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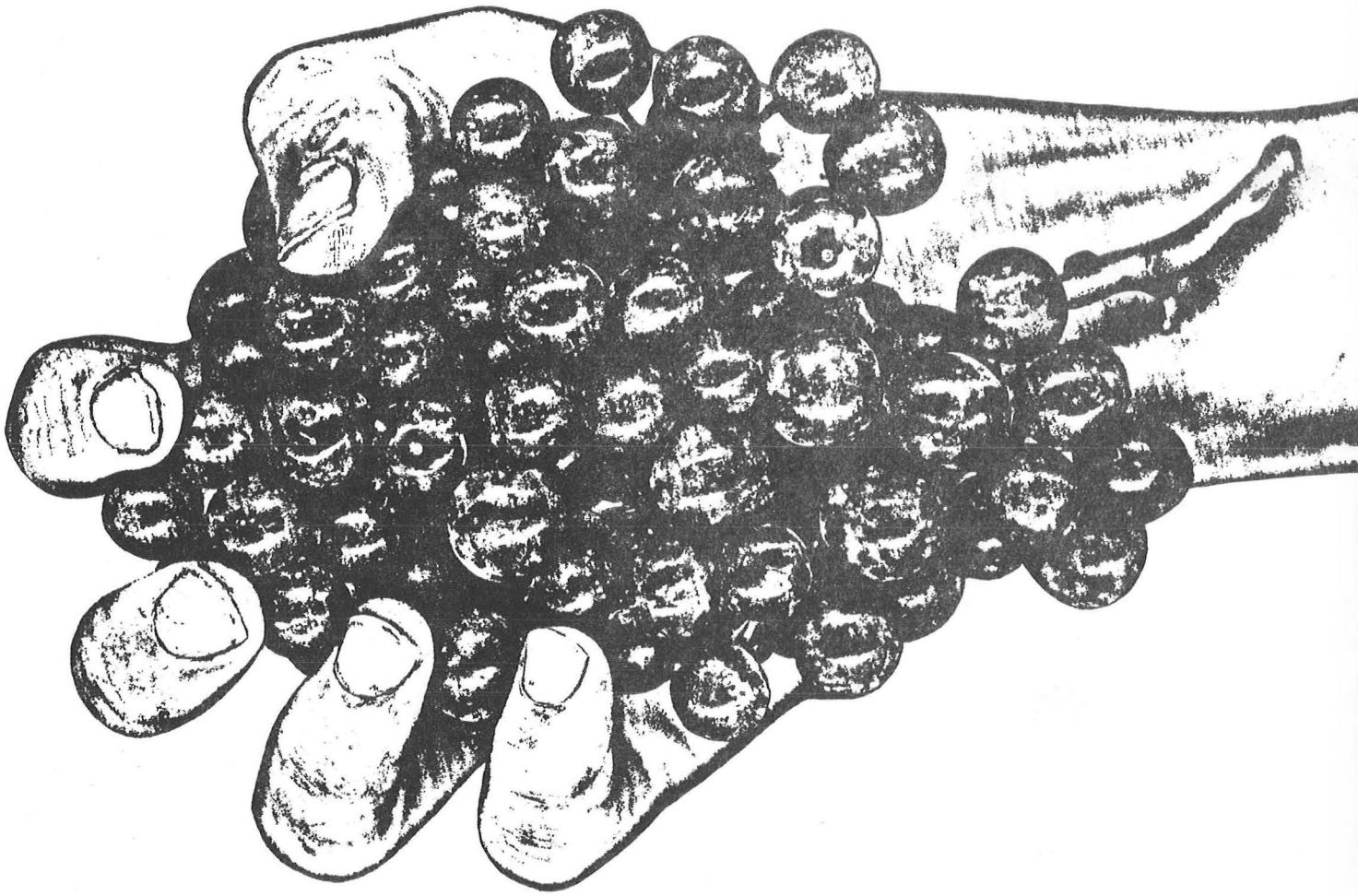

STAPHYLOCOCCAL PROBLEMS FOR THE 1980'S

MEDICAL GRAND ROUNDS
PARKLAND MEMORIAL HOSPITAL
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STAPHYLOCOCCUS AUREUS: TWO IMPORTANT PROBLEMS FOR THE 1980's

A. Toxic shock syndrome

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Cover photo: Staphylococcus (G. staphyle, a bunch of grapes, kokkos, a berry)

Unwashed hand: most important mode of spread of Methicillin Resistant Staphylococcus aureus.

Photo by Kodak EKTAPRINT 100 copier-duplicator

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TOXIC SHOCK SYNDROME

Clinical features. In 1978, Dr. James Todd and his colleagues in Colorado reported a series of 7 children that had experienced an unusual illness (7). All of the children had high fever (39 - 41°C), headache, confusion, injected conjunctivae, a non-pruritic scarlatiniform rash on the trunk and extremities, edema of the face and limbs, and a tendency toward sudden, profound hypotension. They named this illness "Toxic Shock Syndrome" and presented evidence that it was caused by S. aureus. The occurrence of a similar illness in adult women was not publicized until 1980, when the Centers for Disease Control launched an investigation into an epidemic of the syndrome.

To date, most studies of TSS have used highly restrictive case definitions in order to avoid including non-cases. The most severe cases have thus been selected. The CDC case definition, used for their epidemiologic studies, was the following (19).

Toxic-shock syndrome case definition

1. Fever (temperature ≥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 ≤90 mm Hg. for adults or <5th percentile by age for children <16 years of age, or orthostatic syncope).
5. Involvement of 3 or more of the following organ systems:
   A. Gastrointestinal (vomiting or diarrhea at onset of illness).
   B. Muscular (severe myalgia or creatine phosphokinase level ≥2 x ULN*).
   C. Mucous membrane (vaginal, oropharyngeal, or conjunctival hyperemia).
   D. Renal (BUN† or Cr‡ ≥2 x ULN or ≥5 white blood cells per high-power field--in the absence of a urinary tract infection).
   E. Hepatic (total bilirubin, SGOT§, or SGPT¶ ≥2 x ULN).
   F. Hematologic (platelets ≤100,000/mm³).
   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.

*Twice upper limits of normal for laboratory.
†Blood urea nitrogen level.
‡Creatinine level.
§Serum glutamic oxaloacetic transaminase level.
¶Serum glutamic pyruvic transaminase level.

Table 1, from reference 19

Subsequently, the CDC have broadened their case definition to include orthostatic dizziness as an indication of hypotension, and not to exclude patients who have positive blood cultures for S. aureus. Reports from clinicians in Minnesota and elsewhere have presented persuasive evidence that TSS is indeed a spectrum of illness that occurs in mild as well as severe forms (1-3,5,8,9). The cardinal features of the "modified" case definition are conjunctival and pharyngeal erythema and a diffuse erythroderma with desquamation. Actually, the requirement for desquamation seems to exclude some true cases (5).

Striking multisystem involvement has occurred in severe and moderately severe cases. Rhabdomyolysis, hypocalcemia, hypophosphatemia, and hypoalbuminema have commonly occurred, as have DIC, cholestasis, and renal failure. Not surprisingly, shock is the feature that most reliably predicts the occurrence of multisystem complications.

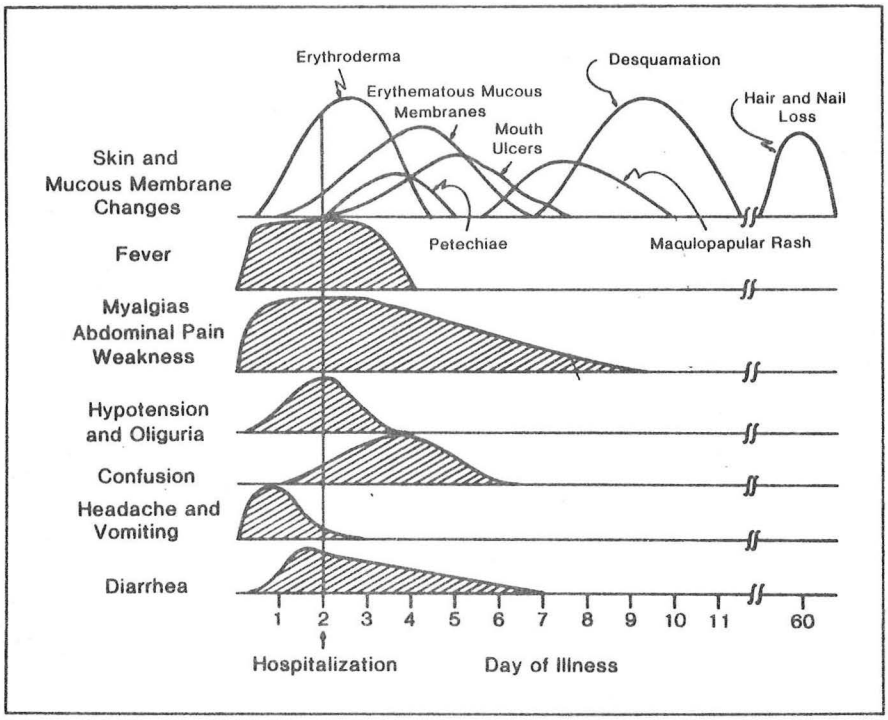


Fig. 1, from reference 2

The frequency of various clinical findings in severe TSS is shown in the following Table (from reference 19).

Frequency of Signs, Symptoms, and Laboratory Abnormalities in 52 Patients with Toxic-Shock Syndrome.*

Clinical Sign or Symptom	Percentage	Laboratory Finding	Percentage
Diarrhea	98	Elevated serum creatinine §	69
Myalgia	96		
Vomiting	92	Thrombocytopenia †	59
Temperature ≥40°C	87	Hypocalcemia ‡	58
Headache	77	Azotemia §	57
Sore throat	75	Hyperbilirubinemia §	54
Conjunctival hyperemia	57	Elevated hepatic enzymes §	50
Decreased sensorium	40	Leukocytosis ¶	48
Vaginal hyperemia	33	Abnormal urinary sediment ‖	46
Vaginal discharge	28		
Rigors	25	Elevated CPK §	41
		Immature leukocytes ≥50%	36

*100 per cent of patients had the first four criteria listed in Table 1.

†Platelet count <100,000 per millimeter.

‡Serum calcium ≤7.5 mg per deciliter.

§Value greater than or equal to twice the upper limit of normal for laboratory.

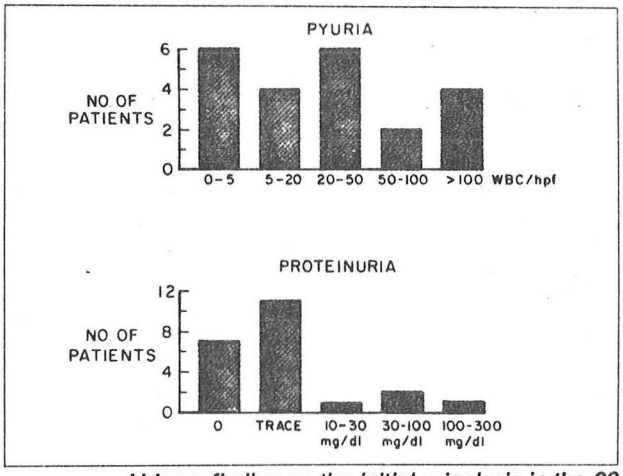
¶White-cell count ≥15,000 per cubic millimeter.

‖At least 5 white cells per high-power field, ≥2 red cells per high-power field, or presence of red-cell casts.

Table 2, from reference 19

Several of the clinical features of TSS deserve comment.

Hypotension is thought to result from vasodilatation and extravascular movement of fluid. Edema is often present. Vasopressors and large volumes of IV fluid are often required to support the blood pressure. The character of the diarrhea has been poorly described but PMNs have been noted when microscopic examination of the stool has been performed. Renal failure has been both oliguric and non-oliguric. Sterile pyuria has been common (see Fig 2). Hypocalcemia has been attributed in part to hypoalbuminemia, yet a calcitonin-like substance has been found in the blood of some TSS patients with hypocalcemia. Hypophosphatemia has also been common in severe cases and has occurred even in the presence of acute renal failure. The dermatologic manifestations are diverse; most prominently, there is erythema of the mucous membranes (including a "beefy red" vagina in some patients), a diffuse erythroderma, and desquamation of the palms and soles late in the course. Reversible hair and nail loss has occurred as a late complication in a few patients.



Urinary finding on the initial urinalysis in the 23 patients before each patient underwent catheterization.

Fig. 2, from reference 1

Differential diagnosis. Before the recognition of TSS as a distinct entity, patients with TSS were thought to have a variety of illnesses, including:

Kawasaki Disease	Meningococcemia
Streptococcal scarlet fever	Acute rheumatic fever
Pyclonephritis	Rocky Mountain Spotted Fever
Septic shock	Endemic typhus
Drug eruptions	Leptospirosis

Some differential features are outlined on the following page (adapted from reference 10).

TOXIC SHOCK SYNDROME: DIFFERENTIAL DIAGNOSIS

	Kawasaki Disease	Erythema Multiforme	Streptococcal Scarlet Fever	Staphylococcal Scarlet Fever	Toxic Shock Syndrome	Leptospirosis	Meningococcemia
Age, yr	Usually < 5	All ages	Usually 2-8	Usually 2-8	Usually adolescent - Adult	Usually > 2	Usually < 30
Fever	Prolonged	Prolonged	Variable	Variable	Usually < 10 days	Variable	Often high
Eyes	Hyperemia of the ocular conjunctivae	Hyperemia of the ocular conjunctivae; palpebral edema	No change	Hyperemia of the ocular conjunctivae	Hyperemia of the ocular conjunctivae	Hyperemia of the ocular conjunctivae; uveitis	Conjunctivae petechiae
Lips	Red, dry, fissured	Erosions; ulcerations	No change	No change	Red	No change	No change
Oral cavity	Diffuse erythema; "strawberry tongue"	Erosions, aphthous-like ulcerations, bullae	Pharyngitis; palatal petechiae; "strawberry tongue"	Pharyngitis	Erythema; pharyngitis	Pharyngitis	No change
Peripheral extremities	Erythema of palms and soles; indurative edema; periungal desquamation	No change	Periungal membranous desquamation	No change	Swelling of the hands and feet; dry gangrene	Gangrene of the hands and feet (rare)	Distal gangrene
Exanthem	Erythematous, polymorphous	Erythematous, polymorphous; iris lesions, bullae	Finely papular erythroderma; Pastia's lines; circumoral pallor	Finely papular erythroderma; Pastia's lines	Erythroderma	Erythematous maculopapular petechial or purpuric	Petechiae, purpura
Cervical lymph nodes	Nonpurulent swelling; unilateral (frequent)	No change	Nonpurulent or purulent swelling (frequent)	Nonpurulent or purulent swelling (occasional)	No change	Nonpurulent swelling (infrequent)	No change
Other	Meatitis; diarrhea; arthralgia and arthritis; meningitis; rhinorrhea (uncommon); ECG changes	Malaise; rhinorrhea; arthralgia; recurrent episodes	Malaise; vomiting		Headache; confusion; hypotension; icteric hepatitis; diarrhea; coagulopathy; renal injury	Headache; myalgia; abdominal pain; icteric hepatitis; meningitis	Abrupt onset; meningitis, DIC

Association of TSS with S. aureus infection. This association is based on 3 observations:

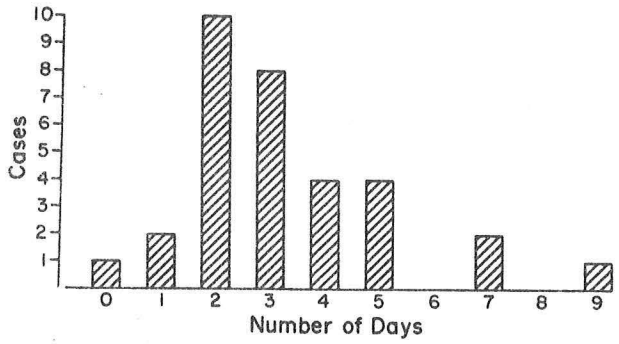
(1) A very high percentage of patients with TSS have had positive cultures of S. aureus from sites such as wounds, bone, blood, and vagina. In a CDC matched-control study, the frequency of S. aureus carriage in the vagina of menstruating women with TSS was 96%, whereas only 10% of menstruating women that did not have TSS had S. aureus carriage. Moreover, almost all men and non-menstruating women with TSS have had positive wound, blood, or vaginal cultures for S. aureus (39/43 of those with cultures performed in one study).

(2) Recurrences of TSS have occurred less often in women that were treated with antistaphylococcal antibiotics during the first attack (13).

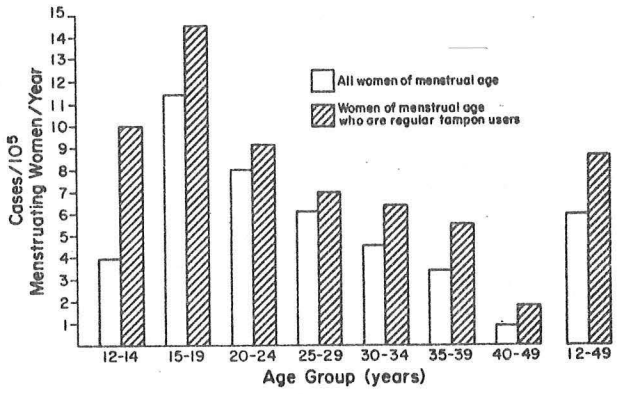
(3) S. aureus isolates from patients with TSS have produced similar exotoxins; isolates from control patients have produced these exotoxins less frequently (25,26).

On the other hand, it should be noted that S. aureus isolates from TSS patients have fallen into several phage groups and antimicrobial sensitivity testing patterns, suggesting that these characteristics are not important for disease occurrence or useful as epidemiological markers (19).

Occurrence in menstruating women: association with tampon use. The epidemic curve of TSS cases reported to CDC demonstrated an impressive peak in mid-1980. Several investigations found that almost all of these cases were in women. Their ages ranged from 12 to 49 years; almost without exception, the onset of illness occurred during menstruation. The incidence of TSS in women of menstrual age in Wisconsin was 6/100,000/year (13). Less than 2 percent of the cases in menstruating women were in non-whites or Hispanics (18). The mean duration from onset of the menstrual period to onset of illness was approximately 3.8 days (13,19).



Days from Onset of Menstrual Bleeding to Onset of Toxic-Shock Syndrome among Women in Wisconsin.
All women depicted were menstruating at the time of onset. Two women with onsets within 48 hours of termination of menses and one woman with onset during menses are not depicted.



Minimum Crude Incidence of Toxic-Shock Syndrome by Age Group in Wisconsin.
Rates for all women of menstrual age and rates adjusted for regular tampon usage are expressed per 100,000 menstruating women per year.

Figs. 3 & 4, from reference 13

Case-control studies by CDC, the Utah State Health Department, and the Tri-state TSS Study (Minnesota, Wisconsin, Iowa) found that tampon use was a significant risk factor. Other factors (contraceptive use, sexual practices, duration or quantity of menstrual flow, frequency of tampon change, use of deodorized tampons, etc.) were not implicated as risk factors in these studies. Cultures of over 500 tampons failed to show intrinsic contamination with S. aureus (11). (Actually, this does not entirely exclude the intrinsic contamination hypothesis, since examination of a much larger sample would be necessary to rule out a contamination rate of 6/100,000).

The attribution of increased risk of TSS to users of Rely tampons has provoked considerable controversy.

The following observations have been made:

(1) users of Rely tampons had a greater risk of developing TSS than the users of other tampons. This conclusion derived from a CDC matched case-control study in which patients with TSS were matched with two controls (friends of the cases) and questioned about their use of tampons during the menstrual period closest to the onset of TSS in the patient. 71% of the cases and 26% of the controls used only Rely tampons. This difference was highly significant; a difference of this magnitude was not found for the other tampons on the market (12). A case-control study by the Tri-State TSS study reached a similar conclusion (17).

Distribution of tampon brands among toxic-shock syndrome cases and controls using only one tampon brand

Tampon brand	Cases (N=42)	Controls (N=114)
Rely	71%	26%
Playtex	19%	25%
Tampax	5%	25%
Kotex	2%	12%
OB	2%	11%

Table 3, from reference 12

This conclusion was also reached from the results of case-control study in Utah. Here the controls were selected from women who lived in the same neighborhood as each case. All 29 of the TSS patients and 70 of 91 controls (77%) used tampons during the month of the TSS patient's illness. Of the 25 TSS patients and 60 controls who used one brand of tampon exlusively during their menstrual period, 60% of the cases and 23% of the controls used Rely tampons.

(2) Withdrawal of Rely tampons from the market in September, 1980, was followed by a dramatic decrease in the number of TSS cases reported to CDC. A similar epidemic curve was found in Utah.

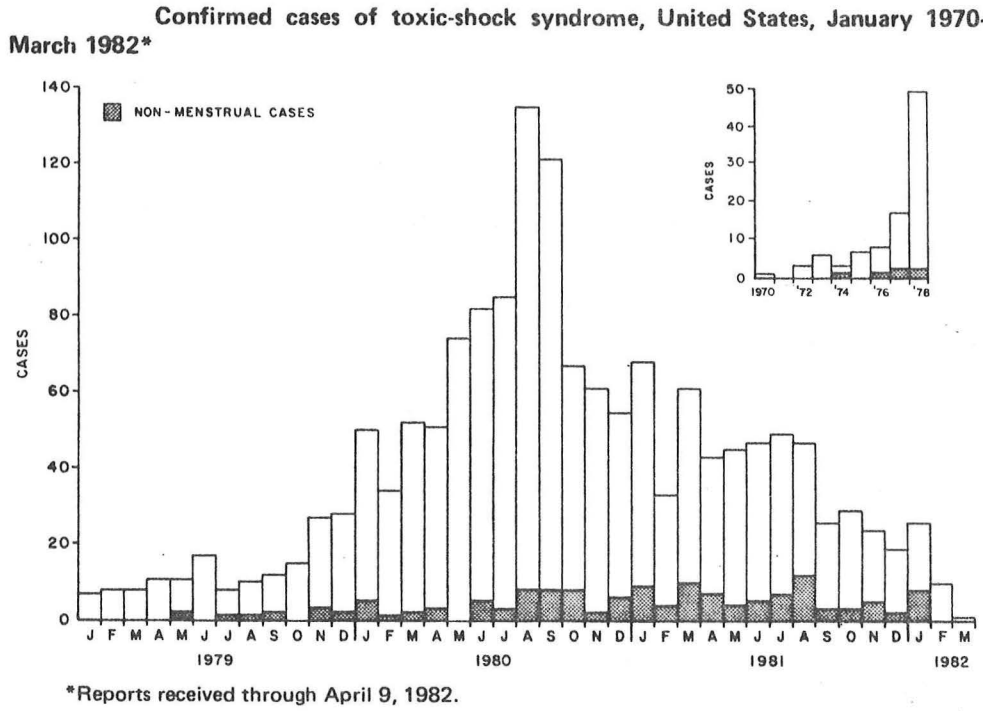


Fig. 5, from reference 27

(3) In one CDC study, 43% of Rely users had vaginal colonization with S. aureus, compared with only 7-10% of users of other brands (11).

(4) In preliminary CDC studies, S. aureus was found to persist longer on artificially contaminated Rely tampons than on the other tampons tested (11).

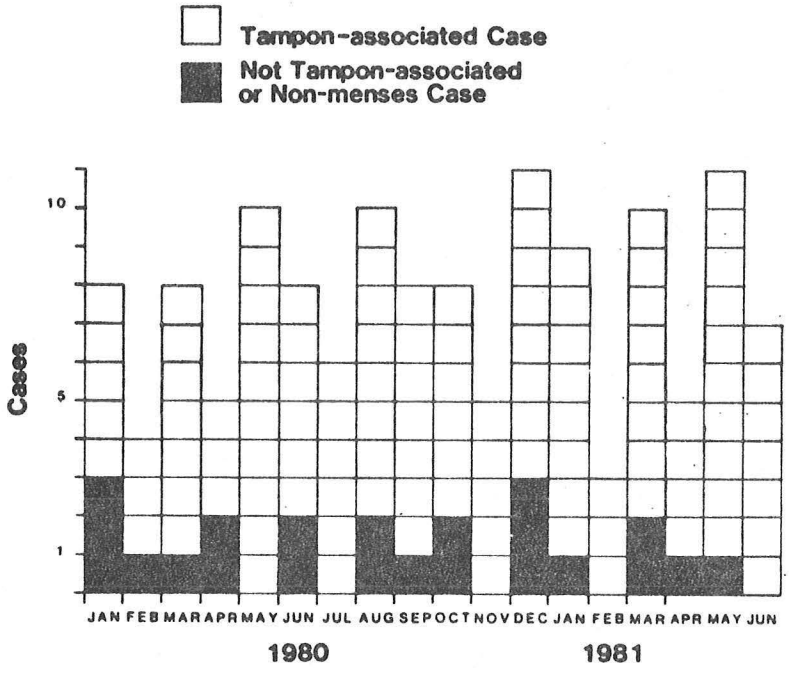
A somewhat different view has been championed by members of the Tri-State study group (14,15,17). They argue that

(1) When compared with non-use of tampons, an increased risk of TSS is associated with the use of all tampon brands (with the possible exception of Tampax and o.b.).

(2) The highest risk (odds ratio) is found for use of Rely, yet when tampon brands are considered with respect to their absorbancy, similarly high odds ratios are found for other high-absorbancy tampons, and lower odds ratios were found for low absorbancy tampons. (Interestingly, the risk of TSS was actually greater with Rely-Regular (fluid capacity of 13.2 g) than with Rely-Super (fluid capacity of 18.5), in apparent contradiction of this hypothesis).

Microulcerations of the vaginal mucosa have been noted more frequently in users of high absorbancy tampons than in users of low absorbancy tampons (16). The "absorbancy" hypothesis suggests that these microulcerations may enhance absorption of the toxin.

(3) The removal of Rely tampons from the market had no apparent effect upon the incidence of TSS in Minnesota, a state in which both active and passive surveillance for TSS cases was carried out.



Cases of toxic-shock syndrome in Minnesota by status with respect to menses and tampon use and by date of onset, January 1980–June 1981.

Fig. 6, from reference 17

The Tri-State group demonstrated an effect of publicity upon the passive reporting of TSS in Wisconsin and suggested that the peak incidence observed in the CDC data may result from the heightened publicity given to TSS in the fall of 1980. The subsequent decrease in cases might thus be related to a decrease in reporting of the disease, or even to a general decrease in tampon use, and not specifically to the withdrawal of Rely.

In summary,

(1) Many tampon brands and styles have been associated with the development of TSS.

(2) It seems likely that Rely tampons were associated with a greater risk of TSS than were other tampons in use at the time.

(3) The importance of factors such as tampon composition and absorbancy is uncertain.

(4) Tampons probably contribute to the pathogenesis of TSS by providing a favorable environment for S. aureus to grow or by facilitating the production and/or penetration of the presumed toxin.

Prevention of Menses-associated TSS:

The CDC workers have suggested that women should avoid using tampons continuously throughout menstruation. The Tri-State data did not reveal that women who used tampons continuously had an increased risk of TSS, however; and the Tri-State Study group emphasizes that low-absorbancy tampons have a low risk of TSS and should be used whenever it is not possible to avoid using tampons at all. The manufacturers' determinations of the absorbancy of various tampon brands are given in the following table:

Absorbency, tampon brand style	Mean fluid capacity (g)
Group 1	19.11
Playtex Super Plus (deodorant/non-deodorant)	20.53
o.b. Super Plus	19.55
Tampax Super Plus	19.23
Rely Super	18.50
Kotex Super (Security/Stick)	18.45
Playtex Super (deodorant/nondeodorant)	18.40
Group 2	16.09
o.b. Super	16.63
Playtex Regular (deodorant/nondeodorant)	15.55
Group 3	12.91
Kotex Regular (Security/Stick)	13.28
Rely Regular	13.23
o.b. Regular	12.98
Tampax Super	12.15
Group 4	10.30
Tampax Slender Regular	10.30

Table 4, from reference 17

Other recommendations include:

(1) Women who have had TSS should not use tampons at all.

(2) Women who have given birth should not use tampons for 6 to 8 weeks after delivery (a recommendation of an Institute of Medicine panel (28)).

Occurrence in men and in non-menstruating women. In contrast to the cases in menstruating women, which showed a striking peak incidence in August-September, 1980, cases of TSS in men and non-menstruating women have occurred with approximately the same frequency over the past 3 years. A recent analysis of 54 cases reported to CDC revealed that TSS occurred in several defined settings (17):

(1) Post-surgical wound infections. The average incubation period from surgery to onset of TSS was only 2 days, and often there was no gross infection in the wound that was culture-positive for exotoxin-producing S. aureus.

(2) Post-partum. Most (8) cases followed vaginal delivery, while 3 occurred after Caesarean section and 1 after a septic abortion.

(3) Cutaneous or subcutaneous non-surgical lesions. This category accounted for almost 40% of the patients. Lesions included infected traumatic wounds, subcutaneous abscesses, infected insect bites, hydradenitis suppurativa, and an infected burn.

These cases may represent the "background noise" against which the epidemic occurred in menstruating women. We may also expect TSS to occur in these settings as the epidemic of menses-associated cases abates.

Staphylococcal skin diseases: role of exotoxins. Staphylococcus aureus may produce an exotoxin (called exfoliative toxin, exfoliatin, epidermolytic toxin, and other names) that has been associated with several related diseases. Together, these diseases have been called the "Staphylococcal Scalded Skin Syndrome (SSSS)." See Table 5.

—Clinical Forms of Staphylococcal Scalded Skin Syndrome

Disease	Synonyms	Culture From Intact Bullae	Age Distribution
Bullous impetigo	Pemphigus neonatorum	+	All ages
Bullous impetigo with generalization	Pemphigus neonatorum	+	Biphasic (neonates and immune-compromised adults)
Scarlatiniform rash	None	—	Neonates and young children
Generalized scalded skin syndrome	Toxic epidermal necrolysis, Ritter disease, Lyell disease	—	Neonates and young children

Table 5, from reference 20

Generalized SSSS occurs in neonates and young children. It is thought to occur when toxin-producing S. aureus infect an immunologically susceptible host. The infection is usually localized; the toxin spreads hematogenously to involve most skin surfaces, and cultures of the exfoliative lesions are negative. Bullous impetigo probably occurs when toxin-producing S. aureus infect the skin of an immune (or at least mature) host; the resulting disease remains localized to the infected area. Cultures of the bullous lesions are positive for S. aureus. The third form of SSSS, scarlatiniform rash, is probably a mild form of generalized SSSS that does not go on to exfoliate. Unlike streptococcal scarlet fever, there is no palatal enanthem or strawberry tongue, and desquamation begins within 4 days (in scarlet fever, desquamation usually begins 1-3 weeks after the fever). In both scarlatiniform SSSS and scarlet fever, the skin is usually tender and has a sandpaper texture; erythema may be increased in the skin lines (Pastia's lines).

Two exfoliatins are known (A and B). Both are proteins of M.W. 24,000 and they have similar biological properties, yet they are immunologically distinct (24). It seems likely that the genetic information coding for exfoliatin B is on a plasmid, while that for exfoliatin A is chromosomal. In both man and an animal model (the neonatal mouse), the dermatopathology is quite characteristic, showing a cleavage plane high in the epidermis. It is thought that the exfoliatin interferes with adhesion between the cells of the stratum granulosum. Clinically, the underlying skin is tender and the Nikolsky sign is positive, often in uninvolved as well as clinically involved skin. Because of the high level of the cleavage plane, fluid loss is not severe. The skin lesions usually heal without scarring (20).

It is no longer acceptible to refer to "Toxic Epidermal Necrolysis (TEN)" as part of the SSSS. Although TEN is an acute exfoliative disease, it occurs primarily in adults and is usually associated with a drug reaction or graft-versus-host reaction. The cleavage plane is deep to the epidermis, resulting in the sloughing of the entire epidermis in involved areas and the loss of much fluid. Healing is often associated with scarring or pigmentary change. TEN might be confused with generalized SSSS in children (a skin biopsy should allow quick differentiation of the two diseases) but the generalized form of SSSS has not been reported in adults (20).

—Differentiation of Toxic Epidermal Necrolysis (TEN) and Staphylococcal Scalded Skin Syndrome (SSSS)*

	TEN	SSSS
History	Drug intake; often milder episodes preceding	Variable drug intake, first episode
Family history	Noncontributory	Members of family often have impetigo or harbor staphylococci
Epidemiologic features	Case sporadic	Sometimes linked to epidemics of impetigo
Age predilection	Over 40 yrs	Under 5 yrs
Exanthemata	Generalized without clear distribution pattern	Typical distribution pattern and succession of development (face, neck, axillae, groin first)
Cutaneous tenderness	Mild to moderate	Marked
Nikolsky sign	Positive only in lesions	Positive also in apparently uninvolved skin
Mucous membranes	Severely afflicted	Uninvolved
Course	Protracted (1-3 weeks)	Brief (2-4 days)
Mortality	High (25%-50%)	Very low; high incidence spontaneous recovery
Systemic therapy	High corticosteroids, water, electrolyte and blood-volume maintenance	Penicillinase-resistant penicillins; corticosteroids alone contraindicated
Histologic features†	Necrosis of epidermis, starting in basal layer	Acantholysis; subgranular cleavage plane
Exfoliative cytologic features†	Necrotic epidermal cells, polymorphs, debris	Normal-appearing acantholytic cells

*This table contains only points where differences exist between the two diseases, and only considers the rules not the exceptions.
†Particularly useful for rapid bedside differential diagnosis.

Table 6, from reference 20

Toxic Shock Syndrome: search for a toxin. The clinical features of TSS obviously suggest that the disease is caused by a toxin, and the diffuse rash with desquamation suggested that the toxin might be related to the exfoliatins discussed above. Two laboratories have now claimed success in identifying a toxin from S. aureus strains that were isolated from patients with TSS.

Schlievert et. al. (26) found a protein exotoxin of M.W. 22,000 in all of 28 isolates from patients with TSS but only 5 (16%) of 32 control isolates. The toxin was shown to produce fever in rabbits and to augment the toxicity (lethality) of Gram-negative bacterial endotoxin. The protein had an isoelectric point of 7.2. They named the toxin "Pyrogenic exotoxin C".

Bergdoll et. al. (25) found that 61 of 65 (94%) S. aureus strains isolated from 65 patients with TSS produced an enterotoxin-like protein that they called "enterotoxin F." The toxin had an isoelectric point of 6.8 and a M.W. of 20,000. It produced emesis and diarrhea in monkeys when injected intragastrically. Antibodies to the toxin (detected by radioimmunoassay) were found more commonly in control women than in women with TSS. Interestingly, only one third of the women with TSS had an increase in titer from acute to convalescent specimens.

The toxins isolated by these two groups apparently give a line of identity in agar gel immunodiffusion. The physical-chemical differences cited above may be artifactual; direct comparisons of the two toxins are underway. Although both groups examined specimens from TSS patients and controls blindly, thus increasing the probable significance of the differences that they found between cases and controls, it should be noted that neither TSS toxin has been shown to produce a rash in experimental animals. These toxins are therefore NOT similar to the staphylococcal exfoliatins discussed above. This is not surprising, since the dermatopathology of TSS does not show the high epidemic cleavage seen with SSSS, and Nicolsky's sign is positive in SSSS but not in TSS.

TSS: why now? Good answers do not exist. It seems unlikely that Rely tampons were responsible, or that a disease of such severity could have gone unnoticed until 1978. The most interesting clue comes from recent work at the CDC: 9% of S. aureus isolates received from 1956-1964 produced Schlieverts exotoxin, compared with 40% of the isolates received from non-TSS cases in 1979 (11).

Treatment: Supportive therapy includes intravenous fluids, pressors, and antipyretics. Corticosteroids have been given to some severely ill patients. Antibiotic administration to eradicate staphylococcal infection or carriage is also indicated; high-dose (8-12 g/day) nafcillin or cephalothin are reasonable, at least during the acute stages of the illness. If blood cultures are negative and the patient is clinically convalescing, or if the illness is mild, oral cloxacillin should be adequate. Vancomycin (500 mg iv q6h) is the drug of choice for penicillin-allergic patients.

Recurrences. TSS has recurred (as many as 5 times) in women with the disease. This has happened less often when the patient has received appropriate antistaphylococcal therapy during the first course of the disease.

RESISTANCE OF S. AUREUS TO PENICILLINS

Three types of resistance of S. aureus to penicillins are recognized. First, the bacteria may make penicillinases (beta lactamases) that degrade (hydrolyze) penicillins. Methicillin and the other semi-synthetic penicillins (nafcillin, cloxacillin, etc.) are not degraded by these penicillinases and thus overcome this form of resistance. Second, the bacteria may be "intrinsically" resistant to penicillins; the mechanism for this form of resistance is not understood. This form of resistance is present in the so-called "methicillin-resistant S. aureus" (MRSA). Finally, S. aureus may be "tolerant" to the killing action of penicillins. This is usually defined as a large (16-fold or greater) discrepancy between the minimal inhibitory and minimal bactericidal concentrations of the drug.

Table 7. Contrasting features of different forms of penicillin resistance.

CHARACTERISTIC	TYPE OF PENICILLIN RESISTANCE		
	PENICILLINASE	INTRINSIC	TOLERANCE
M.I.C.	Very high	High	Low
M.B.C.	Very high	High	High
Limited to beta-lactam antibiotics	Yes	Yes	No
Approximate phenotypic expression	99.9%	10^{-5}	10^{-2}
Clinical importance	Yes	Yes	Probably
Occurrence	Widespread	Focal Outbreaks	Variable

Adapted from Sabath, 1977. (42)

(A fourth type of β-lactam resistance in S. aureus has been recently reported by Lacey (Lancet 1:1049, 1981). This resistance is specific for cephalosporins that contain a substituted amino group and a six-membered carboxylic ring at the 7-position (cephalexin, cefaclor, cephradine). Since the presence of this side chain is required for absorption from the GI tract, the implications of this form of resistance may be important.)

HOW DO PENICILLINS KILL S. AUREUS?

Penicillin G inhibits the cross-linking step in peptidoglycan synthesis. For many years it was thought that this inhibition created weakened areas of the cell wall that led to osmotic disruption and death of the cells.

The mechanism now seems to be much more complicated (29,30). It appears that this inhibitory action of penicillin will stop bacterial growth but that

it is not sufficient, in itself, to kill bacterial cells. In order for cell death to occur, there must be a further process of autolysis. This process is carried out by bacterial enzymes that are probably activated when cell wall synthesis stops. It appears that bacterial cells that are deficient in autolytic activity (whether from enzyme deficiency or from inhibitors) are resistant to killing by penicillins. In other words, the concentration of penicillin that is required to kill them (MBC) is much greater than the concentration that inhibits their growth (MIC). The strains are thus said to be penicillin tolerant. In pneumococci, tolerance is probably mediated by the release of lipoteichoic acids, cell wall molecules that inhibit autolysin activity. A similar mechanism seems likely in staphylococci.

ANTIBIOTIC TOLERANCE IN S. AUREUS

Interest in the phenomenon of tolerance in staphylococci was stimulated by a report by Sabath et. al. in 1977 (42). This report described 7 isolates that were tolerant to nafcillin. The isolates were from patients with serious staphylococcal infections, yet it was not clear from the paper that the laboratory phenomenon of tolerance was clinically significant. Subsequently, two other reports suggested that tolerant staphylococci may be more difficult to treat than non-tolerant isolates (39,41). Up to 46% of the S. aureus isolates examined in these studies were tolerant to methicillin or nafcillin..

Antibiotic Tolerance: in Vitro Studies

Further study of tolerance has uncovered several technical problems:

(1) Definitions of tolerance differ. The bactericidal test is usually read at 24 hours, and the MBC is that concentration of drug at which 99.9% of the inoculum is killed. Some workers have defined tolerant strains as having MBC/MIC > 8; others have used a minimal ratio of 16 or 32. Interestingly, more cells are killed with further incubation, so that by 48 hours the MBC falls and the MBC/MIC ratio usually decreases to levels found with sensitive strains (MBC/MIC $\leq$ 2). So many tolerant strains are simply killed more slowly (42).

(2) Demonstration of tolerance is medium-dependent (33-36). Strains have been shown to be tolerant when tested in certain media but not in others. Mueller-Hinton broth is probably the most widely used medium. Some workers have found that stationary-phase organisms are more likely to exhibit tolerance than log-phase ones (34).

(3) When carefully examined, most cultures will contain some tolerant organisms. In one study, testing of all of the colonies grown from blood culture bottles revealed that 0.5 - 50% of the colonies were tolerant (31). Thus the number of tolerant strains that would be detected by studying only 1 or 2 colonies from a given culture could be quite misleading.

Other in vitro studies have shown that cross-tolerance may occur (ie., methicillin-tolerant strains may be tolerant to other antibiotics, such as vancomycin and cephalothin, that act by inhibiting cell wall synthesis) (34,42). There is suggestive evidence that tolerance may be transmitted from cell to cell within a culture by a bacteriophage (32).

Antibiotic tolerance: animal models

Two groups of investigators have evaluated the significance of antibiotic tolerance in animal models. In both studies, animals were infected with tolerant and non-tolerant S. aureus and the response of the animals to treatment with antibiotics was monitored. Antibiotic tolerance was found to have little influence on the prophylaxis or therapy of S. aureus endocarditis (rabbit model) (37) or on the therapy of pyelonephritis (rat model) (38) with methicillin.

Antibiotic tolerance: clinical significance

The clinical significance of antibiotic tolerance in S. aureus is uncertain. Several reports have described patients with staphylococcal endocarditis due to tolerant strains who did not respond to methicillin alone but who responded when gentamicin or rifampin was added (46,47). Denny studied 20 patients with serious staphylococcal infections; 10 of the patients had infections that were due to methicillin-tolerant strains. These patients had prolonged bacteremia and higher mortality, suggesting that tolerance may influence the course of patients with staphylococcal infections (39).

Rajashekariah et al studied 50 patients with endocarditis and 54 patients with bacteremia due to S. aureus. In 32 of the patients with endocarditis and 35 of those with bacteremia, the strains were classified as tolerant. Patients with endocarditis who had a tolerant strain were more likely to have prolonged fever, more complications, a greater number of admissions to the intensive care unit, and a higher mortality. On the other hand, the tolerance or non-tolerance of the strain did not influence in the response to therapy in bacteremic patients without endocarditis. These authors concluded that antibiotic tolerance was clinically important only in patients with endocarditis (41).

How important is tolerance? It appears that tolerant staphylococci are killed more slowly than sensitive staphylococci in vitro. This may correlate with a slower clinical response, although none of the published clinical studies has been prospective, and none has correlated the in vitro sensitivity data with blood levels of drug in individual patients. It seems likely that if the peak drug concentration exceeds the MBC by a sufficient margin, organisms that have a high MBC/MIC should still be killed. At least in Dallas, tolerance appears to be an infrequent clinical problem; attempts to detect tolerant S. aureus have not been successful in two different laboratories.

S. aureus endocarditis: use of combinations of antibiotics

Combination therapy for infections caused by a single organism can potentially be advantageous for 3 reasons:

(1) The combination may be synergistic (e.g., penicillin plus streptomycin for enterococcal endocarditis)

(2) The combination may be additive and may enable more effective agents to be administered with diminished toxicity (e.g., amphotericin B plus 5-fluorocytosine for cryptococcal meningitis

(3) The combination may diminish or prevent the development of resistance (e.g., INH plus ethambutol for tuberculosis).

The addition of gentamicin to nafcillin produces an enhanced (synergistic) bactericidal effect toward S. aureus in vitro and in experimental staphylococcal endocarditis in rabbits (48,52). A similar augmentation of bactericidal activity has been observed in the serum of selected patients with S. aureus bacteremia (48). In a large collaborative trial of the treatment of addicts with S. aureus endocarditis, the combination of nafcillin with gentamicin led to more rapid clearing of bacteremia in patients with infection on the right side of the heart than did nafcillin alone (2.5 vs 3.5d) (52). There was no difference in the outcome in the 2 groups, however, probably because the prognosis of this form of endocarditis is so good (4% mortality). Similar results were found in a smaller study of addicts with S. aureus endocarditis (43). It is not possible to extrapolate from this experience to the non-addict population, in whom S. aureus endocarditis is generally more severe, and an ongoing cooperative trial is designed to address this problem.

At present, we use high-dose (8-12 gm/d) nafcillin or methicillin alone for 4 to 6 weeks as therapy for the usual patient with S. aureus endocarditis, monitoring the efficacy of the regimen with serumcidal tests. The shorter course is usually adequate in the addict with right-sided endocarditis. Six weeks of therapy are recommended for patients with a complicated course (including prolonged fever) and for patients with prosthetic valve infection. In the latter groups, the addition of gentamicin may result in more rapid clearance of the bacteremia, but there is no evidence that this alters the course of the disease. Most authorities would use nafcillin-gentamicin for patients with prosthetic valve endocarditis due to S. aureus, hoping for a beneficial effect.

Rifampin is the most potent antistaphylococcal agent known yet staphylococci rapidly develop resistance to rifampin in vitro and in vivo. Rifampin should only be used in combination with another agent (usually nafcillin or vancomycin) in order to prevent the emergence of rifampin resistance (50). In vitro testing of the effects of rifampin in combination with other antibiotics have given conflicting results (53-55); it is uncertain that these in vitro tests have great relevance to the clinical situation, where rifampin is avidly taken up by phagocytic cells and may achieve very high intracellular concentrations (49). There is little experience that indicates the appropriate dose of rifampin for patients who receive combination therapy--one group used 18 mg/kg/day orally in three divided doses (45).

The choice of therapy for patients whose S. aureus isolates are shown to be tolerant to methicillin (nafcillin) in vitro poses a difficult problem. There are anecdotal reports that the addition of gentamicin or rifampin to nafcillin (46) or vancomycin (45) led to dramatic improvement in patients whose bacteremic S. aureus strains were tolerant to the original drug. On the other hand, there are no large, prospective studies that show a benefit of combined therapy as opposed to single drug therapy for tolerant strains. It would seem reasonable at present to base the therapeutic decision on the results of serumcidal tests: if a peak serumcidal titer of 1:8 can be achieved with nafcillin alone, do not add another drug. If low serumcidal

levels are found with high-dose (12 g/d) nafcillin, try vancomycin. If vancomycin in optimal doses does not achieve serumcidal levels of 1:8 or greater, add rifampin or gentamicin and repeat the serumcidal test.

RESISTANCE OF S. AUREUS TO METHICILLIN ("METHICILLIN-RESISTANT S. AUREUS")

In contrast to strains that are tolerant to penicillins, the growth of MRSA is not inhibited by methicillin or its relatives (nafcillin, oxacillin). Many of the strains are also not inhibited by cephalosporins (25). The mechanism of methicillin resistance is not known; the responsible genes appear to be on the bacterial chromosome rather than on a plasmid (58). Two groups have reported that the penicillin-binding proteins in MRSA have decreased affinity for methicillin (56,57).

Detection

Testing for methicillin resistance should be done at 35°C, with incubation for 24 hours; growth at a lower temperature (30°C) enhances methicillin resistance. The inhibition zone should be examined for colonies of resistant bacteria ("heteroresistance"). MRSA will grow in the presence of 16 ug/ml methicillin. Certain of the newer automated antibiotic sensitivity testing devices (for example, the MS-2) will not detect methicillin-resistant S. aureus and should not be used for this purpose (59).

Clinical disease

MRSA may cause significant disease; patients with bacteremia, osteomyelitis, endocarditis, and other major infections have been reported frequently (61,62). Epidemic strains appear to be fully virulent (63).

Epidemiology

Although MRSA were isolated commonly in European hospitals in the 1960's, the emergence of MRSA as a problem in hospitals in the United States occurred during the 1970's. The following features of the epidemic in the U.S. have been described:

(1) MRSA have usually been reported from large, medical school-affiliated, tertiary care centers. In some hospitals, MRSA have accounted for 30-50% of all postoperative staphylococcal wound infections. Introduction of MRSA into hospitals from the community has also been described, particularly by intravenous drug abusers. In a recent outbreak in Detroit, drug abusers whose isolates were methicillin resistant had more often taken cephalosporins (Keflex) than drug abusers with methicillin sensitive S. aureus isolates (72). To date, only 1 instance of community-acquired MRSA infection has been noted at Parkland Memorial Hospital - a 28 year-old i.v. drug abuser with endocarditis due to MRSA, admitted to the hospital in January, 1982.

(2) Rarely, MRSA have been isolated "de novo" from patients undergoing long-term antibiotic therapy. This happened in a patient hospitalized at Parkland: a 45 year old woman with mixed connective tissue disease had a MRSA isolated from her maxillary sinus while she was receiving intensive antibiotic therapy for odontogenic sinusitis.

(3) Following introduction of MRSA into a hospital, usually by a patient that is transferred from another hospital or a nursing home (71), the strains have spread principally on burn and surgical services. There is evidence that burn units serve as a focus of MRSA, allowing transmission (via personnel) to patients without burns (65,67). Colonized burn patients also tend to remain colonized longer than patients without burns (64).

(4) Patients who have developed MRSA infection in the hospital have had a greater duration of hospitalization and received a larger number of antibiotics than patients with methicillin-sensitive nosocomial staphylococcal infections (64,66). Widespread use of gentamicin ointment has been associated with outbreaks of infection due to gentamicin and methicillin resistant S. aureus (68).

(5) Transmission from patient to patient on the hands of personnel is probably the major route of spread (71). Nasal colonization has usually been found in less than 5% of the hospital personnel cultured; certain nasal carriers appear to have been important in the propagation of outbreaks, however. Environmental cultures (objects in patient's rooms, air sampling, etc.) have almost always been negative (60,61,67,71).

(Approximately 30-50% of normal adults harbor S. aureus in the anterior nasal vestibule [76]; this site is thought to be the major reservoir of S. aureus in normal people. Like the axilla and perineum [two other sites of frequent S. aureus carriage], the anterior nasal vestibule has apocrine sweat glands, suggesting that these glands may be the focus of staphylococcal multiplication. In hospitalized patients, nasal carriage increases - more rapidly in those who receive antibiotics [73]. Nasal colonization has also been associated with an increased risk of staphylococcal disease - as in postoperative wound sepsis [76]. In most of the recent studies of S. aureus nasal carriage in hospital personnel, the frequency of carriage of methicillin sensitive S. aureus has greatly exceeded that of MRSA [Table 8]. The reason for this finding is uncertain.)

NASAL CARRIAGE OF S. AUREUS BY HOSPITAL PERSONNEL

Outbreak Location	Number of Personnel cultured	Percent with positive nasal cultures for S. aureus Methicillin-sensitive	Methicillin-resistant
Seattle, 1969 (O'Toole)	210	24	0
Hartford, 1974 (Klimek)	202	17.8	2.5
Chicago, 1979 (Grieble)	94	33.0	0
Minneapolis, 1977 (Crossley)	74	--	8.1
Houston, 1978 (Boyce)	220	--	6.3
Boston, 1979 (Craven)	92	14.1	3.2
Dallas (Luby)			
June-Nov., 1981	272		2.6
Jan.-June, 1982	175		9.1

Table 8

Haley has emphasized the importance of the housestaff-patient transfer circuit as a factor in the spread of MRSA within a community (74). Interhospital spread occurs via the transfer of infected patients and housestaff from hospital to hospital or to and from nursing homes. The recent spread of MRSA from Parkland to the Dallas V.A. Hospital illustrates this point: the probable vector was a burn patient with a colonized wound.

Prevention.

Preventing spread of MRSA requires intensive efforts to

- identify patients with MRSA (disease or colonization) with appropriate culture techniques. Patients who are contacts of patients with known MRSA should be screened with cultures of the nasal vestibule, wounds, and catheter drainage. Sputum should be cultured if there is an endotracheal tube.

- Isolate MRSA-infected patients using "barrier" techniques**; these should be most stringent when MRSA are found in decubitus ulcers, areas of dermatitis, or other cutaneous lesions

**One or two-bed room; no roommate with drainage tubes or Foley. Careful handwashing on entering and leaving room. Wear gloves for all patient or secretion contact. Discard all secretions in plastic bags. Handle linen separately from other patients (79).

- identify colonized hospital personnel and institute measures to eradicate colonization; culture-positive employees with dermatitis and those associated epidemiologically with spread of infection should be assigned to nonclinical duties while treatment is instituted to eradicate their colonization. Nasal carriers have been shown to be the major "spreaders" of MRSA in some outbreaks (64), so identification of these personnel cannot be neglected.

- discharge infected or colonized patients as soon as is medically feasible; the risk of spread to healthy family members is probably small. The medical record should be labeled prominently so that appropriate culturing and isolation can be performed if the person is readmitted. If the patient is transferred to another institution, notification of the presence of MRSA should be done, even if the patient is thought to be "clean."

Transfer of culture-positive patients to nursing homes represents a special problem. The risk of spread of MRSA to other patients in nursing homes is unknown, and the benefit of isolating patients within nursing homes is uncertain. The nursing home personnel should be made aware of the potential problem. It would seem reasonable not to transfer patients with infected skin lesions to nursing homes, since these lesions seem to have the greatest potential for spreading infection.

Efforts to eradicate MRSA from the inanimate environment (i.e., hospital rooms, floors) have an uncertain role in the control of epidemics. As noted above, environmental contamination with MRSA has been noted infrequently. It is generally accepted that rooms should be disinfected with activated glutaraldehyde (Staphene, Cidex) before new patients occupy them, however.

MRSA have seldom been totally eradicated from hospitals in the U.S. (13 of 104 hospitals surveyed) (77), in spite of measures such as those outlined above. Successful eradication has been reported in newborn nurseries, possibly because of rigid patient-staff cohorting that was possible in these units (78). In many institutions with a MRSA problem, moreover, preventive measures have led to impressive reductions in the frequency of MRSA colonization and disease (60,61).

Therapy of MRSA.

(1) Eradication of nasal colonization. Application of 0.1% bacitracin ointment to the anterior nares two or three times daily, combined with Phisohex (0.3% hexachlorophene) cleansing of the face, axillae, and perineum, usually suffices to eradicate MRSA. Alternative local antibiotic treatments include gentamicin and neomycin ointments. Occasionally it is necessary to remove colonized personnel from the hospital environment before their colonization can be eradicated (81).

(2) Treatment of disease. The only reliable, available antibiotic that is effective therapy for MRSA is vancomycin. Cephalosporins may appear to be efficacious in vitro but have usually failed in clinical practice (80,83). For less serious disease (such as wound,skin, or urinary tract infections) the observed sensitivities of the isolate to oral agents such as erythromycin and clindamycin may possibly be useful in guiding therapy; there is little published information on this point, however (82).

CHOICE OF ANTIBIOTICS FOR SERIOUS INFECTIONS DUE TO S. AUREUS

Semisynthetic penicillins remain the drugs of choice for serious S. aureus infections and should be used for empiric therapy when possible. Indications for adding another drug or substituting vancomycin are outlined above.

Methicillin vs. nafcillin.

For many years after its introduction in 1960, methicillin remained the mainstay of therapy for serious S. aureus infections. Recently, because of the occurrence of nephritis in a high percentage of persons who receive high-dose methicillin for prolonged periods (33% of those who were treated for 11 days or more in one series (90)), alternative semi-synthetic penicillins have replaced methicillin in most hospital formularies. Nafcillin appears to have a much lower risk of interstitial nephritis (85,86). Its major side effect, neutropenia, occurs rather uncommonly and is usually readily reversible when the drug is stopped. In one retrospective study, patients who received methicillin were much more likely to have experienced an adverse reaction (16 of 41 treated) than those who received nafcillin (4 of 29 treated); these reactions included fever, rash, neutropenia, and urinary toxicity. The risk of an adverse reaction was dose-related and time-dependent; on average, reactions appeared on the 21st day of therapy (86).

Both methicillin and nafcillin have a serum half-life of 0.5 hours in patients with normal renal function. Methicillin is excreted almost entirely by the kidneys while nafcillin is also cleared by the liver. Liver disease may therefore increase the serum $t_{1/2}$ of nafcillin. Nafcillin is more protein-bound than methicillin (87% vs 35%).

Nafcillin interferes with the commonly used tests for urinary protein (TCA, SSA) and has been associated with "massive pseudoproteinuria" (83,88). The dipstick for albumin is not influenced by the drug and thus will not reflect the same degree of proteinuria. Nafcillin has also been associated with hypokalemia (when used in extremely large doses)(84,89) and with cutaneous necrosis as a result of extravasation at the site of intravenous injection (91).

At the present time, the charge to the Parkland patient for nafcillin and methicillin is $10.91 and $8.06 per gram, respectively.

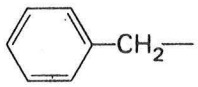
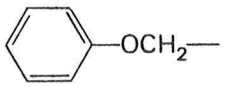
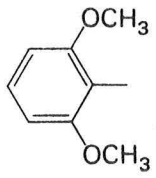
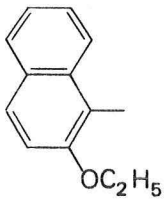
Name	Side chain	Stability in acid	Spectrum of action	Sensitivity to penicillinase
Penicillin G		Poor	Narrow	Sensitive
Phenoxymethyl penicillin (Pen V)		Good	Narrow	Sensitive
Methicillin		Poor (not given orally)	Narrow	Resistant
Nafcillin		Poor	Narrow	Resistant

Figure 7, from reference 100

Vancomycin.

This highly effective antistaphylococcal agent is produced by a microorganism (Streptomyces orientalis) that was found in a soil sample from a jungle trail in Borneo. Studies in the early 1950's established the potent antibacterial effect and the remarkable stability of the drug. Clinical usage was limited, however, by (1) animal tests indicating that the drug, as then purified, was otoxic and nephrotoxic and (2) the appearance of methicillin and cephalothin as effective antistaphylococcal agents with a better safety record. The rejuvenation of interest in vancomycin in recent years has come about because of its novel efficacy in a number of clinical situations and the availability of highly purified preparations that lack the toxicity of the earlier drug.

Structure. Vancomycin is a glycopeptide antibiotic that has a complicated structure.

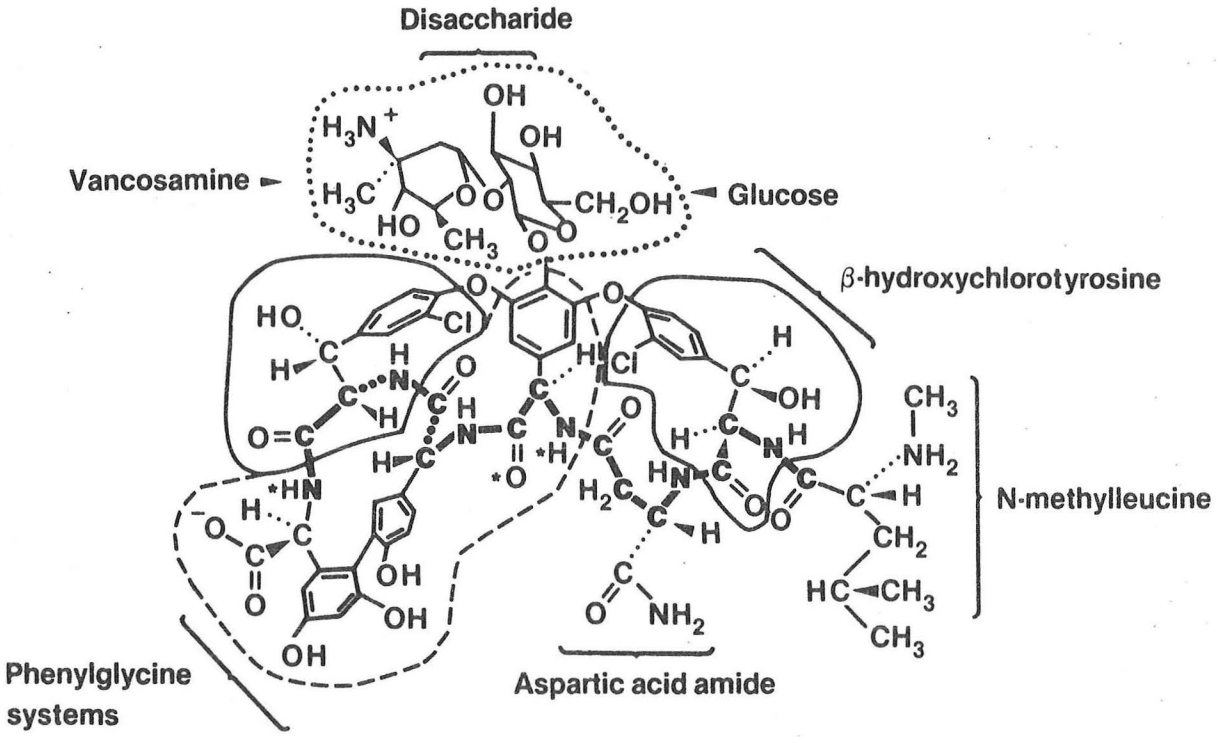
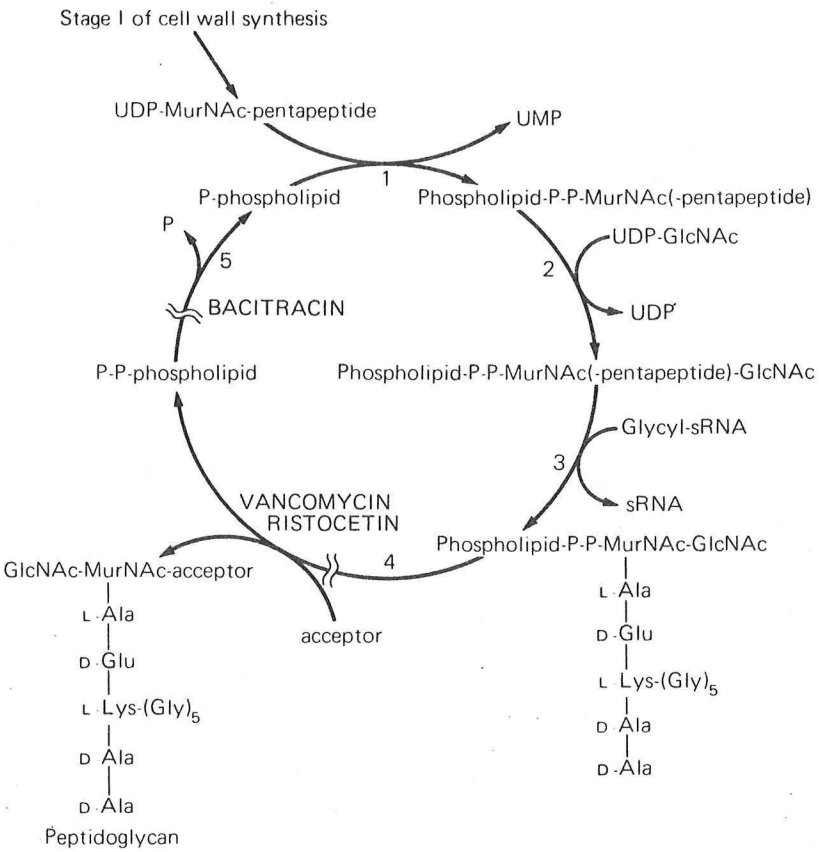


Figure 8 from reference 99

Mechanism of action. Although several modes of antimicrobial action have been ascribed to vancomycin, it seems likely that its effect on cell wall synthesis is most important. As shown in Figure 9, vancomycin and ristocetin (another glycopeptide antibiotic, used only for research) inhibit the biosynthetic cycle by which peptidoglycan is assembled. It is thought that vancomycin binds tightly to the D-ala-D-ala at the end of the pentapeptide chain. Vancomycin is a bactericidal drug.



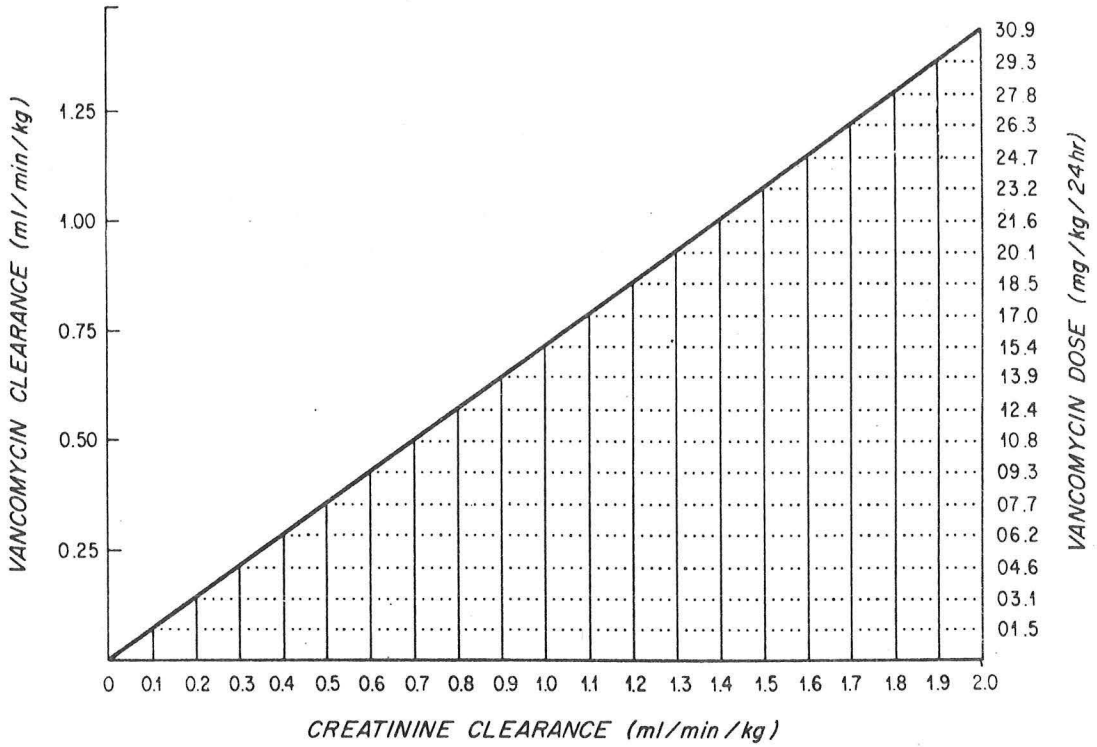
The second stage of cell wall synthesis in *S. aureus*. An ATP-requiring amidation of glutamic acid that occurs between reaction 2 and reaction 3 has been omitted. The sites of inhibition by bacitracin, vancomycin, and ristocetin are indicated by the break marks.

Figure 9 from reference 100

Antimicrobial spectrum. Vancomycin is effective in vitro against most aerobic Gram-positive cocci, including S. aureus, S. epidermidis, and streptococci including enterococci. It is also effective against Clostridia and some strains of Actinomyces and lactobacillus. Sensitive isolates generally have a MIC of <3µg/ml (104). No vancomycin-resistant clinical isolates of S. aureus have been reported.

Pharmacokinetics. Absorption of vancomycin from the intestinal tract is negligible. After intravenous administration, the drug is excreted by glomerular filtration; there is virtually total recovery in the urine (96,101).

The standard intravenous dose of vancomycin is 7.5 mg/kg every 6h or 15 mg/kg every 12 h.



Dosage nomogram for administration of vancomycin to patients with impaired renal function. The nomogram is not valid for functionally anephric patients undergoing dialysis; for such patients the dose is 1.9 mg/kg every 24 hr.

Figure 10 from reference 96

A dosage nomogram has been derived for patients with impaired renal function; this is intended to provide steady-state levels of 15 µg/ml in serum (96). An alternative method, intended to produce a serum concentration of 20 µg/ml, is the formula of Nielsen et al. (98):

maintenance dose = (C_{Cr} x 15)mg per day + 150 mg per day.

Toxicity. When infused rapidly, vancomycin has been associated with

(1) hypotension (97)

(2) the "red neck syndrome." This is an erythema multiform-like reaction that is associated with intense pruritis. The rash involves only the face, neck, upper trunk, back and upper arms, with sparing of the rest of the body (83).

Infusing vancomycin over a period of 30 minutes or more avoids these reactions.

Ototoxicity was noted in early studies at serum levels greater than 50 µg/ml, and recently a patient was reported who developed ototoxicity while receiving vancomycin and rifampin, with vancomycin serum levels of less than

50 µg/ml (103). Nephrotoxicity was also reported during the early stages of vancomycin testing but seems to be unusual now. Impurities in the original preparations may have caused the early reactions.

Vancomycin blood levels may be obtained through Dr. Roger Bawdon (688-3577).

Indications for vancomycin.

A. In patients without penicillin allergy

1. Methicillin tolerant or resistant strains of S. aureus
2. Antibiotic-associated (pseudomembranous) colitis -- oral therapy with 125 mg or 500 mg QID (92)
3. S. epidermidis strains that are resistant to methicillin and cephalosporins
4. Once-weekly therapy for sensitive organisms in dialysis patients (15 mg/kg every 7 to 10 days)
5. Diphtheroid endocarditis
6. (Possibly) meningitis caused by selected organisms (94)
7. D-lactic acidosis in patients with short bowel (102)

B. In patients with penicillin allergy. The above plus

1. Therapy of serious infections caused by sensitive strains of bacteria.
   Note: endocarditis caused by S. fecalis or S. faecium (enterococci) should be treated with the combination of vancomycin and an aminoglycoside (usually gentamicin).

2. Endocarditis prophylaxis in patients with abnormal heart valves
   Regimen:

   a. Dental procedures (Streptococcus one-half hour before procedure.

      . Vancomycin 0.5 gm IV (single administration)

   b. GU/GI/Obstetrical procedures (enterococcus)

      . Vancomycin 0.5 gm IV plus gentamicin 80 mg IM q 8h x 3 doses

Cost. At the present time, vancomycin costs $66 per gram (charge to Parkland patients).

TOXIC SHOCK SYNDROME

Clinical Features

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