific epitope.

Recently, multiple monoclonal antibodies to TSST-1 which have permitted further characterization of the serologically and biologically active sites of TSST-1 have been prepared (22; C. Edwin, J. Parsonnet, and E. H. Kass, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 19, p. 19; P. N. Kokan, and M. S. Bergdoll, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 21, p. 21).

Other Toxins and Extracellular Products

Although TSST-1 was the first protein that was well characterized and related to TSS-associated *S. aureus* strains, a number of other *S. aureus* proteins have been statistically associated with TSS (Table 2). The epidermal toxin described by Kapral and co-workers was found in all strains associated with the cases in the original description of TSS (88, 167). Although not yet completely characterized, this higher-molecular-weight (approximately 60,000) *S. aureus* protein causes epidermolysis at the basal cell layer in newborn mouse skin. This effect is distinct from that of the exfoliatin (or epidermolytic) toxin associated with *S. aureus* strains isolated from patients with staphylococcal scalded skin syndrome, which causes epidermolysis at the granular cell layer in the same model.

From immunoblots that reacted with convalescent human antisera (41), Cohen and Falkow described two membrane-associated antigens (30 and 32 kilodaltons) found in *S. aureus* strains associated with TSS. Using similar methods, a number of investigators have described proteins with

TABLE 2. Proteins phenotypically associated with TSS *S. aureus* strains

Protein	Mol wt	Sentinel biologic activity
TSST-1	22,000	Fever in rabbits, vomiting in monkeys, interleukin-1 induction, TSS-like syndrome in rabbits
Epidermal toxin	60,000	Epidermolysis in newborn mice
Bacteriocin	90,000	Growth-inhibitory activity
Membrane-associated antigens	30,000 32,000	Detected on immunoblots
Anti-TSST-1 cross-reacting proteins	36,000 52,000	Detected on immunoblots
Type II protease	12,000	Cysteine-enhanced proteolysis
Enterotoxins B, C	27,000	Vomiting in animals

molecular weights ranging from 27,000 to 52,000 which react with polyclonal and monoclonal anti-TSST-1 antibodies (151, 192; Lawellin et al., Abstr. Int. Symp. T.S.S. 1987; D. F. Scott, G. K. Best, J. M. Kling, P. F. Bonventre, and M. R. Thompson, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 35, p. 35). Because the gene (*tst*) for TSST-1 has been cloned and sequenced (20, 90) and codes for a protein of 22,049 molecular weight, it seems that these higher-molecular-weight anti-TSST-1-reacting proteins represent either a shared epitope or protein aggregates; their relationship to TSS is unknown.

Two staphylococcal proteases have been associated with TSS. Barbour first demonstrated increased protease activity in *S. aureus* strains isolated from TSS patients (7). In one phenotypic study, protease activity and TSST-1 production correlated strongly with each other and with TSS-associated *S. aureus* strains (173). This protease activity has been shown to be due to the type II (thiol) protease (174). More recently, the type I (serine) protease has been shown to digest TSST-1 in vitro and is found in significantly higher concentrations in TSS-associated *S. aureus* strains which do not appear to produce TSST-1 (J. K. Todd, A. Franco-Buff, C. Smith, and D. Lawellin, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 20, p. 20).

It has been noted that many *S. aureus* strains isolated from focal infections in patients with TSS do not produce detectable TSST-1. These patients may have high levels of anti-TSST-1, and their organisms are often found to produce enterotoxins B or C (44, 45, 53, 111, 157; P. M. Schlievert, Letter, Lancet i:1149–1150, 1986), further suggesting that the syndrome of TSS can be caused by more than one *S. aureus* exoprotein. TSST-1 remains the most commonly associated and best studied of the candidate toxins.

Effects of Growth Conditions

Because of the marked interest in a possible relationship of tampons to the production of toxins mediating TSS, many studies have been performed to assess the growth conditions which might affect TSST-1 production in vitro. Various in vitro tampon models have been developed in an attempt to clarify the mechanism of the epidemiologically noted relationship of TSS and tampon use. Initially, it was proposed that the carboxymethyl cellulose component of Rely tampons might produce glucose upon breakdown with cellulase. Glucose then could be used as an energy source that would permit the increased growth of *S. aureus* strains in vivo and theoretically increase toxin production (164). As *S. aureus* does not produce a cellulase, it was postulated that other vaginal microflora might facilitate the necessary breakdown of carboxymethyl cellulose. This theory has not been substantiated (154) and, in fact, the use of increased glucose in the growth medium has actually been shown to decrease TSST-1 production (145).

Similar to other *S. aureus* proteins, the optimal production of TSST-1 by TSS-related *S. aureus* strains requires certain in vitro growth conditions (145, 146, 176). Organism growth is severely limited in anaerobic environments and at low pH (145, 176). At a neutral pH with added oxygen, strains are able to grow actively and produce more TSST-1 (145, 146, 176). The addition of protein and 5% CO_2 increases toxin and protease production further (176), as well as hemolytic activity (30). Chu et al. have shown that most TSST-1-producing strains require tryptophan for growth and suggest that the TSST-1 gene may be inserted in the tryptophan operon (39).

Mills and others have studied the effect of divalent cations on TSST-1 production in vitro with conflicting results (109, 144, 176; J. F. James, L. Lee, S. A. Peck, and M. E. Melish, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 25, p. 25; E. H. Kass, J. Parsonnet, and J. T. Mill, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 26., p. 26; M. W. Reeves, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 23, p. 23; D. Taylor and K. T. Holland, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 24, p. 24). It does appear that small amounts of magnesium are essential for organism growth and that high levels of magnesium may, in fact, suppress TSST-1 production. The original studies were performed in a defined chemical medium; however, in more complex media, magnesium seems to have less of a controlling effect (144, 176). Although it has been postulated that the polyacrylate component in some high-absorbancy tampons may absorb magnesium and permit increased TSST-1 production, these effects are medium dependent and may not truly reflect conditions in the patient. Epidemiologic studies do not confirm an increased risk of polyacrylate-containing tampons independent of absorbancy (15).

The addition of human blood to several in vitro models has also variously affected TSST-1 production. In one study an artificial medium was constructed to match human menses; this medium was the most effective in increasing TSST-1 production and was not affected by the addition of human blood (J. J. Kirkland, C. A. Ryan, K. A. Kohrman, and P. J. Danneman, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 30, p. 30). Similarly, many studies have been performed that evaluate the potential effects of tampons and related material on in vitro production of TSST-1 (76, 93, 101, 135, 137, 139, 146, 163; V. A. Fischetti, F. Chapman, E. Grun, and J. B. Zabriskie, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 28, p. 28; R. F. Reiser, L. K. Denzin, and M. S. Bergdoll, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 29, p. 29; R. N. Robbins, B. J. Kelly, and M. S. Bergdoll, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 31, p. 31; P. M. Tierno, Jr., and B. A. Hanna, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 27, p. 27). Depending on the model and the conditions, there are very divergent reports of both increases and decreases of toxin production.

It is clear that variations in growth conditions and the presence or absence of various materials in vitro affect the production of TSST-1 (Fig. 1). It is problematic, however, to extrapolate these controlled observations to the patient, because the conditions in the test tube may not replicate those in vivo. Todd et al. measured a number of the identified critical factors in focal infection material from patients with TSS and found the in situ conditions to be as follows: aerobic, neutral pH, high protein, low glucose, low to normal magnesium, and high CO_2. When replicated in vitro, these conditions significantly increased the production of TSST-1 and protease (176).

Host Defenses

Most adults have preexisting antibody to TSST-1, and most patients who have menstrually associated TSS have little or none (12, 21, 103, 138, 157, 182). On the other hand, *S. aureus* strains that do not produce TSST-1 are isolated from approximately 40% of patients with nonmenstrually associated TSS. Interestingly, even though these patients have clear-cut clinical TSS, they have antibody to TSST-1 (103, 157). Those patients with low antibody titers before the TSS episode may develop increased antibody titers to TSST-1 after the clinical illness. However, many patients show no rise in titer to TSST-1, even after multiple episodes of clinical disease (21, 37, 111, 160). One study suggests that such patients may have a selective immunoglobulin G subclass deficiency (subclass 2 or 4) (38), while another demonstrated that TSST-1 is capable of suppressing B-cell responses in vitro (125). These data suggest that TSST-1 is not the only toxin associated with TSS, that a lack of antibody is a risk factor in some patients, and that immunity does not develop readily to TSST-1, at least in patients who have clinical disease.

In serological and microbiological surveys, patients who have TSST-1-producing *S. aureus* strains in their nasal cultures also tend to have the highest level of anti-TSST-1 even though they have never had a history of TSS (86, 138). In addition, it is clear that many patients become colonized with TSST-1-producing *S. aureus* strains and develop no clinical illness although they may develop high levels of anti-TSST-1 (138). This is further evidence that the *S. aureus* strain needs to grow under specific clinical conditions that permit expression of the causative toxin(s), conditions not usually present in the nasopharynx (see Fig. 2).

One additional host variable may be important in some patients. Many of the patients at high risk of TSS have altered hormonal states (menstruation, postpartum, childhood) characterized by low levels of sex hormones. In one study, several menstrual age females with existing focal *S. aureus* infections had the onset of tampon-associated TSS with the onset of menses (177). Epidemiologic studies suggest that oral steroid contraception is associated with a decreased risk of TSS (112) and, anecdotally, steroids have been useful in preventing recurrences (106). In one study, a defect in *S. aureus* 502A (not a TSS strain) neutrophil killing was noted to be menses associated. In addition, methylprednisolone has been shown to be effective in treating early clinical TSS (175) and has been effective in several animal models (121; H. Igarashi, H. Fujikawa, and H. Usami, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 33, p. 33). Finally, several studies have demonstrated steroid-regulated suppression of *S. aureus* exoprotein production in vitro (Todd, unpublished observations). These data support a role for steroid hormones in the pathogenesis of TSS.

GENETICS AND REGULATION OF PHENOTYPIC EXPRESSION

TSST-1-producing *S. aureus* strains can be isolated from most cases of menstrually associated TSS and many cases of nonmenstrual TSS. TSST-1 production by *S. aureus* strains has been phenotypically linked to pigment production, lack of alpha-hemolysin, heavy-metal resistance, bacteriocin susceptibility, absence of plasmids, and protease production (173).

Most TSST-1-producing strains contain no detectable free plasmids (91, 92, 173). Schutzer et al. reported that *S. aureus* strains producing TSST-1 could be induced to produce bacteriophages which lysed several specific indicator strains, suggesting that the TSST-1 gene might be carried by a bacteriophage (150). These observations could not be reproduced by Kreiswirth et al., who have cloned the TSST-1 gene (*tst*) and demonstrated its chromosomal location (90). The *tst* gene has been sequenced and codes for a protein of 22,049 molecular weight, consistent with TSST-1 molecular weight measurements (20). *S. aureus* strains which express TSST-1 uniformly possess the *tst* gene (P. F. Bonventre and L. Weckback, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 11, p. 11) while other strains do not. Subsequent work has shown that most TSST-1-positive strains are tryptophan auxotrophs (39) and that *tst* may be physically inserted into the tryptophan operon (M. C. Chu, B. N. Kreiswirth, P. A. Pattee, R. P. Novic, M. E. Melish, and J. F. James, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 15, p. 15). There also appears to be a chromosomal linkage between the TSST-1 gene and the beta-lactamase gene, the latter being traditionally thought of as a plasmid-mediated product (B. Kreiswirth, P. Schlievert, and R. Novick, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 10, p. 10). It has been proposed that the TSST-1 gene may be on a transposon (perhaps a plasmid fragment) which is most frequently inserted at a site within the tryptophan operon but occasionally may be found at other chromosomal sites. The observation that the *tst* gene chromosomal insertion decreases the production of a number of genetically unlinked exoproteins points to an accessory gene regulator (*agr*) functioning as a control element for multiple genes.

It is also interesting that most TSST-1-positive strains produce very little alpha-hemolysin (27, 40, 173) even though most strains tested contain the alpha-toxin gene (M. O'Reilly and T. J. Foster, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 14, p. 14). These data further suggest that certain genetic events may lead to repression of some genes (i.e., alpha-toxin) at the same time that the expression of other genes (i.e., TSST-1) is enhanced.

Although some level of genetic regulation is operative in TSST-1 production, it also appears that TSST-1-positive *S. aureus* strains have the potential for posttranslational modification of extracellular protein expression (Fig. 1). Todd et al. demonstrated that most TSST-1-positive strains of *S. aureus* produce large amounts of the type II (thiol) protease (174) which is enhanced by the same conditions that encourage TSST-1 production in vitro (i.e., CO_2, oxygen, and neutral pH) (176). More recently, it has been shown under in vitro conditions that TSS-associated, TSST-1-negative strains produce large amounts of the type I (serine) protease and that the serine protease in vitro fully digests TSST-1 (Todd et al., Abstr. Int. Symp. T.S.S. 1987).

It is clear that many *S. aureus* strains associated with TSS contain the *tst* gene and excrete TSST-1 in vitro. However, some TSST-1-negative strains can also be related to cases of

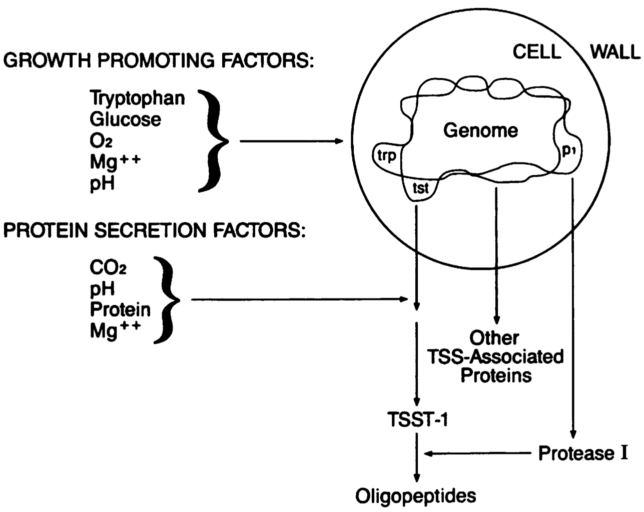

FIG. 1. Regulation and expression of TSST-1-producing *S. aureus* strains. *trp*, Tryptophan operon; *tst*, TSST-1 gene; p1, protease I gene.

TSS, and these strains are more likely to produce enterotoxins B and C. The gene for enterotoxin B appears not to have homology with *tst* (G. A. Bohach and P. M. Schlievert, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 9, p. 9).

MEDIATORS

TSST-1 is known to have multiple biologic effects (143). When combined with endotoxin, it produces fever and increased mortality in rabbits (148, 149). In vitro it is a potent stimulator of interleukin-1 (11, 83, 117, 119), interleukin-2 (108, 181), and T-suppressor cells (124, 142, 181) and has also been shown to increase human neutrophil oxidative metabolism (66). Recently, TSST-1 has been shown to stimulate the secretion of tumor necrosis factor, a potent substance which is a biologic mediator of shock (T. Ikejima, S. Oksawa, J. W. M. VanDerMeer, and C. A. Dinarello, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 46, p. 46; J. Parsonnet and Z. A. Gillis, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 47, p. 47). It has also been shown that TSST-1 binds to (and is capable of penetrating) epithelial cells (94, 95), human mononuclear cells (126), and endothelium of human blood vessels (V. M. Kushnaryov, H. S. MacDonald, M. S. Bergdoll, and R. Reiser, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 43, p. 43). Since the pathophysiology of TSS appears to be related to capillary leakage, a direct toxin effect on capillary permeability is possible but could also be mediated by factors such as tumor necrosis factor. Treatment studies in the rabbit model show that prostaglandin inhibitors (indomethacin and salicylates) reduce fever, but only specific immunoglobulin G or corticosteroids reduce lethality (Igarashi et al., Abstr. Int. Symp. T.S.S. 1987).

ANIMAL MODELS

The reproduction of staphylococcal scalded skin syndrome (toxic epidermal necrolysis) in the newborn mouse model was a significant precedent for subsequent understanding of that staphylococcal toxin disease. When TSS was described in 1978, the same model was utilized to probe TSS-related *S. aureus* strains and a potentially new epidermal toxin was described which caused cleavage at the basal cell layer (167). Thereafter, it was shown that TSS-associated *S. aureus* strain filtrates were not particularly toxic when given intravenously in rabbits or chicken embryos (7, 52). Schlievert et al. first demonstrated the endotoxin-potentiated effects of TSST-1 in the rabbit model resulting in fever and increased mortality (149), while at the same time Bergdoll et al. showed that the purified protein caused vomiting in monkeys (12).

Since that time, many investigators have given purified TSST-1 to various species of animals with various results (127). Bolus injection seems to have less reproducible effects than does continuous toxin exposure, which has been achieved in various ways. Currently, a popular model for TSS involves the use of New Zealand White rabbits with a subcutaneous (4, 129, 152) or intrauterine (51) reservoir. The injection of TSST-1 (or of TSST-1-producing *S. aureus* strains) into the reservoirs is sufficient to result in a clinical illness in the rabbits similar to TSS in humans (although no rash is seen), while isogenic strains not possessing the *tst* gene do not cause a similar illness (51, 128). Additional studies have been conducted with a continuous subcutaneous infusion of TSST-1 (J. Parsonnet, Z. A. Gillis, M. R. Thompson, L. Adinolfi, and P. F. Bonventre, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 34, p. 34). Insertion of a TSST-1-saturated tampon into the vagina of female rabbits has produced a similar syndrome (M. E. Melish, S. Murata, and C. Fukunaga, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 39, p. 39), as did the use of tampon material saturated with TSST-1 and endotoxin in mice (165). In several studies young rabbits were less responsive to toxin than older ones, males were more susceptible than females (18), and estradiol given to susceptible animals mitigated the pathologic response (17).

Overall, TSST-1 alone seems to have little effect in mice, rats, hamsters, guinea pigs, and most monkeys, whereas some symptoms are seen in rabbits, goats, and baboons. Nonetheless, it is difficult to state that the latter animals represent a reliable model of TSS as TSST-1-negative strains isolated from patients with (and without) proven TSS may also cause TSS-like symptoms in rabbits, possibly related to independent enterotoxin (or other exoprotein) production (4; K. A. Kohrman, J. J. Kirkland, and P. J. Danneman, Abstr. Int. Symp. T.S.S. 1987, abstr. no. 38, p. 38). That *S. aureus* strains produce a wide number of extracellular products (e.g., alpha-toxin, leukocidin, epidermolytic toxin, and enterotoxins) which cause severe biologic effects in some animals makes it difficult to confirm that the symptoms noted in animals given TSST-1 or infected with TSST-1-producing strains are specific for TSS in humans. In addition, recent data suggesting that most TSST-1 preparations are not pure (Chow et al., Abstr. Int. Symp. T.S.S. 1987) raise the possibility that highly potent contaminants might contribute to the symptoms noted in animals. Nonetheless, most animal model data relating to the effects of TSST-1 strongly support its role as the most prominent toxin causing TSS.

PATHOGENIC MODEL

The above data raise many questions regarding the pathogenesis of TSS. In the early 1980s, the answers seemed simpler than they do now. Initially it was thought that TSS was caused solely by TSST-1 and that its production was enhanced by interaction with tampon materials in vivo. It is now clear that this initial concept is insufficient to fully explain our current understanding of the complexity of the biology of TSS-associated *S. aureus* strains. The evidence

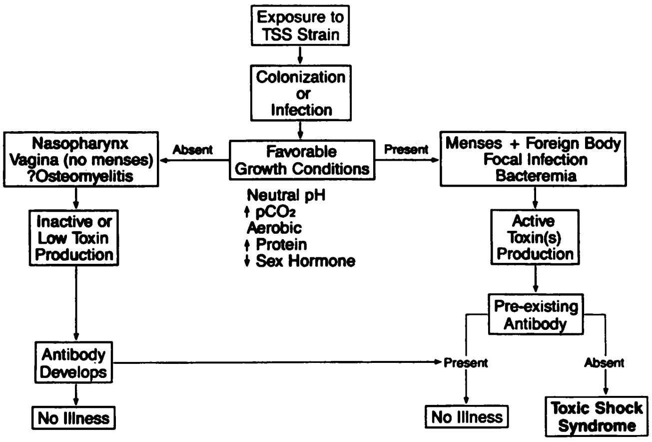

FIG. 2. Pathogenesis of TSS.

that many TSS patients have focal sites of *S. aureus* infection (compared with scalded skin syndrome) (176) and that many patients carry TSST-1-producing *S. aureus* strains in the nose and have high titers of antibody to that toxin without ever having a history of disease suggests that TSST-1-producing strains of *S. aureus* must be grown in vivo under special conditions to fully express their toxic potential (Fig. 1). Whether the causative toxin of TSS is TSST-1, an enterotoxin, or some other protein is not clearly defined: the exact cause in individual cases may vary depending on the host immunity, the organism, or its growth conditions in vivo. Thus, abscesses and other focal infections seem to provide these *S. aureus* strains with the proper environmental milieu to allow the fullest expression of toxin potential, a potential which would less likely be expressed in the nasopharynx or in the anaerobic, acidic vagina, unless during menstruation when protein concentrations would be higher, the pH would be neutral, and oxygen could be inserted into the normally anaerobic vagina by a tampon (183).

The pathogenesis of TSS requires exposure of a nonimmune individual to a toxin-producing *S. aureus* strain (Fig. 2). To allow optimal production, these *S. aureus* strains must grow under conditions which promote toxin expression. These conditions are best found in focal soft-tissue *S. aureus* infections or in the vagina during menstruation and in the presence of an inserted vaginal foreign body (e.g., tampon or barrier contraceptive device). A similar situation occurs after nasal surgery with the insertion of a nasal pack. Under optimal growth conditions, the organism produces one or more toxins which are systemically distributed and seem to have a final effect, either directly or via activated mediators, on capillary integrity. This results in a noninflammatory lesion which causes capillary leakage, hypotension, erythema, and multiorgan system involvement related to the hypotension.

SUMMARY

In the past 10 years, we have learned much about TSS and *S. aureus* and its toxins. A number of important biologic principles have been reemphasized in this first decade of TSS research: *S. aureus* is a very complex organism, one not likely to yield quick answers; in vitro observations must always be confirmed in the patient; animal models may not always be reliable replicates of human disease; and epidemiologic associations cannot be equated with causation.

Toxic shock is an intricate phenomenon with many interesting scientific facets. Unraveling its mysteries will undoubtedly teach us more about the complex interaction of patients and microorganisms.

ACKNOWLEDGMENTS

The assistance of Donna Shambaugh, Bernita Bruns, and Lynda Donegan is gratefully acknowledged. The suggestions and comments of David Lawellin are greatly appreciated.

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