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.

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.5,10,20 Hippocrates, in the 5th century BCE, wrote...
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

Table I. Toxin-mediated streptococcal and staphylococcal diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Toxin(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplastic shock</td>
<td>SPE-A, SPE-B, SPE-C</td>
</tr>
<tr>
<td>Scarlet fever</td>
<td>SSA</td>
</tr>
<tr>
<td>Necrotizing fasciitis</td>
<td>SSA</td>
</tr>
<tr>
<td>Kawasaki disease†</td>
<td>SSA</td>
</tr>
<tr>
<td>Atopic dermatitis†</td>
<td>SSA</td>
</tr>
<tr>
<td>Food poisoning†</td>
<td>SSA</td>
</tr>
</tbody>
</table>

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

Table II. Streptococcal and staphylococcal toxins

<table>
<thead>
<tr>
<th>Organism</th>
<th>Toxin(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A streptococci</td>
<td>SPE-A, SPE-B, SPE-C</td>
</tr>
<tr>
<td>Groups B, C, F, and G streptococci</td>
<td>SSA</td>
</tr>
<tr>
<td>Staphylococci</td>
<td>SSA</td>
</tr>
<tr>
<td>TSST-1</td>
<td>SSA</td>
</tr>
<tr>
<td>SEA, SEB, SEC, SED, SEE, SEG</td>
<td>SSA</td>
</tr>
<tr>
<td>Exfoliative toxin A, B</td>
<td>SSA</td>
</tr>
</tbody>
</table>

SEA, Staphylococcal enterotoxin; SPE, streptococcal pyrogenic exotoxin; SSA, streptococcal superantigen; TSST-1, toxic shock syndrome toxin-1.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{36-40}

**SUPERANTIGENS**

The concept of “superantigens” was first described in 1989 by White et al\textsuperscript{41} and refers to a unique group of proteins manufactured by bacteria and viruses.\textsuperscript{42} Superantigens produce their clinical effects by bypassing certain elements of the usual antigen-mediated immune response sequence.\textsuperscript{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.\textsuperscript{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.\textsuperscript{42,45-52} Whereas conventional antigens require recognition of all 5 elements of the T-cell receptor (V\(\alpha\), J\(\alpha\), V\(\beta\), D\(\beta\), J\(\beta\)), the recognition sequence for superantigens is almost entirely dependent on V\(\beta\) only.\textsuperscript{42,43,48,50,53-56}

Because only a limited amount of V\(\beta\) genes exists,
Route of administration, 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.

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. 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. 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. Currently, the incidence of nonmenstrual TSS exceeds that of menstrual TSS. 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.

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. The eruption of TSS is defined as “diffuse macular erythoderma”; however, a scarlatiniform eruption,

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Fig 3. The superantigen/cytokine cascade.
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.\textsuperscript{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.\textsuperscript{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.

**Fig 4.** A, Perineal erythema. B, Acral desquamation. C, Strawberry tongue. (C, Courtesy William D. James, MD, Philadelphia, Pa.)
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. The mortality rate is approximately 5%, and recurrences have been reported in as many as 30% to 40% of cases.

Both menstrual and nonmenstrual forms of TSS have been linked to toxin-producing strains of *S. aureus*. More than 90% of menstrual TSS is mediated by TSST-1 production, which is associated with massive release of TNF-α and IL-1. These cytokines have been demonstrated to produce fever, rash, hypotension, tissue injury, and shock. 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. 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.

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). 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.

**Streptococcal TSS**

In the late 1980s, a disease similar in appearance to TSS, yet caused by invasive streptococci, was recognized. Also known as “toxic strep” or “streptococcal toxic shock-like syndrome,” streptococcal TSS (STSS) was found to share many clinical features with TSS. In the majority of cases toxin-producing group A streptococci have been isolated, with SPE-A production being most closely linked with invasive disease. 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. Lymphocyte Vβ profiles consistent with superantigen induction have been noted. 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.

Not surprisingly, very young, elderly, diabetic, or immunocompromised persons are more susceptible to the acquisition of invasive streptococcal infection such as STSS. However, the majority of cases of STSS have occurred in young, otherwise healthy persons between 20 and 50 years of age. An absence of protective immunity is postulated as a potential risk factor in this population. STSS has also been well described as a complication of wounds, varicella, and influenza A.

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.

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. 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.

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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. 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. Cutaneous signs may include localized edema and erythema, a bullous and hemorrhagic cellulitis, necrotizing fasciitis or myositis, and gangrene. Soft-tissue involvement of this nature is distinctly uncommon in staphylococcal TSS. STSS may uncommonly occur in the absence of cutaneous involvement; in these cases differentiation from staphylococcal TSS...
becomes more difficult. Blood cultures are positive in more than 50% of patients with STSS, as compared with less than 15% in TSS.\textsuperscript{5,6} In addition, mortality rates are more than 5 times higher in STSS.\textsuperscript{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 some 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.\textsuperscript{5} Intravenous γ-globulin has been reported to be dramatically effective in STSS, but is not yet in widespread use.\textsuperscript{20}

**Recalcitrant, erythematous, desquamating disorder**

In 1992, Cone et al\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{7,84} Treatment of these disorders is similar; antibiotics, fluid replacement, and supportive care are paramount.

In most patients with RED disorder, toxin-producing \textit{S aureus} has been isolated, with sources including skin, sinuses, and blood.\textsuperscript{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.\textsuperscript{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 \textit{Streptococcus pyogenes} organisms isolated from patients with scarlet fever.\textsuperscript{5}

Scarlet fever remains primarily a disease of children, with most cases occurring between the ages of 1 and 10 years.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{18} Recurrence rates of scarlet fever have been reported to be as high as 18%.\textsuperscript{110}

Diagnosis of scarlet fever is usually apparent clinically, but can be further confirmed by sup-
Toxin-mediated erythema (recurrent toxin-mediated perineal erythema)

In 1996, Manders et al\textsuperscript{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.\textsuperscript{17} Culture of the pharynx during the acute episodes reveal toxin-producing \textit{S. aureus} or \textit{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.\textsuperscript{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.\textsuperscript{111-114} Failure to adequately clear the toxin appears to predispose the very young to SSSS, as well as those with renal failure.\textsuperscript{106}

Toxin-producing \textit{S. aureus} can be detected in every case of SSSS, with most isolates belonging to phage group II, types 71 and 55.\textsuperscript{106} In children the infectious focus is usually in the nasopharynx or conjunctivae.\textsuperscript{106} Staphylococcal pneumonia or bacteremia may be present in adults, but the source of infection may be difficult to ascertain.\textsuperscript{111} Exfoliative toxins A and B (ETA and ETB) have been implicated in the pathogenesis of SSSS; however, other factors, such as \(\delta\)-hemolysin, may contribute to the clinical presentation.\textsuperscript{111} Childhood cases of SSSS are primarily associated with solely ETA production; however, occasional isolates produce ETA and ETB, or rarely, ETB alone.\textsuperscript{114} The frequency of the different toxins in adult cases is unclear.\textsuperscript{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 inter-desmosomal splitting.\textsuperscript{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.\textsuperscript{111}

Clinical features of SSSS include fever, irritability, skin tenderness, and scarlatiniform erythema with accentuation in flexural areas.\textsuperscript{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.\textsuperscript{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.\textsuperscript{115}

Necrotizing fasciitis

Necrotizing fasciitis (NF) is a rapidly advancing
soft-tissue infection that is associated with systemic toxicity and a high mortality rate.\textsuperscript{18} Many organisms, including aerobes and anaerobes, may be isolated, often in combination.\textsuperscript{25,118,119} Streptococcal gangrene, or type II NF, is characterized microbiologically by the isolation of group A streptococcus alone or in combination with \textit{S. aureus}.\textsuperscript{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.\textsuperscript{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.\textsuperscript{18,119-121} Clinically NF can affect any body part, but usually involves an extremity.\textsuperscript{121} Localized painful erythema and edema rapidly progress over hours to days, with development of cyanosis, blistering, and necrosis.\textsuperscript{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.\textsuperscript{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.\textsuperscript{118} Rapid streptococcal diagnostic kits, usually utilized for pharyngeal infections, have been recently reported to be effective in identifying \textit{S. pyogenes} from aspirates of infected tissue in NF.\textsuperscript{122}

Treatment includes aggressive surgical debridement, antibiotic therapy, and supportive care.\textsuperscript{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 \textit{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.\textsuperscript{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.\textsuperscript{18,125} Other antibiotic choices for streptococci include cephalosporins or erythromycin.\textsuperscript{118} The mortality rate for NF ranges from 35\% to 40\%; however, prompt intervention lowers the rate to 12\%.\textsuperscript{118}

### Kawasaki disease

Kawasaki disease (KD) is a multisystem illness, primarily occurring in infants and young children.\textsuperscript{42,126} Originally described in Japan, KD is now well recognized worldwide.\textsuperscript{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.\textsuperscript{126,129} KD most commonly presents in winter and early spring.\textsuperscript{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.\textsuperscript{42,131,132}

Clinically, KD is defined by fever of 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

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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.\textsuperscript{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.\textsuperscript{126,129} Histopathologic examination reveals a necrotizing vasculitis, especially of medium-sized arteries such as the coronary arteries.\textsuperscript{132,136,137} These pathologic findings are usually not evident on skin biopsy.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{126,139}

Intravenous \(\gamma\)-globulin is the cornerstone of therapy for KD and may be given either as a 4-day regimen or as a single, larger dose.\textsuperscript{140,141} Antiplatelet therapy with aspirin is recommended, with dipyridamole as an alternative agent for patients unable to take aspirin.\textsuperscript{126} Angioplasty, thrombolytic therapy, or even coronary artery bypass surgery may be required for patients with severe coronary involvement.\textsuperscript{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.\textsuperscript{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.\textsuperscript{126} Nonetheless, a specific microbial cause has been elusive.

Increasing evidence suggests that KD may be a toxin-mediated, superantigen-driven disease.\textsuperscript{42,132,142} Leung et al\textsuperscript{142} isolated toxin-producing bacteria (primarily \(S\)\textit{aureus}, less frequently \(S\)\textit{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 \(S\)\textit{aureus} were white and were therefore easily missed for coagulase-negative staphylococci (which may account for the failure to isolate \(S\)\textit{aureus} in previous studies).\textsuperscript{142} The primary toxin elaborated was TSST-1, with the streptococcal isolates producing SPE-B and SPE-C.\textsuperscript{142-145} In support of a superantigen-mediated process, marked expansion of the T-cell population bearing \(V\beta^{2+}\) and \(V\beta^{8.1+}\) was observed in acute, but not convalescent, blood samples of patients with KD.\textsuperscript{143} Although this latter study has been confirmed by others,\textsuperscript{146} it has not been uniformly accepted.\textsuperscript{147} Advocates of a superantigen-mediated pathophysiology have postulated that the efficacy of \(\gamma\)-globulin in the treatment of KD is due to antibodies that inhibit the activation of T cells by staphylococcal or streptococcal superantigens.\textsuperscript{148}

\textbf{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.\textsuperscript{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.\textsuperscript{42,150,151}

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The potential association of guttate psoriasis with a preceding streptococcal infection has been recognized for decades.\textsuperscript{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.\textsuperscript{154,155} In addition, \(T\) lymphocytes from patients with psoriasis have been demonstrated to have enhanced proliferative responses to group A streptococcal antigens.\textsuperscript{156}

Selective expansion of \(V\beta^{2+}\) T cells in the lesional and perilesional skin of patients with guttate psoriasis has been demonstrated.\textsuperscript{150,157} This was shown to be a localized phenomenon because there was no concurrent clonal expansion of T cells in the peripheral blood.\textsuperscript{157} All streptococcal isolates
from patients with guttate psoriasis produced SPE-C, a toxin which has been associated with the selective expansion of Vβ2+ 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 Vβ2+ T cells bearing CLA in local lymph nodes. This is followed by localization of these Vβ2+/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


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