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CONTINUING MEDICAL EDUCATION

Toxin-mediated streptococcal and staphylococcal disease

Steven M. Manders, MD *Camden, New Jersey*

After several decades of seemingly decreasing virulence, streptococcal and staphylococcal infections have reemerged as a major source of morbidity and mortality. Within the past 2 decades, not only have well-established diseases such as rheumatic fever begun to reappear, but also many new entities, such as toxic shock syndrome, streptococcal toxic shock syndrome, recurrent toxin-mediated perineal erythema, and recalcitrant erythematous desquamating disorder have been described. Central to the renewed importance of these bacteria has been the production of circulating toxins, which often function as superantigens in causing the clinical manifestations, morbidity and mortality associated with these diseases. (J Am Acad Dermatol 1998;39:383-98.)

Learning objective: At the conclusion of this learning activity, participants should be familiar with the spectrum of toxin-mediated illnesses caused by streptococci and staphylococci. Participants should also have a greater understanding of toxins and superantigens as well as their role in these diseases.

After several decades of seemingly decreasing virulence, streptococcal and staphylococcal infections have reemerged as a major source of morbidity and mortality.[1-6] Within the past 2 decades, not only have many new diseases caused by these pathogens been described, such as toxic shock syndrome (TSS), streptococcal toxic shock syndrome, recurrent toxin-mediated perineal erythema, and recalcitrant erythematous desquamating (RED) syndrome, but also "older" diseases such as rheumatic fever have begun to reappear more frequently.[6-17]

Although several factors may account for the renewed virulence of *Streptococcus* and *Staphylococcus*, one crucial element in the reemergence of the seriousness of these infections is their ability to produce circulating toxins, which often lead to clinical disease. In addition to mediating TSS, scarlet fever, staphylococcal scalded-skin syndrome (SSSS), and many other well-defined bacterial diseases, these toxins are being increasingly recognized as potential causes, or exacerbating factors, in previously "non-bacterial" diseases such as Kawasaki disease (KD), guttate psoriasis, and atopic dermatitis. An increasing spectrum of disease directly, or indirectly, caused by toxin-producing streptococci and staphylococci is emerging (Table I), and its clinical expression is likely dependent on host factors as well as bacterial properties.[6,18,19]

HISTORICAL PERSPECTIVE

Bacterial infections caused by streptococci and staphylococci have been in existence since antiquity.[6,10,20] Hippocrates, in the 5th century BCE, wrote

From the Division of Dermatology, Department of Medicine, University of Medicine and Dentistry of New Jersey—Robert Wood Johnson Medical School at Camden.
Reprint requests: Steven M. Manders, MD, 100 Brick Rd, Suite 306, Marlton, NJ 08053.

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Table I. Toxin-mediated streptococcal and staphylococcal diseases

Toxic shock syndrome
Streptococcal toxic shock syndrome
Recalcitrant erythematous desquamating disorder
Scarlet fever
Toxin-mediated erythema (eg, recurrent toxin-mediated perineal erythema)
Staphylococcal scalded-skin syndrome
Necrotizing fasciitis
Kawasaki disease*
Guttate psoriasis*
Atopic dermatitis*
Food poisoning†

*Possibly toxin-mediated.
†Not discussed in this article.

Table II. Streptococcal and staphylococcal toxins

Organism	Toxin(s)
Group A streptococci	SPE-A, SPE-B, SPE-C
	SSA
	Mitogenic factor
Groups B, C, F, and G streptococci	SPEs
Staphylococci	TSST-1
	SEA, SEB, SEC, SED, SEE, SEG
	Exfoliative toxin A, B

SEA, Staphylococcal enterotoxin; *SPE*, streptococcal pyrogenic exotoxin; *SSA*, streptococcal superantigen; *TSST-1*, toxic shock syndrome toxin-1.

that "…many were attacked by the erysipelas all over the body…the erysipelas would quickly spread in all directions. Flesh, sinews, and bones fell away in large quantities…," undoubtedly referring to necrotizing fasciitis.[21,22] Scarlet fever appears to have been present during Hippocrates' time as well and indeed is believed to be the cause of the "Plague of Athens," which led to the end of Greece's Golden Age.[6,10] George Washington is believed to have died rapidly after acquiring a virulent strain of *Streptococcus* while on his farm in 1799.[21] Although the morbidity and mortality from gram-positive bacterial, especially streptococcal, infections decreased substantially during the mid to late portion of the 20th century, clearly streptococci and staphylococci have reemerged as major pathogens during the past 2 decades.[6,10,23,24] The prominent media coverage of the "outbreak" of necrotizing fasciitis in 1994 and the description of such "new" diseases such as TSS have again raised public awareness of the potential seriousness of infection with these bacteria.[25]

FACTORS INVOLVED IN VIRULENCE AND REEMERGENCE

Several factors may account for the reemergence of serious streptococcal and staphylococcal infections in the past 2 decades. Surface proteins, host factors, and toxin production have all contributed to the renewed virulence of these bacteria.

Surface proteins on group A β-hemolytic streptococci (GABHS) have been strongly associated with the invasiveness of a given strain of *Streptococcus*. Dozens of M-surface proteins exist, forming the basis for the Lancefield classification system.[26] The M-1 and M-3 surface proteins in particular have been shown not only to greatly facilitate bacterial adherence to infected tissue, but also to have antiphagocytic properties directed against polymorphonuclear leukocytes, whereby the host immune response is markedly blunted.[6,8,26,27] From epidemiologic data, it is clear that a decreased prevalence of the M-1 and M-3 surface proteins during the middle part of this century correlated well with a decreased seriousness of GABHS infection.[28] Conversely, the apparent reemergence of invasive GABHS infections, such as necrotizing fasciitis and streptococcal TSS (STSS), has been closely linked with the renewed prevalence of group A streptococci bearing M-1 and M-3 surface proteins.[4-6,13,28-33]

Host factors in the general population appear to be partially responsible for the reemergence of streptococci and staphylococci as major pathogens.[6,10,18,19] Not surprisingly, very young, elderly, and immunocompromised persons are at high risk for infection with these bacteria.[3] However, a large percentage of patients who have serious streptococcal and staphylococcal disease are young, otherwise healthy adults.[5,6,13,18,32] This is postulated to be due to the absence of previous exposure to these more virulent strains of bacteria, because an absence of protective antibody appears to predispose persons to infection.[5,6,10,18]

Finally, bacterial toxin production has been shown to be a highly important factor in the increased frequency of serious streptococcal and staphylococcal disease. Toxins produced by *Staphylococcus aureus*, GABHS, and to a lesser

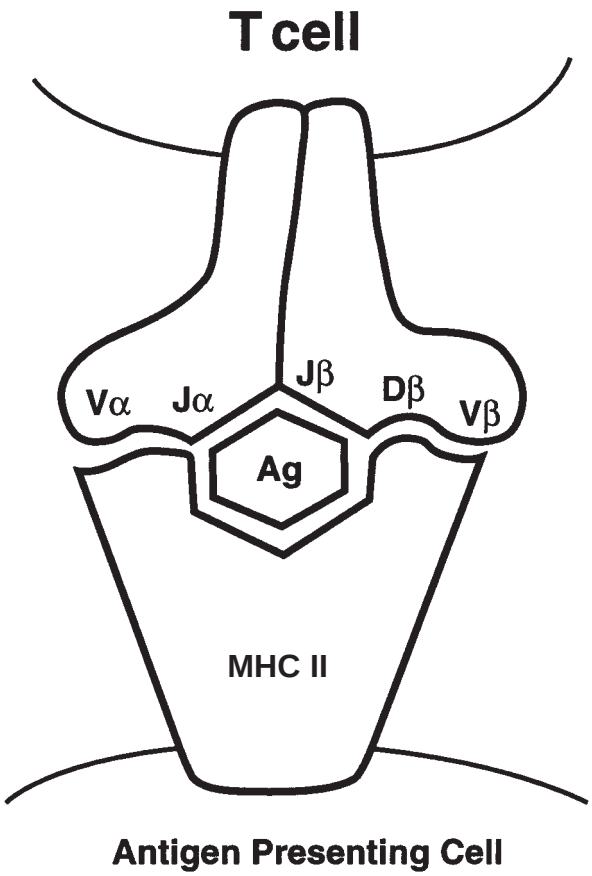

Fig 1. Conventional antigen presentation.

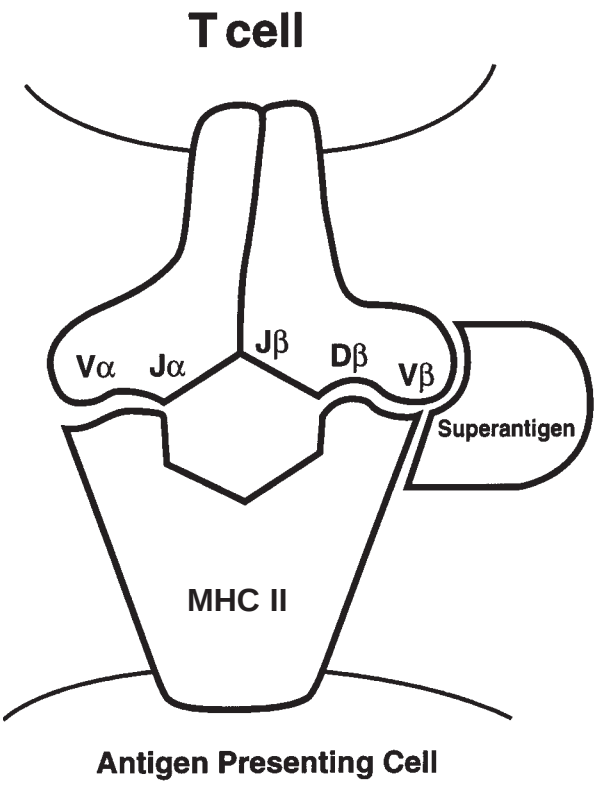

Fig 2. Superantigen interaction with T cell.

degree non-group A streptococci (Table II), have been implicated in the pathophysiology of a multitude of both well-established, and more recently described, diseases.[6,34,35] Indeed, the increased prevalence of serious invasive GABHS infections in the United States has been linked closely with the production of streptococcal pyrogenic exotoxin-A (SPE-A) by the infecting streptococcal strain.[4,5,8,18,34] The majority of these toxins produce their clinical effects in large part by functioning as "superantigens," an emerging concept for which a basic understanding is necessary to gain insight into the pathogenesis of these toxin-mediated illnesses.[36-40]

SUPERANTIGENS

The concept of "superantigens" was first described in 1989 by White et al[41] and refers to a unique group of proteins manufactured by bacteria and viruses.[42] Superantigens produce their clinical effects by bypassing certain elements of the usual antigen-mediated immune response sequence.[43,44] Conventional antigens are processed within the antigen-presenting cell, and protein fragments of the antigen are then expressed on the cell surface in the groove of the major histocompatibility type II complex (MHCII) (Fig 1). The antigen-MHCII complex then interacts with the T-cell receptor in a very specific, antigen-restricted fashion. The segment of T cells bearing the receptor that corresponds to the antigen are then activated, with resultant cytokine production and specific immune activation.[44]

Conversely, superantigens are able to bypass many elements of the typical immune response sequence. Superantigens are not processed by antigen-presenting cells, but bind directly to the MHCII complex outside of the groove (Fig 2) and therefore are able to interact with T cells in a relatively nonspecific fashion.[42,45-52] Whereas conventional antigens require recognition of all 5 elements of the T-cell receptor (Vα, Jα, Vβ, Dβ, Jβ), the recognition sequence for superantigens is almost entirely dependent on Vβ only.[42,43,48,50,53-56] Because only a limited amount of Vβ genes exists,

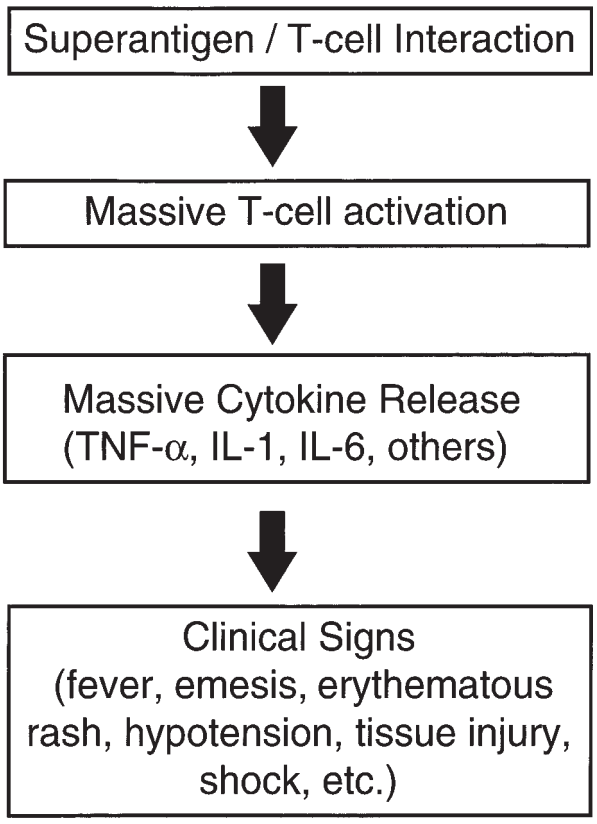

Fig 3. The superantigen/cytokine cascade.

a given superantigen–T-cell interaction may lead to the activation of 5% to 30% of the entire T-cell population, whereas conventional antigens activate approximately 0.01% to 0.1% of the body's T cells.[43,49,52,57,58] This large-scale activation of T cells by superantigens leads to massive cytokine production, especially that of tumor necrosis factor–α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6)[31,42,56,59-64] (Fig 3). These cytokines, especially TNF-α and IL-1, have been shown to mediate clinical effects such as fever, erythematous rash, emesis, hypotension, tissue injury, and shock.[6,13,42,49,65,66] Certain superantigen-mediated illnesses appear to induce a large-scale depletion of particular Vβ subsets; this may result from apoptosis of initially activated T cells.[20,24,56]

A single bacterial toxin, acting as a superantigen, can lead to a broad spectrum of clinical disease. For instance, TSS toxin-1 (TSST-1) has been implicated in the pathogenesis of TSS, recurrent toxin-mediated perineal erythema, RED syndrome, KD, and possibly atopic dermatitis.[42,62,65] Route of admininistration, as well as dose, of toxin has been shown to directly influence the clinical response. In addition, host factors such as local pH, glucose level, oxygen level, age, and presence or absence of antibodies will have a direct impact on the clinical expression of toxin-mediated illness.[67-69]

Certain physical signs are frequently present in toxin-mediated illness caused by streptococci and staphylococci. For instance, strawberry tongue, acral erythema with subsequent desquamation, and an erythematous eruption with frequent perineal accentuation have been described in TSS, scarlet fever, recurrent perineal erythema, and KD, among others (Fig 4). The frequent clinical overlap between toxin-mediated diseases is not limited to only streptococcal illnesses, or only staphylococcal illnesses, per se, but also is readily noted between these 2 groups of bacteria, as evidenced by the similarity of TSS and streptococcal TSS.[8,62] Disease overlap has been attributed to the significant degree of sequence homology at a molecular level of toxins not only within these 2 groups of bacteria, but also between streptococci and staphylococci.[48,49,62,70-73] Ultimately, though, the phenotypic expression of a given toxin-mediated disease is not solely dependent on the toxin itself, but is modified by environmental factors such as the host factors described earlier.

TOXIN-MEDIATED DISEASES

Toxic shock syndrome (TSS)

TSS represents the prototypical superantigen-mediated disease. Originally described in 1978 and soon thereafter associated with tampon use, TSS is now recognized to occur in both menstrual and nonmenstrual forms.[74-76] Currently, the incidence of nonmenstrual TSS exceeds that of menstrual TSS.[77,78] Most cases of nonmenstrual TSS occur in the postoperative setting; however, TSS has been described in association with influenza, sinusitis, tracheitis, intravenous drug use, HIV infection, cellulitis, burn wounds, allergic contact dermatitis, gynecologic infection, and the postpartum period.[62,79-86]

Clinically, both menstrual and nonmenstrual TSS have similar features. Fever, rash, desquamation, hypotension, and multiple-organ involvement are the hallmarks of both variants of TSS.[42,74,76,87] The eruption of TSS is defined as "diffuse macular erythroderma"; however, a scarlatiniform eruption,

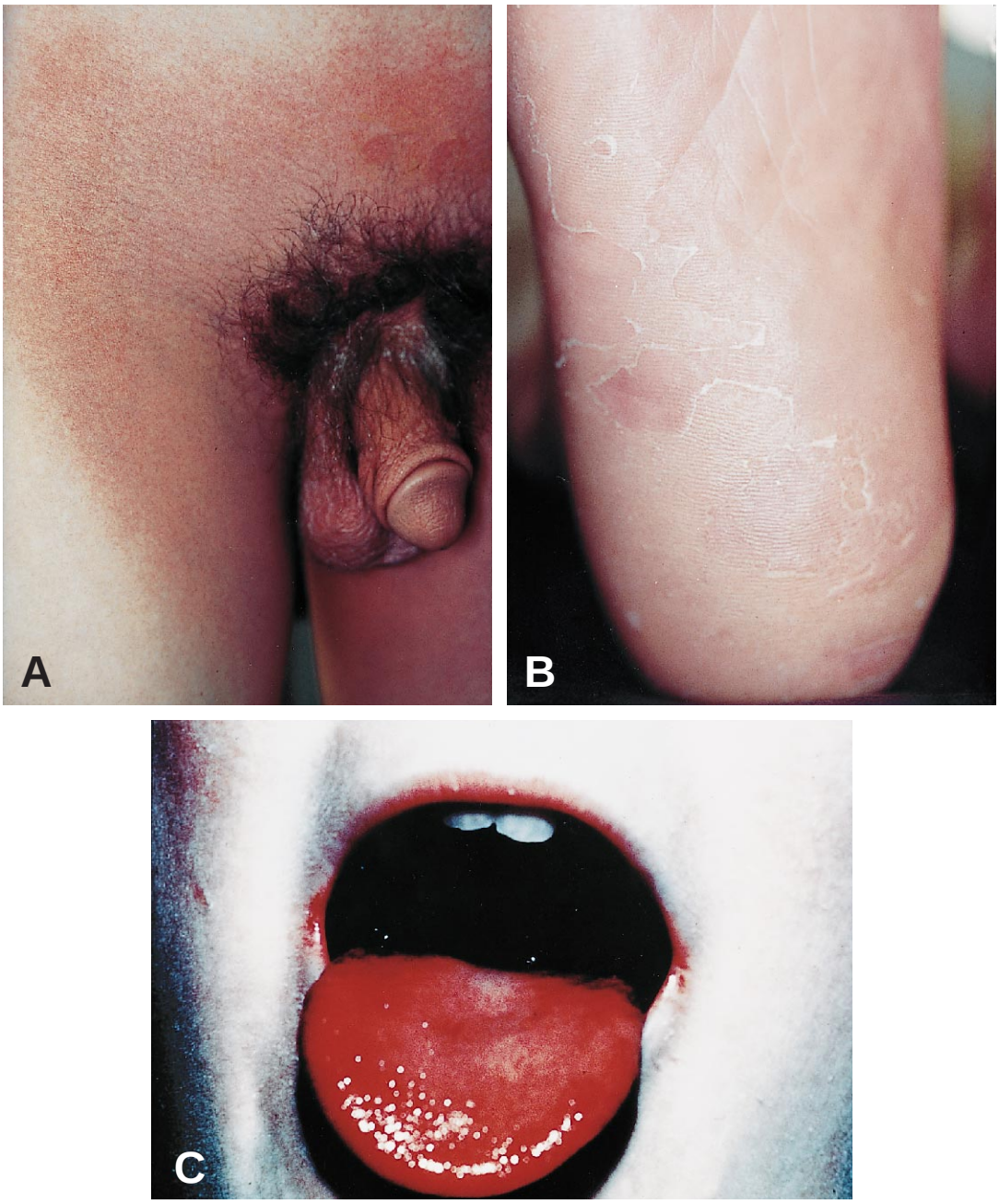

Fig 4. A, Perineal erythema. **B,** Acral desquamation. **C,** Strawberry tongue. (**C,** Courtesy William D. James, MD, Philadelphia, Pa.)

often with flexural accentuation, is frequently present. Erythema and edema of palms and soles, hyperemia of conjunctiva and mucous membranes, and strawberry tongue are often noted.[84] Desquamation of the palms and soles, as seen in many bacterial toxin-mediated disorders, usually follows the onset of the illness by 1 to 2 weeks. Importantly, in nonmenstrual TSS caused by a postoperative infection, the classic signs of localized infection such as erythema, tenderness, and purulence may be absent from the site of infection, thereby making clinical diagnosis challenging.[77] Multiple-organ involvement may include the gastrointestinal, muscular, renal, hepatic, hematologic, or central nervous systems.

Treatment of TSS includes supportive therapy, including hydration, vasopressors, penicillinase-resistant antibiotics, and drainage of infected sites.

In vitro studies have suggested that sublethal concentrations of silver sulfadiazine cream leads to increased toxin production by *S aureus;* therefore mupirocin ointment or povidone iodine solution may be better choices for topical care of infected sites.[88] The mortality rate is approximately 5%, and recurrences have been reported in as many as 30% to 40% of cases.[5,76,89]

Both menstrual and nonmenstrual forms of TSS have been linked to toxin-producing strains of *S aureus*.[90-93] More than 90% of menstrual TSS is mediated by TSST-1 production, which is associated with massive release of TNF-α and IL-1.[62,65,94] These cytokines have been demonstrated to produce fever, rash, hypotension, tissue injury, and shock.[65] The absence of antibody to TSST-1 has been shown to be a major risk factor for acquisition of TSS; failure to generate anti-TSST-1 antibody after an episode of TSS predisposes patients to recurrent episodes.[42,77,81,93,95,96] In support of the concept of TSS as a superantigen-mediated disease, studies of patients with TSS revealed that up to 70% of T cells bear Vβ2 during active disease, correlating well with in vitro findings that TSST-1 leads to Vβ2 expression on T cells.[36,42]

Isolates of *S aureus* from nonmenstrual TSS produce TSST-1 in approximately 50% of cases, whereas the remainder produce staphylococcal enterotoxin B and C (SEB, SEC).[62] Staphylococcal enterotoxins have been shown to be potent mediators of cytokine production and release in a similar fashion to TSST-1 and thereby produce clinically similar diseases.[61,70]

Streptococcal TSS

In the late 1980s, a disease similar in appearance to TSS, yet caused by invasive streptococci, was recognized.[13,14] Also known as "toxic strep" or "streptococcal toxic shock-like syndrome," streptococcal TSS (STSS) was found to share many clinical features with TSS.[13,97] In the majority of cases toxin-producing group A streptococci have been isolated, with SPE-A production being most closely linked with invasive disease.[6,8,34] However, group A streptococci producing SPE-B, SPE-C, streptococcal superantigen, and mitogenic factor, as well as non-group A streptococci, have been found to be causative in individual cases of STSS as well.* In a similar manner to classic TSS, the clinical signs of STSS are postulated to be mediated by massive cytokine release (primarily TNF-α, IL-1b, and IL-6) as a result of toxin/superantigen activity.[6,18,31,61,66] Lymphocyte Vβ profiles consistent with superantigen induction have been noted.[24,43] In addition, streptolysin O, produced by 100% of streptococcal strains associated with STSS, has also been shown to cause TNF-α and IL-1β production, and has been demonstrated to act synergistically with SPE-A.[66]

Not surprisingly, very young, elderly, diabetic, or immunocompromised persons are more susceptible to the acquisition of invasive streptococcal infection such as STSS.[3] However, the majority of cases of STSS have occurred in young, otherwise healthy persons between 20 and 50 years of age.[5,6,13,18,77] An absence of protective immunity is postulated as a potential risk factor in this population.[18,102] STSS has also been well described as a complication of wounds, varicella, and influenza A.[3,13,18,62] A controversial association of invasive group A streptococcal infections such as STSS with prior nonsteroidal anti-inflammatory drug (NSAID) use has been suggested; the link has been proposed to be depression of the cellular immune response by NSAIDs.[18,62,67]

Clinically, STSS shares many features with TSS. Fever, hypotension, myalgias, liver abnormalities, diarrhea, emesis, renal dysfunction, and hematologic abnormalities may be present in TSS caused by either staphylococci or streptococci.[5] Diffuse macular erythroderma likewise is frequently present in disease caused by both bacteria and is often accompanied by mucous membrane findings, such as conjunctival injection and delayed desquamation of palms and soles.[5,6,38,106]

Nonetheless, certain important differences exist between STSS and TSS. The skin is often the portal of entry in STSS, with soft-tissue infections developing in 80% of patients.[6,13,18,107] The initial presentation of STSS is often localized pain in an extremity, which rapidly progresses over 48 to 72 hours to manifest both local and systemic signs of STSS.[5,6,13,29] Cutaneous signs may include localized edema and erythema, a bullous and hemorrhagic cellulitis, necrotizing fasciitis or myositis, and gangrene.[6,13,16,29,100] Soft-tissue involvement of this nature is distinctly uncommon in staphylococcal TSS.[5,62] STSS may uncommonly occur in the absence of cutaneous involvement; in these cases differentiation from staphylococcal TSS

*References 6, 16, 18, 24, 29, 44, 62, 98-101.

becomes more difficult. Blood cultures are positive in more than 50% of patients with STSS, as compared with less than 15% in TSS.[5,6] In addition, mortality rates are more than 5 times higher in STSS.[3,5,6,62,100]

Management of STSS is similar to that of TSS. Supportive therapy, vasopressors, and antibiotics are the cornerstones of treatment. The increasingly reported clinical resistance of streptococci to penicillin G, as well as the difficulty in being able to distinguish STSS from TSS in somes cases, suggests the need for adequate antimicrobial coverage for both staphylococci and penicillin-resistant streptococci. Consideration should be given to clindamycin, erythromycin, cephalosporins, or other agents as deemed appropriate by clinical presentation and culture results.[5] Intravenous γ-globulin has been reported to be dramatically effective in STSS, but is not yet in widespread use.[20]

Recalcitrant, erythematous, desquamating disorder

In 1992, Cone et al[7] reported a novel presentation of toxin-mediated illness, known as recalcitrant, erythematous, desquamating (RED) disorder. Described exclusively in patients with AIDS, RED disorder shares many features with TSS. Fever and hypotension, 2 of the hallmarks of TSS, are present in RED disorder as well. Diffuse macular erythema, ocular and oral mucosal injection, strawberry tongue, and delayed desquamation are likewise noted in both entities.

Nonetheless, several important distinctions allow separation of these clinical entities. The natural history of RED disorder is that of a prolonged illness (mean duration, 50 days) with frequent recurrences, whereas TSS presents in an abrupt, fulminant fashion.[7,108] Although both are multisystem diseases, most patients with RED disorder have a less aggressive course, with usually fewer than 3 organ systems being involved.[7] However, probably because of the underlying medical condition of patients with RED disorder, there is a higher mortality rate with RED disorder than with TSS.[7,84] Treatment of these disorders is similar; antibiotics, fluid replacement, and supportive care are paramount.

In most patients with RED disorder, toxin-producing *S aureus* has been isolated, with sources including skin, sinuses, and blood.[7] Most of these strains have produced TSST-1; SEA and SEB production is less frequent. A single case caused by group A streptococcus has been reported as well.[7] Because of the clinical and microbiologic overlap, RED disorder is postulated to be a variant of TSS, caused by similar bacteria, yet modified by host factors.

Scarlet fever

Scarlet fever is no longer the major public health threat that it was in the past. Morbidity, mortality, and sequelae are much less serious today not only because of the development of antibiotics, but also because of changes in the streptococci responsible for the majority of cases of scarlet fever. Whereas the bacteria that caused scarlet fever in the beginning of this century primarily produced the more virulent SPE-A toxin, currently SPE-B and SPE-C are produced by most *Streptococcus pyogenes* organisms isolated from patients with scarlet fever.[5]

Scarlet fever remains primarily a disease of children, with most cases occurring between the ages of 1 and 10 years.[18] SPEs have been shown to elicit the cutaneous manifestations of scarlet fever by enhancing delayed-type hypersensitivity to streptococcal products, thereby requiring previous exposure for expression of disease.[109] This explains the rarity of cases of scarlet fever in infancy because most infants have not had previous exposure to these streptococcal toxins and therefore have not generated antitoxin antibody.

Clinical findings include the abrupt onset of fever, sore throat, headache, and chills.[18] Mucocutaneous findings include a finely papular erythematous "sandpaper" rash on the trunk and extremities, with circumoral pallor. Pastia's lines represent linear petechial streaks found especially in flexural locations such as the antecubital fossae, the axilla, and the inguinal region. Erythema and edema of the pharyngotonsillar area, punctate erythematous and petechial macules on the palate, and strawberry tongue are commonly present. Large, thick sheets of skin may desquamate from the hands and feet, especially in the convalescent phase. Uncommon complications include pneumonia, pericarditis, meningitis, hepatitis, glomerulonephritis, and rheumatic fever.[18] Recurrence rates of scarlet fever have been reported to be as high as 18%.[110]

Diagnosis of scarlet fever is usually apparent clinically, but can be further confirmed by sup-

portive serologies and isolation of group A streptococci from the pharynx. First-line treatment is with penicillin; erythromycin, cephalosporins, ofloxacin, rifampin, and the newer macrolides are other alternatives.

Toxin-mediated erythema (recurrent toxin-mediated perineal erythema)

In 1996, Manders et al[17] described a previously unrecognized toxin-mediated illness, recurrent toxin-mediated perineal erythema (RPE). The hallmark of RPE is a striking diffuse macular erythema in the perineum occurring abruptly after (within 24 to 48 hours) a bacterial pharyngitis. Oral mucosal changes, such as strawberry tongue, as well as erythema, edema, and convalescent desquamation of the hands and feet are usually present as well. Systemic signs such as fever or hypotension are absent; however, diarrhea may occur. Recurrences are frequent, with one of the original patients now having experienced 12 distinct episodes during a 19-year course.[17] Culture of the pharynx during the acute episodes reveal toxin-producing *S aureus* or *S pyogenes*.

Since the original publication, it has become clear that RPE is part of an expanding clinical spectrum of toxin-mediated skin diseases that do not easily fit into previously described clinical entities. Recurrent erythroderma associated with a preceding bacterial pharyngitis, isolated episodes of toxin-mediated erythema without recurrences, and patients with episodic mild hypotension, fever, and typical mucocutaneous findings in the absence of full criteria for TSS have been encountered in my own experience or in consultation with colleagues. The common feature, aside from a large degree of clinical overlap, has been the repeated ability to isolate toxin-producing bacteria from normally sterile sites. Given the clinical variations, it is more appropriate to refer to this group of entities as "toxin-mediated erythema," although most cases are recurrent with a propensity for perineal involvement.

Staphylococcal scalded-skin syndrome

Staphylococcal scalded-skin syndrome (SSSS) is primarily a disease of young children; the majority of patients are younger than 5 years of age.[106,111] Adults with SSSS have rarely been reported; predisposing factors in this population include renal failure, malignancy, immunosuppression, chronic alcohol abuse, and HIV-1 infection.[111-114] Failure to adequately clear the toxin appears to predispose the very young to SSSS, as well as those with renal failure.[106]

Toxin-producing *S aureus* can be detected in every case of SSSS, with most isolates belonging to phage group II, types 71 and 55.[106] In children the infectious focus is usually in the nasopharynx or conjunctivae.[106] Staphylococcal pneumonia or bacteremia may be present in adults, but the source of infection may be difficult to ascertain.[111] Exfoliative toxins A and B (ETA and ETB) have been implicated in the pathogenesis of SSSS; however, other factors, such as δ-hemolysin, may contribute to the clinical presentation.[111] Childhood cases of SSSS are primarily associated with solely ETA production; however, occasional isolates produce ETA and ETB, or rarely, ETB alone.[114] The frequency of the different toxins in adult cases is unclear.[115] Although clearly toxin-mediated, ETA and ETB may not act as superantigens because ET has been postulated to cause blistering in the granular layer by directly binding desmoglein I and causing interdesmosomal splitting.[106,116,117] An appropriate antibody response to ET appears to limit clinical disease expression to bullous impetigo; an inadequate humoral immune response may predispose patients to development of SSSS.[111]

Clinical features of SSSS include fever, irritability, skin tenderness, and scarlatiniform erythema with accentuation in flexural areas.[106] Within 24 to 48 hours sterile blisters and erosions develop; Nikolsky's sign is characteristically present. Intraoral lesions do not occur because of the absence of a granular layer to which the toxin may bind; however, involvement of the keratinized external lip with crusting and fissuring is frequently encountered. Sepsis is rare in children but common in adults, likely accounting for the greater severity of disease in this group.[111,114]

Therapy for SSSS includes intravenous penicillinase-resistant penicillins, fluid and electrolyte management, and topical care. The mortality rate is low in children (3%) but exceeds 50% in adults, especially in the setting of immunocompromise; NSAID use may predispose patients to a poorer outcome.[115]

Necrotizing fasciitis

Necrotizing fasciitis (NF) is a rapidly advancing

soft-tissue infection that is associated with systemic toxicity and a high mortality rate.[18] Many organisms, including aerobes and anaerobes, may be isolated, often in combination.[25,118,119] Streptococcal gangrene, or type II NF, is characterized microbiologically by the isolation of group A streptococcus alone or in combination with *S aureus*.[118] In addition to the surface M proteins that facilitate tissue adherence and invasiveness, the virulence of streptococci in NF is, at least in part, due to the pyrogenic exotoxins, which exert not only a local toxic effect, but probably also function as superantigens in contributing to systemic involvement.[32,118] Indeed, some cases of streptococcal NF may progress to streptococcal TSS; however, streptococcal NF frequently occurs in the absence of STSS, and vice versa.

Predisposing conditions for the acquisition of NF include trauma (often trivial), previous surgery, diabetes mellitus, immunosuppression, renal failure, arteriosclerosis, odontogenic infection, malignancy, and alcoholism.[18,119-121] Clinically NF can affect any body part, but usually involves an extremity.[121] Localized painful erythema and edema rapidly progress over hours to days, with development of cyanosis, blistering, and necrosis.[18,118] Untreated, NF may progress to deep gangrene and sloughing of tissue. Systemic signs and symptoms include high fever, anxiety, altered mental status, tachypnea, tachycardia, and hypocalcemia.[18,118] Diagnosis is made primarily clinically, but can be aided by aspirate for Gram's stain and culture, frozen tissue sections showing massive polymorphonuclear infiltrate in the fascia and subcutaneous tissue, and radiographic studies that may demonstrate gas (if coinfection is present) or extensive fluid in soft tissue planes.[118] Rapid streptococccal diagnostic kits, usually utilized for pharyngeal infections, have been recently reported to be effective in identifying *S pyogenes* from aspirates of infected tissue in NF.[122]

Treatment includes aggressive surgical debridement, antibiotic therapy, and supportive care.[21] Hyperbaric oxygen may be a useful adjunct. Antibiotic choices should cover the variety of potential causative organisms, unless a definite bacterium can be isolated. In cases caused by *S pyogenes*, penicillin G remains the antibiotic of choice; however, invasive group A streptococcal infections are sometimes characterized by concentrations of bacteria so high that many enter a stationary phase, in which susceptibility to penicillin is diminished.[18,123,124] Clindamycin may be a better choice in such instances because its efficacy is not affected by inoculum size; furthermore, there is some evidence that clindamycin suppresses toxin production by streptococci.[18,125] Other antibiotic choices for streptococci include cephalosporins or erythromycin.[118] The mortality rate for NF ranges from 35% to 40%; however, prompt intervention lowers the rate to 12%.[118]

Table III. Kawasaki disease

Fever of at least 5 days' duration *plus* at least 4 of the 5 following signs or symptoms:
• Peripheral extremity changes (eg, edema, erythema, desquamation)
• Polymorphous exanthem
• Bilateral conjunctival injection
• Changes of lips and oral cavity (eg, erythema, strawberry tongue)
• Acute, nonpurulent cervical lymphadenopathy

Kawasaki disease

Kawasaki disease (KD) is a multisystem illness, primarily occurring in infants and young children.[42,126] Originally described in Japan, KD is now well recognized worldwide.[126-128] The majority of patients with KD are younger than 5 years of age, with a peak incidence between 12 and 24 months of age.[126,129] KD most commonly presents in winter and early spring.[129,130] Although KD is an acute self-limited illness, the sequelae can be potentially fatal. Indeed, KD is a leading cause of acquired heart disease in children.[42,131,132]

Clinically, KD is defined by fever of 5 days' duration, as well as at least 4 of 5 other clinical criteria (Table III).[132] Mucocutaneous findings include bilateral conjunctival injection, erythematous or fissured lips, strawberry tongue, pharyngeal erythema, edema and erythema of the extremities, and convalescent thick "membranous" desquamation of the hands and feet. The cutaneous eruption of KD is classified as "polymorphous" and has been described as macular, morbilliform, urticarial, scarlatiniform, erythema multiforme–like, pustular, and resembling erythema marginatum.[126,129,133-135] Importantly, the eruption in up to two thirds of patients with KD manifests as perineal erythema.[133] In addition to the major clinical criteria, other frequently occurring physical signs

include central nervous system involvement (irritability, lethargy, aseptic meningitis), urethritis, cardiac abnormalities (gallop rhythm, pericarditis, myocarditis, congestive heart failure), liver dysfunction, arthritis, abdominal pain, and diarrhea.[126,129,130]

Laboratory findings in KD include elevations in leukocyte count, erythrocyte sedimentation rate, and platelet count. Thrombocytosis peaks in the convalescent phase, usually 2 to 3 weeks after onset of illness. Likewise, coronary artery aneurysms usually manifest after 2 weeks of illness; it is recommended that a baseline echocardiogram be obtained, with a repeat echocardiogram approximately 3 and 8 weeks after disease onset.[126,129] Histopathologic examination reveals a necrotizing vasculitis, especially of medium-sized arteries such as the coronary arteries.[132,136,137] These pathologic findings are usually not evident on skin biopsy.[129,138]

Although KD is self-limited, the most serious sequelae involve aneurysms of the coronary arteries, which can develop during the convalescent phase of disease in up to 20% of patients.[126,129] Myocardial infarction is the primary cause of death in KD, occurring in 2% of patients, and usually presenting within the first year subsequent to acute disease.[126,129] Incomplete or "atypical" forms of KD have been reported and are characterized by cardiac involvement in the absence of 5 of 6 clinical criteria.[126,139]

Intravenous γ-globulin is the cornerstone of therapy for KD and may be given either as a 4-day regimen or as a single, larger dose.[140,141] Antiplatelet therapy with aspirin is recommended, with dipyridamole as an alternative agent for patients unable to take aspirin.[126] Angioplasty, thrombolytic therapy, or even coronary artery bypass surgery may be required for patients with severe coronary involvement.[126,129]

Although unproven, an infectious origin has been suspected for KD because of the self-limited nature, occasional epidemics, geographic clustering, and seasonal incidence.[126,127,136] In addition, the paucity of cases in children younger than 6 months, or older than 5 years, of age suggests the possibility of a protective antibody to an infectious agent.[126] Nonetheless, a specific microbial cause has been elusive.

Increasing evidence suggests that KD may be a toxin-mediated, superantigen-driven disease.[42,132,142] Leung et al[142] isolated toxin-producing bacteria (primarily *S aureus*, less frequently *S pyogenes*) in 13 of 16 patients with KD, as compared with only 1 of 15 control subjects. Cultures were obtained from the throat, axilla, groin, and rectum; of note is the fact that most colonies of *S aureus* were white and were therefore easily missed for coagulase-negative staphylococci (which may account for the failure to isolate *S aureus* in previous studies).[142] The primary toxin elaborated was TSST-1, with the streptococcal isolates producing SPE-B and SPE-C.[142-145] In support of a superantigen-mediated process, marked expansion of the T-cell population bearing Vβ2+ and Vβ8.1+ was observed in acute, but not convalescent, blood samples of patients with KD.[143] Although this latter study has been confirmed by others,[146] it has not been uniformly accepted.[147] Advocates of a superantigen-mediated pathophysiology have postulated that the efficacy of γ-globulin in the treatment of KD is due to antibodies that inhibit the activation of T cells by staphylococcal or streptococcal superantigens.[148]

Psoriasis

As more is learned regarding the pathogenesis of psoriasis, it is becoming clear that T-lymphocyte activation and infiltration play a crucial role in the initiation and maintenance of clinical disease.[42,149] In guttate psoriasis, and perhaps to a lesser degree chronic plaque psoriasis, there appears to be a potential role for bacterial superantigens in the induction of the localized inflammatory response that leads to the clinical lesions of psoriasis.[42,150,151]

The potential association of guttate psoriasis with a preceding streptococcal infection has been recognized for decades.[152,153] More recently, it has been shown that intradermal injections of streptococcal extracts into normal skin of patients with psoriasis can lead to lesions histologically consistent with psoriasis.[154,155] In addition, T lymphocytes from patients with psoriasis have been demonstrated to have enhanced proliferative responses to group A streptococcal antigens.[156]

Selective expansion of $V\beta2^+$ T cells in the lesional and perilesional skin of patients with guttate psoriasis has been demonstrated.[150,157] This was shown to be a localized phenomenon because there was no concurrent clonal expansion of T cells in the peripheral blood.[157] All streptococcal isolates

from patients with guttate psoriasis produced SPE-C, a toxin which has been associated with the selective expansion of $V\beta2^+$ T cells.[150] It has also been demonstrated that superantigens may upregulate the expression of cutaneous lymphoid antigen (CLA), the skin homing receptor, on T cells.[158,159] Taken together, these findings suggest one potential model for the pathogenesis of guttate psoriasis, in which a pharyngeal infection with toxin-producing streptococci leads to the expansion of $V\beta2^+$ T cells bearing CLA in local lymph nodes. This is followed by localization of these $V\beta2^+/CLA^+$ T cells to the skin where, in combination with local factors such as cytokine production, the clinical lesions of guttate psoriasis are produced.[42,150]

Chronic plaque psoriasis has been less closely linked with preceding, or concurrent, bacterial infection than guttate psoriasis. Nonetheless, the findings of persistent T-cell clones bearing Vβ3 or Vβ13.1 in skin biopsy specimens from patients with chronic plaque psoriasis suggest the possibility of a superantigen-induced inflammatory response.[160] One potential hypothesis to explain the persistence of autoreactive T cells in the skin of patients with plaque psoriasis involves the abnormal recognition by T cells of specific skin antigens, perhaps modified by host genetic factors and chronic superantigen exposure, although this is yet unproved.[42,149,150]

Atopic dermatitis

Although the exact pathogenesis of atopic dermatitis (AD) remains to be elucidated, it is clear that multiple factors, including local inflammation with monocytes and T cells, mast cell degranulation, humoral and cellular immunity, and a personal and/or family history of atopy all contribute.[161] The precise role of each of these elements, as well as the contribution from exogenous factors such as allergens or infection, is yet to be determined.

Bacterial colonization has been well described as a potential initiating or exacerbating factor in AD, with *S aureus* being isolated from the affected skin of more than 90% of patients.[162] More than half of the *S aureus* strains isolated from patients with AD have been shown to secrete toxins, primarily SEA, SEB, and TSST-1.[145,163] Furthermore, SEB applied directly to the skin of normal subjects, as well as to the uninvolved skin of patients with AD, has been shown to result in erythema and induration.[164]

Several potential mechanisms by which *S aureus* may contribute to the pathogenesis of skin inflammation in AD have been proposed, many involving toxins. In one model, toxins may directly stimulate TNF-α or IL-1α release from macrophages, Langerhans cells, keratinocytes, or dermal dendritic cells, leading to leukocyte infiltration into the skin.[42,165]

Another potential role for toxins in the pathogenesis of AD involves a superantigen-mediated stimulation of T cells to locally produce cytokines that mediate tissue inflammation, which has been demonstrated in mice with the application of SEB.[42,166] Activated keratinocytes, unlike "normal" keratinocytes, express MHCII and therefore can function as superantigen-presenting cells to neighboring T cells, leading to further cytokine release and inflammation, which in turn could lead to further activation of keratinocytes, thereby essentially self-perpetuating the inflammatory sequence.[42,52,167,168]

Finally, toxins from *S aureus* may function as allergens in the pathogenesis of AD. The majority of patients with AD have circulating IgE specific for TSST-1, SEB, and SEA; these antibodies may lead to mast cell degranulation on exposure to toxins that have penetrated an already compromised epidermal barrier.[42,145] Histamine release from mast cells may then contribute to the pruritus that is characteristic of AD.[42]

CONCLUSION

The resurgence of serious streptococcal and staphylococcal infections within the past 15 years has led to a renewed interest in some "classic" infectious diseases, the recognition of several new clinical entities, and the reevaluation of the potential role of bacteria in well-recognized conditions with unclear pathogenesis. Central to the reemergence of *Streptococcus* and *S aureus* as major pathogens has been the production of toxins, which often function as "superantigens" in mediating disease by a massive inflammatory response which bypasses the conventional immune sequence. Other innate bacterial properties likely contribute to disease expression as well. The ability of individual toxins to produce varying manifestations of clinical disease is probably due to the level of toxin production in a given person, as well as host factors such as age, immune status, local pH, and oxygen and glucose levels. Clinically, certain common features are frequently present in these toxin-mediated

illnesses, such as an erythematous eruption with frequent perineal accentuation, mucosal changes such as strawberry tongue, and extremity changes of erythema, edema, and desquamation. The potential role of these bacteria in entities such as KD, psoriasis, and AD is intriguing, but is still unproved.

REFERENCES

1. Quinn R. Comprehensive review of morbidity and mortality trends for rheumatic fever, streptococcal disease, and scarlet fever: the decline of rheumatic fever. Rev Infect Dis 1989;11:928-53.
2. Givner LB, Abramson JS, Wasilauskas B. Apparent increase in the incidence of invasive group A beta-hemolytic streptococcal disease in children. J Pediatr 1991;118:341-6.
3. Davies HD, McGeer A, Schwartz B, Green K, Cann D, Simor AE, et al. Invasive group A streptococcal infections in Ontario, Canada. N Engl J Med 1996;335:547-54.
4. Cockerill FR, MacDonald KL, Thompson RL, Roberson F, Kohner PC, Besser-Wiek J, et al. An outbreak of invasive group A streptococcal disease associated with high carriage rates of the invasive clone among school-aged children. JAMA 1997;277:38-43.
5. Wolf JE, Rabinowitz LG. Streptococcal toxic shock-like syndrome. Arch Dermatol 1995;131:73-7.
6. Bronze MS, Dale JB. The reemergence of serious group A streptococcal infections and acute rheumatic fever. Am J Med Sci 1996;311:41-54.
7. Cone LA, Woodard DR, Byrd RG, Schulz K, Kopp SM, Schlievert PM. A recalcitrant, erythematous, desquamating disorder associated with toxin-producing staphylococci in patients with AIDS. J Infect Dis 1992;165:638-43.
8. Stollerman GH. The nature of rheumatogenic streptococci. Mt Sinai J Med 1996;63:144-58.
9. Veasy V, Wiedmeier SE, Orsmond GS, Ruttenberg HD, Boucek MM, Roth SJ, et al. Resurgence of acute rheumatic fever in the intermountain area of the United States. N Engl J Med 1987;316:421-7.
10. Katz AR, Morens DM. Severe streptococcal infections in historical perspective. Clin Infect Dis 1992;14:298-307.
11. Congeni B, Rizzo C, Congeni J, Sreenivasan VV. Outbreak of acute rheumatic fever in northeast Ohio. J Pediatr 1987;111:176-9.
12. Wallace MR, Garst PD, Papadimos TJ, Oldfield EC III. The return of acute rheumatic fever in young adults. JAMA 1989;262:2557-61.
13. Stevens DL, Tanner MH, Winship J, Swarts R, Ries KM, Schlievert PM, et al. Severe group A streptococcal infections associated with a toxic shock-like syndrome and scarlet fever toxin A. N Engl J Med 1989;321:1-7.
14. Cone LA, Woodard DR, Schlievert PM, Tomory GS. Clinical and bacteriologic observations of a toxic shock-like syndrome due to *Streptococcus pyogenes*. N Engl J Med 1987;317:146-9.
15. Bartter T, Dascal A, Carroll K, Curley FJ. 'Toxic strep syndrome': a manifestation of group A streptococcal infection. Arch Intern Med 1988;148:1421-4.
16. Hoge CW, Schwartz B, Talkington DF, Breiman RF, MacNeill EM, Englender SJ. The changing epidemiology of invasive group A streptococcal infections and the emergence of streptococcal toxic shock-like syndrome. JAMA 1993;269:384-9.
17. Manders SM, Heymann WR, Atillasoy E, Kleeman J, Schlievert PM. Recurrent toxin-mediated perineal erythema. Arch Dermatol 1996;132:57-60.
18. Stevens DL. Invasive group A streptococcus infections. Clin Infect Dis 1992;14:2-13.
19. Holm SE, Norrby A, Bergholm AM, Norgren M. Aspects of pathogenesis of serious group A streptococcal infections in Sweden, 1988-1989. J Infect Dis 1992;166:31-7.
20. Stevens DL. The toxic shock syndromes. Infect Dis Clin North Am 1996;10:727-46.
21. Brantigan CO, Senkowsky J. Group A beta hemolytic streptococcal necrotizing fasciitis. Wounds 1995;7:62-8.
22. Descamps V, Aitken J, Lee MG. Hippocrates on necrotising fasciitis. Lancet 1994;344:556.
23. Brackett AS. Scarlet fever from 1675 to 1954. Conn State Med J 1955;19:410-2.
24. Watanabe-Ohnishi R, Low DE, McGeer A, Stevens DL, Schlievert PM, Newton D, et al. Selective depletion of V beta-bearing T cells in patients with severe invasive group A streptococcal infections and streptococcal toxic shock syndrome. J Infect Dis 1995;171:74-84.
25. Stone DR, Gorbach SL. Necrotizing fasciitis: the changing spectrum. Dermatol Clin 1997;15:213-20.
26. Lancefield RC. Current knowledge of type-specific M antigens of group A streptococci. J Immunol 1962;89: 307-13.
27. Peter G, Smith A. Group A streptococcal infections of the skin and pharynx. N Engl J Med 1977;297:311-6.
28. Schwartz B, Facklam RR, Breiman RF. Changing epidemiology of group A streptococcal infection in the USA. Lancet 1990;336:1167-71.
29. Demers B, Simor AE, Vellend H, Schlievert PM, Byrne S, Jamieson F, et al. Severe invasive group A streptococcal infections in Ontario, Canada: 1987-1991. Clin Infect Dis 1993;16:792-800.
30. Musser JM, Hauser AR, Kim MH, Schlievert PM, Nelson K, Selander RK. *Streptococcus pyogenes* causing toxic-shock-like syndrome and other invasive disease: clonal diversity and pyrogenic exotoxin expression. Proc Natl Acad Sci U S A 1991;88:2668-72.
31. Norrby-Teglund A, Pauksens K, Norgren M, Holm SE. Correlation between serum TNFα and IL6 levels and severity of group A streptococcal infections. Scand J Infect Dis 1995;27:125-30.
32. Chausee MS, Liu J, Stevens DL, Ferretti JJ. Genetic and phenotypic diversity among isolates of *Streptococcus pyogenes* from invasive infections. J Infect Dis 1996; 173:901-8.
33. Hauser AR, Stevens DL, Kaplan EL, Schlievert PM. Molecular analysis of pyrogenic exotoxins from *Streptococcus pyogenes* isolates associated with toxic shock-like syndrome. J Clin Microbiol 1991;29:1562-7.
34. Talkington DF, Schwartz B, Black CM, Todd JK, Elliott J, Breiman RF, et al. Association of phenotypic and genotypic characteristics of invasive *Streptococcus pyogenes* isolates with clinical components of streptococcal toxic shock syndrome. Infect Immun 1993;61:3369-74.
35. Reda KB, Kapur V, Mollick JA, Lamphear JG, Musser JM, Rich RR. Molecular characterization and phylogenetic distribution of the streptococcal superantigen gene (SSA) from *Streptococcus pyogenes*. Infect Immun 1994;62:1867-74.
36. Choi Y, Lafferty JA, Clements JR, Todd JK, Gelfand EW, Kappler J, et al. Selective expansion of T cells expressing vβ2 in toxic shock syndrome. J Exp Med 1990;172:981-4.

37. Choi Y, Kotzin B, Herron L, Callahan J, Marrack P, Kappler J. Interaction of *Staphylococcus aureus* toxin "superantigens" with human T cells. Proc Natl Acad Sci U S A 1989;86:8941-5.
38. Michie C, Scott A, Cheesbrough J, Beverley P, Pasvol G. Streptococcal toxic shock-like syndrome: evidence of superantigen activity and its effects on T lymphocyte subsets in vivo. Clin Exp Immunol 1994;98:140-4.
39. Abe J, Forrester J, Nakahara T, Lafferty JA, Kotzin BL, Leung DYM. Selective stimulation of human T cells with streptococcal erythrogenic toxins A and B. J Immunol 1991;146:3747-50.
40. Braun MA, Gerlach D, Hartwig UF, Ozegowski JH, Romagne F, Carrel S, et al. Stimulation of human T cells by streptococcal "superantigen" erythrogenic toxins (scarlet fever toxins). J Immunol 1993;150:2457-66.
41. White J, Herman A, Pullen AM, Kubo R, Kappler JW, Marrack P. The Vβ-specific superantigen staphylococcal enterotoxin B: stimulation of mature T cells and clonal deletion in neonatal mice. Cell 1989;56:27-35.
42. Leung DYM, Travers JB, Norris DA. The role of superantigens in skin disease. J Invest Dermatol 1995; 105(Suppl):37s-42s.
43. Rosen H. Superantigens. Int J Dermatol 1997;36:14-6.
44. Schlievert PM. Role of superantigens in human disease. J Infect Dis 1993;167:997-1002.
45. Fraser J. High affinity binding of staphylococcal enterotoxins A and B to HLA-DR. Nature 1989;339:221-3.
46. Dellabona P, Peccoud J, Kappler J, Marrack P, Benoist C, Mathis D. Superantigens interact with MHC class II molecules outside of the antigen groove. Cell 1990;62: 1115-21.
47. Von Bonin A, Ehrlich S, Malcherek G, Fleischer B. Major histocompatibility complex class II-associated peptides determine the binding of the superantigen toxic shock syndrome toxin-1. Eur J Immunol 1995;25:2894-8.
48. Marrack P, Kappler J. The staphylococcal enterotoxins and their relatives. Science 1990;248:705-11.
49. Johnson HM, Torres BA, Soos JM. Superantigens: structure and relevance to human disease. Proc Soc Exp Biol Med 1996;212:99-109.
50. Goujard C, Wallon C, Rudent A, Boue F, Barre-Sinoussi F, Delfraissy JF. Staphylococcal superantigens activate HIV-1 replication in naturally infected monocytes. AIDS 1994;8:1397-404.
51. Fuleihan R, Trede N, Chatila T, Geha RS. Superantigens activate HIV-1 gene expression in monocytic cells. Clin Immunol Immunopathol 1994;72:357-61.
52. Skov L, Baadsgaard O. Superantigens: Do they have a role in skin diseases? Arch Dermatol 1995;131:829-32.
53. Kotzin B, Leung DYM, Kappler J, Marrack P. Superantigens and their potential role in human disease. Adv Immunol 1993;54:99-166.
54. Acha-Orbea H. Retroviral superantigens. Chem Immunol 1993;55:65-86.
55. Pullen A, Bill J, Kubo RT, Marrack P, Kappler JW. Analysis of the interaction site for the self superantigen M1s-1 on T cell receptor Vβ. J Exp Med 1991;173:1183-92.
56. Schafer R, Sheil JM. Superantigens and their role in infectious disease. Adv Pediatr Infect Dis 1995;10: 369-90.
57. Makida R, Hofer MF, Takase K, Cambier JC, Leung DYM. Bacterial superantigens induce Vβ-specific T cell receptor internalization. Mol Immunol 1996;33:891-900.
58. Herman A, Kappler J, Marrack P, Pullen AM. Superantigens: mechanism of T-cell stimulation and role in immune responses. Annu Rev Immunol 1991;9: 745-72.
59. Jupin C, Anderson S, Damais C, Alouf JE, Parant M. Toxic shock syndrome toxin 1 as an inducer of human tumor necrosis factors and gamma-interferon. J Exp Med 1988;167:752-61.
60. Parsonnet J, Gillis ZA. Production of tumor necrosis factor by human monocytes in response to toxic shock syndrome toxin-1. J Infect Dis 1988;158:1026-33.
61. Fast DJ, Schlievert PM, Nelson RD. Toxic shock syndrome-associated staphylococccal and streptococcal pyrogenic toxins are potent inducers of tumor necrosis factor production. Infect Immun 1989;57:291-4.
62. Schlievert PM, Bohach GA, Ohlendorf DH, Stauffacher CV, Leung DYM, Murray DL, et al. Molecular structure of staphylococcus and streptococcus superantigens. J Clin Immunol 1995;15(Suppl):4s-10s.
63. Muller-Alouf H, Alouf JE, Gerlach D, Ozegowski JH, Fitting C, Cavaillon JM. Human pro- and anti-inflammatory cytokine patterns induced by *Streptococcus pyogenes* erythrogenic (pyrogenic) exotoxin A and C superantigens. Infect Immun 1996;64:1450-3.
64. Muller-Alouf H, Alouf JE, Gerlach D, Ozegowski JH, Fitting C, Cavaillon JM. Comparative study of cytokine release by human peripheral blood mononuclear cells stimulated with *Streptococcus pyogenes* superantigenic erythrogenic toxins, heat-killed streptococci, and lipopolysaccharide. Infect Immun 1994;62:4915-21.
65. Ikejima T, Okusawa S, van der Meer JWM, Dinarello CA. Induction by toxic-shock-syndrome toxin-1 of a circulating tumor necrosis factor-like substance in rabbits and of immunoreactive tumor necrosis factor and interleukin-1 from human mononuclear cells. J Infect Dis 1988;158:1017-25.
66. Hackett SP, Stevens DL. Streptococcal toxic shock syndrome: synthesis of tumor necrosis factor and interleukin-1 by monocytes stimulated with pyrogenic exotoxin A and streptolysin O. J Infect Dis 1992;165:879-85.
67. Schlievert PM, Blomster DA. Production of staphylococcal pyrogenic exotoxin type C: influence of physical and chemical factors. J Infect Dis 1983;147:236-42.
68. Todd JK, Franco-Buff A, Lawellin DW, Vasil ML. Phenotypic distinctiveness of *Staphylococcus aureus* strains associated with toxic shock syndrome. Infect Immun 1984;45:339-44.
69. Kass EH, Schlievert PM, Parsonnet J, Mills JT. Effect of magnesium on production of toxic-shock-syndrome toxin-1: a collaborative study. J Infect Dis 1988;158:44-51.
70. Uchiyama T, Yan XJ, Imanishi K, Yagi J. Bacterial superantigens: mechanism of T cell activation by the superantigens and their role in the pathogenesis of infectious diseases. Microbiol Immunol 1994;38:245-56.
71. Bohach GA, Hovde CJ, Handley JP, Schlievert PM. Cross-neutralization of staphylococcal and streptococcal pyrogenic toxins by monoclonal and polyclonal antibodies. Infect Immun 1988;56:400-4.
72. Bohach GA, Schlievert PM. Nucleotide sequence of the staphylococcal enterotoxin C1 gene and relatedness to other pyrogenic toxins. Mol Gen Genet 1987;209:15-20.
73. Johnson LP, L'Italien JJ, Schlievert PM. Streptococcal pyrogenic exotoxin type A (scarlet fever toxin) is related to *Staphylococcus aureus* enterotoxin B. Mol Gen Genet 1986;203:354-6.
74. Todd J, Fishaut M. Toxic shock syndrome associated with phage-group-I staphylococci. Lancet 1978;2:1116-8.

75. Todd J. Toxic shock syndrome: scientific uncertainty and the public media. Pediatrics 1981;6:921-3.
76. Shands KN, Schmid GP, Dan BB, Blum D, Guidotti RJ, Hargrett NT, et al. Toxic-shock syndrome in menstruating women: association with tampon use and *Staphylococcus aureus* and clinical features in 52 cases. N Engl J Med 1980;303:1436-42.
77. Strausbaugh LJ. Toxic shock syndrome: Are you recognizing its changing presentations? Postgrad Med 1993;94:107-8, 111-3, 117-8.
78. Gaventa S, Reingold AL, Hightower AW, Broome CV, Schwartz D, Hoppe C, et al. Active surveillance for toxic shock syndrome in the United States: 1986. Rev Infect Dis 1989;11(Suppl 1):s28-34.
79. Bohach GA, Fast DJ, Nelson RD, Schlievert PM. Staphylococcal and streptococcal pyrogenic toxins involved in toxic shock syndrome and related illnesses. Crit Rev Microbiol 1989;17:251-72.
80. MacDonald KL, Osterholm MT, Hedberg CW, Schrock CG, Peterson GF, Jentzen JM, et al. Toxic shock syndrome: a newly recognized complication of influenza and influenza-like illness. JAMA 1987;257:1053-8.
81. Shah A, Moss W, Champion S, Abrams EJ. Nonmenstrual toxic shock syndrome in a young child with human immunodeficiency virus infection. Pediatr Infect Dis J 1996;15:639-41.
82. Finkelstein S, Hyland RH. Toxic shock syndrome as the AIDS-defining diagnosis. Chest 1993;104:950-1.
83. Sparano J, Ferranti E. The acquired immunodeficiency syndrome and nonmenstrual toxic shock syndrome. Ann Intern Med 1986;105:300-1.
84. Woods SL, Jackson B. The human immunodeficiency virus and nonmenstrual toxic shock syndrome: a female case presentation. Nurse Pract 1994;19:68-71.
85. Reingold AL, Hargrett NT, Dan BB, Shands KN, Strickland BY, Broome CV. Nonmenstrual toxic shock syndrome: a review of 130 cases. Ann Intern Med 1982;96:875-80.
86. Ferguson MA, Todd JK. Toxic shock syndrome associated with *Staphylococcus aureus* sinusitis in children. J Infect Dis 1990;161:953-5.
87. Larkin SM, Williams DN, Osterholm MT, Tofte RW, Posalaky Z. Toxic shock syndrome: clinical, laboratory, and pathologic findings in nine fatal cases. Ann Intern Med 1982;96:858-64.
88. Edwards-Jones V, Foster HA. The effect of topical antimicrobial agents on the production of toxic shock syndrome toxin-1. J Med Microbiol 1994;41:408-13.
89. Chesney PJ. Clinical aspects and spectrum of illness of toxic shock syndrome: overview. Rev Infect Dis 1989; 11(Suppl):s1-7.
90. Bergdoll MS, Crass BA, Reiser RF, Robbins RN, Davis JP. A new staphylococcal enterotoxin, enterotoxin F, associated with toxic-shock-syndrome *Staphylococcus aureus* isolates. Lancet 1981;1:1017-21.
91. Schlievert PM, Shands KN, Dan BB, Schmid GP, Nishimura RD. Identification and characterization of an exotoxin from *Staphylococcus aureus* associated with toxic-shock syndrome. J Infect Dis 1981;143:509-16.
92. Bonventre PF, Weckbach L, Staneck J, Schlievert PM, Thompson M. Production of staphylococcal enterotoxin F and pyrogenic enterotoxin C by *Staphylococcus aureus* isolates from toxic shock syndrome-associated sources. Infect Immun 1983;40:1023-9.
93. Rosten PM, Bartlett KH, Chow AW. Serologic responses to toxic shock syndrome (TSS) toxin-1 in menstrual and nonmenstrual TSS. Clin Invest Med 1988;11:187-92.
94. Parsonnet J, Hickman RK, Eardley DD, Pier GB. Induction of human interleukin-1 by toxic-shock-syndrome toxin-1. J Infect Dis 1985;151:514-22.
95. Davis JP, Chesney PJ, Wand PJ, Laventure M. Toxic-shock syndrome: epidemiologic features, recurrence, risk factors and prevention. N Engl J Med 1980;303: 1429-35.
96. Bonventre PF, Linnemann C, Weckbach LS, Staneck JL, Buncher AR, Vigdorth E, et al. Antibody responses to toxic-shock-syndrome (TSS) toxin by patients with TSS and by healthy staphylococcal carriers. J Infect Dis 1984;150:662-6.
97. Working Group on Severe Streptococcal Infections. Defining the group A streptococcal toxic shock syndrome: rationale and consensus definition. JAMA 1993;269:390-1.
98. Yutsudo T, Murai H, Gonzalez J, Takao T, Shimonishi Y, Takeda Y, et al. A new type of mitogenic factor produced by *Streptococcus pyogenes*. FEBS Lett 1992;308:30-4.
99. Mollick J, Miller G, Musser J, Cook R, Grossman D, Rich R. A novel superantigen isolated from pathogenic strains of *Streptococcus pyogenes* with aminoterminal homology to staphylococcal enterotoxins B and C. J Clin Invest 1993;92:710-9.
100. Davies HD, Matlow A, Scriver SR, Schlievert P, Lovgren M, Talbot JA, et al. Apparent lower rates of streptococcal toxic shock syndrome and lower mortality in children with invasive group A streptococcal infections compared with adults. Pediatr Infect Dis J 1994;13:49-56.
101. Wagner JG, Schlievert PM, Assimacopoulos AP, Stoehr JA, Carson PJ, Komadina K. Acute group G streptococcal myositis associated with streptococcal toxic shock syndrome: case report and review. Clin Infect Dis 1996;23:1159-61.
102. Mahieu LM, Holm SE, Goossens HJ, Van Acker KJ. Congenital streptococcal toxic shock syndrome with absence of antibodies against streptococcal pyrogenic exotoxins. J Pediatr 1995;127:987-9.
103. Begovac J, Marton E, Lisic M, Beus I, Bozinovic D, Kuzmanovic N. Group A β-hemolytic streptococcal toxic shock-like syndrome. Pediatr Infect Dis J 1990; 9:369-70.
104. Bradley JS, Schlievert PM, Sample TG Jr. Streptococcal toxic shock-like syndrome as a complication of varicella. Pediatr Infect Dis J 1991;10:77-9.
105. Gonzalez-Ruiz A, Ridgway GL, Cohen SL, Hunt CP, McGrouther G, Adiseshiah M. Varicella gangrenosa with toxic shock-like syndrome due to group A streptococcus infection in an adult: case report. Clin Infect Dis 1995; 20:1058-60.
106. Resnick SD. Staphylococcal toxin-mediated syndromes in childhood. Semin Dermatol 1992;11:11-8.
107. Wood T, Potter M, Jonasson O. Streptococcal toxic shock-like syndrome: the importance of surgical intervention. Ann Surg 1993;217:109-14.
108. Chesney PJ, Davis JP, Purdy WK, Wand PJ, Chesney RW. Clinical manifestations of toxic shock syndrome. JAMA 1981;246:741-8.
109. Schlievert PM, Bettin KM, Watson DW. Reinterpretation of the Dick test: role of group A streptococcal pyrogenic exotoxin. Infect Immun 1979;26:467-72.
110. Chiesa C, Pacifico L, Nanni F, Orefici G. Recurrent attacks of scarlet fever. Arch Pediatr Adolesc Med 1994;148:656-60.

111. Gemmell CG. Staphylococcal scalded skin syndrome. J Med Microbiol 1995;43:318-27.
112. Goldberg NS, Ahmed T, Robinson B, Ascensao J, Horowitz H. Staphylococcal scalded skin syndrome mimicking acute graft-vs-host disease in a bone marrow transplant recipient. Arch Dermatol 1989;125:85-7.
113. Richard M, Mathieu-Serra A. Staphylococcal scalded skin syndrome in a homosexual adult. J Am Acad Dermatol 1986;15:385-9.
114. Cribier B, Peimont Y, Grosshans E. Staphylococcal scalded skin syndrome in adults: a clinical review illustrated with a new case. J Am Acad Dermatol 1994;30: 319-24.
115. Farrell AM, Ross JS, Umasankar S, Bunker CB. Staphylococcal scalded skin syndrome in an HIV-1 seropositive man. Br J Dermatol 1996;134:962-5.
116. Lillibridge CB, Melish ME, Glasgow LA. Site of action of exfoliative toxin in the staphylococcal scalded skin syndrome. Pediatrics 1972;50:728-38.
117. Takagi Y, Futamura S, Asada Y. Action site of exfoliative toxin on keratinocytes [abstract]. J Invest Dermatol 1990;94:52.
118. Morantes MC, Lipsky BA. "Flesh-eating bacteria": return of an old nemesis. Int J Dermatol 1995;34:461-3.
119. Brook I. Aerobic and anaerobic microbiology of necrotizing fasciitis in children. Pediatr Dermatol 1996;13: 281-4.
120. Rea WJ, Wyrick WJ Jr. Necrotizing fasciitis. Ann Surg 1970;172:957-64.
121. Kotrappa KS, Bansal RS, Amin NM. Necrotizing fasciitis. Am Fam Physician 1996;53:1691-7.
122. Ault MJ, Geiderman J, Sokolov R. Rapid identification of group A streptococcus as the cause of necrotizing fasciitis. Ann Emerg Med 1996;28:227-30.
123. Stevens DL, Gibbons AE, Bergstrom R, Winn V. The Eagle effect revisited: efficacy of clindamycin, erythromycin, and penicillin in the treatment of streptococcal myositis. J Infect Dis 1988;158:23-8.
124. Eagle H. Experimental approach to the problem of treatment failure with penicillin. I. Group A streptococcal infection in mice. Am J Med 1952;13:389-99.
125. Gemmell CG, Peterson PK, Schmeling D, Kim Y, Matthews J, Wannamaker L, et al. Potentiation of opsonization and phagocytosis of *Streptococcus pyogenes* following growth in the presence of clindamycin. J Clin Invest 1981;67:1249-56.
126. Gersony WM. Diagnosis and management of Kawasaki disease. JAMA 1991;265:2699-703.
127. Melish ME. Kawasaki syndrome. Pediatr Rev 1996;17: 153-62.
128. Velez-Torres R, Callen JP. Acute febrile mucocutaneous lymph node (Kawasaki) syndrome: an analysis of 24 cases. Int J Dermatol 1987;26:96-102.
129. Wortmann DW. Kawasaki syndrome. Semin Dermatol 1992;11:37-47.
130. Rauch AM. Kawasaki syndrome: critical review of U.S. epidemiology. Prog Clin Biol Res 1987;250:33-44.
131. Rauch AM. Kawasaki syndrome: review of new epidemiologic and laboratory developments. Pediatr Infect Dis J 1987;6:1016-21.
132. Leung DYM, Meissner HC, Fulton DR, Quimby F, Schlievert PM. Superantigens in Kawasaki syndrome. Clin Immunol Immunopathol 1995;77:119-26.
133. Friter BS, Lucky AW. The perineal eruption of Kawasaki syndrome. Arch Dermatol 1988;124:1805-10.
134. Kimura T, Miyazawa H, Watanabe K, Moriya T. Small pustules in Kawasaki disease: a clinicopathological study of four patients. Am J Dermatopathol 1988;10:218-23.
135. Hicks RV, Melish ME. Kawasaki syndrome. Pediatr Clin North Am 1986;33:1151-75.
136. Leung DYM, Meissner C, Fulton D, Schlievert PM. The potential role of bacterial superantigens in the pathogenesis of Kawasaki syndrome. J Clin Immunol 1995; 15(Suppl):11s-17s.
137. Fujiwara H, Hamashima Y. Pathology of the heart in Kawasaki's disease. Pediatrics 1978;61:100-7.
138. Jackson JL, Kunkel MR, Libow L, Gates RH. Adult Kawasaki disease: report of two cases treated with intravenous gamma globulin. Arch Intern Med 1994;154: 1398-405.
139. Levy M, Koren G. Atypical Kawasaki disease: analysis of clinical presentation and diagnostic clues. Pediatr Infect Dis J 1990;9:122-6.
140. Newburger JW, Takahashi M, Burn J, Beiser AS, Chung KJ, Duffy CE, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med 1986;315:341-7.
141. Newburger JW, Takahashi M, Beiser AS, Burns JC, Bastian J, Chung KJ, et al. A single infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med 1991; 324:1633-9.
142. Leung DYM, Meissner HC, Fulton DR, Murray DL, Kotzin BL, Schlievert PM. Toxic shock syndrome toxin-secreting *Staphylococcus aureus* in Kawasaki syndrome. Lancet 1993;342:1385-8.
143. Abe J, Kotzin BL, Jujo K, Melish ME, Glode MP, Kohsak T, et al. Selective expansion of T cells expressing T-cell receptor variable regions Vβ2 and Vβ8 in Kawasaki disease. Proc Natl Acad Sci U S A 1992; 89:4066-70.
144. Abe J, Kotzin BL, Meissner C, Melish ME, Masato T, Fulton D, et al. Characterization of T cell repertoire changes in acute Kawasaki disease. J Exp Med 1993; 177:791-6.
145. Leung DYM, Harbeck R, Bina P, Hanifin JM, Reiser RF, Samson HA. Presence of IgE antibodies to staphylococcal exotoxins on the skin of patients with atopic dermatitis: evidence for a new group of allergens. J Clin Invest 1993;92:1374-80.
146. Curtis N, Zheng R, Lamb JR, Levin M. Evidence for a superantigen mediated process in Kawasaki disease. Arch Dis Child 1995;72:308-11.
147. Pietra BA, DeInocencio J, Giannini EH, Hirsch R. TCR Vβ family repertoire and T cell activation markers in Kawasaki disease. J Immunol 1994;153:1881-8.
148. Takei S, Arora YK, Walker SM. Intravenous immunoglobulin contains specific antibodies inhibitory to activation of T cells by staphylococcal toxin superantigens. J Clin Invest 1993;91:602-7.
149. Valdimarrson H, Baker BS, Jonsdottir I, Powles A, Fry L. Psoriasis: A T-cell-mediated autoimmune disease induced by streptococcal superantigens? Immunol Today 1995;16:145-9.
150. Leung DYM, Travers JB, Giorno R, Norris DA, Skinner R, Aelion J, et al. Evidence for a streptococcal superantigen-driven process in acute guttate psoriasis. J Clin Invest 1995;96:2106-12.
151. Yokote R, Tokura Y, Furukawa F, Takigawa M. Susceptible responsiveness to bacterial superantigens in peripheral blood mononuclear cells from patients with psoriasis. Arch Dermatol Res 1995;287:443-7.

152. Whyte JH, Baughman RD. Acute guttate psoriasis and streptococcal infection. Arch Dermatol 1964;89:350-6.
153. Henderson CA, Highet AS. Acute psoriasis associated with Lancefield group C and group G cutaneous streptococcal infections. Br J Dermatol 1988;118:559-62.
154. Cole GW, Wuepper KD. Isolation and partial characterization of a keratinocyte proliferative factor produced by *Streptococcus pyogenes* (strain NY-5). J Invest Dermatol 1978;71:219-23.
155. Rosenberg EW, Noel PW. The Koebner phenomenon and the microbial basis of psoriasis. J Am Acad Dermatol 1988;18:151-8.
156. Baker BS, Bokth S, Powles A, Garioch JJ, Lewis H, Valdimarrson H, et al. Group A streptococcal antigen-specific T lymphocytes in guttate psoriatic lesions. Br J Dermatol 1993;128:493-9.
157. Lewis HM, Baker BS, Bokth S, Powles AV, Garioch JJ, Valdimarrson H, et al. Restricted T-cell receptor Vβ gene usage in the skin of patients with guttate and chronic plaque psoriasis. Br J Dermatol 1993;129:514-20.
158. Picker LJ, Martin RJ, Trumble A, Newman LS, Collins PA, Bergstresser PR, et al. Differential expression of lymphocyte homing receptors by human memory/effector T cells in pulmonary versus cutaneous immune effector sites. Eur J Immunol 1994;24:1269-77.
159. Leung DYM, Gately M, Trumble A, Ferguson-Darnell B, Schlievert PM, Picker LJ. Bacterial superantigens induce T cell expression of the skin-selective homing receptor, the cutaneous lymphocyte-associated antigen (CLA). J Exp Med 1995;181:747-53.
160. Chang JC, Smith LR, Froning KJ, Schwabe BJ, Laxer JA, Caralli LL, et al. CD8+ T cells in psoriatic lesions preferentially use T-cell receptor V beta 3 and/or V beta 13.1 genes. Proc Natl Acad Sci U S A 1994;91:9282-6.
161. Leung DYM. Atopic dermatitis: the skin as a window into the pathogenesis of chronic allergic diseases. J Allergy Clin Immunol 1995;96:302-18.
162. Leyden JE, Marples RR, Kligman AM. *Staphylococcus aureus* in the lesions of atopic dermatitis. Br J Dermatol 1974;90:525-30.
163. McFadden JP, Noble WC, Camp RDR. Superantigenic exotoxin-secreting potential of staphylococci isolated from atopic eczematous skin. Br J Dermatol 1993;128: 631-2.
164. Strange P, Skov L, Lisby S, Nielsen PL, Baadsgaard O. Staphylococcal enterotoxin B applied on intact normal and intact atopic skin induces dermatitis. Arch Dermatol 1996;132:27-33.
165. Schroder JM. Cytokine networks in the skin. J Invest Dermatol 1995;105(Suppl):20s-24s.
166. Saloga J, Leung DYM, Reardon C, Giorno RC, Born W, Gelfand EW. The cutaneous inflammatory response to bacterial superantigen is T-cell dependent. J Invest Dermatol 1996;106:982-8.
167. Strange P, Skov L, Baadsgaard O. Interferon gamma-treated keratinocytes activate T cells in the presence of superantigens: involvement of major histocompatibility complex class II molecules. J Invest Dermatol 1994; 102:150-4.
168. Nickoloff BJ, Mitra RS, Green J, Zheng XG, Shimuzu Y, Thompson C, et al. Accessory cell function of keratinocytes for superantigens: dependence on lymphocyte function-associated antigen-1/intercellular adhesion molecule-1 interaction. J Immunol 1993;150:2148-59.

Answers to CME examination

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Questions 1-31, Touart DM, Sau P. J Am Acad Dermatol 1998;39:149-71.

1. a
2. c
3. c
4. d
5. b
6. d
7. d
8. e
9. c
10. a
11. e
12. c
13. d
14. a
15. e
16. d
17. b
18. a
19. a
20. c
21. d
22. a
23. a
24. b
25. c
26. b
27. d
28. b
29. a
30. d
31. c