10

Scarlet Fever, Toxic Shock Syndrome, and the Return of Severe, Invasive Streptococcal Disease

Streptococcus pyogenes and *Staphylococcus aureus* are common causes of bacterial infections in humans. Some of the characteristics of these gram-positive pathogens and examples of diseases caused by them are listed in Table 10-1. *Streptococcus* strains are grouped on the basis of carbohydrate surface antigens (**C antigens**). *S. pyogenes* strains comprise group A. Accordingly, *S. pyogenes* is frequently called **group A streptococcus (GAS)**. Before the introduction of antibiotics, *S. pyogenes* and *S. aureus* were major causes of death in people of all ages. After the advent of antibiotics, diseases caused by both of these species declined in incidence and severity. This trend continued until the late 1970s when *S. aureus* suddenly appeared as the cause of a new disease, toxic shock syndrome (TSS). Then, in the 1980s, *S. pyogenes* gave notice that it, too, was capable of reemerging as a cause of severe invasive disease. Disease caused by the new invasive *S. pyogenes* strains often resembled TSS. These two diseases proved to be linked in an unexpected way to each other and to a virtually extinct disease caused by *S. pyogenes*, scarlet fever: All three proved to be associated with the same type of exotoxin.

Fluctuating Fortunes of Scarlet Fever and TSS

Scarlet fever is a childhood disease characterized by a diffuse rash and fever. As with diphtheria, scarlet fever is seen primarily in children because most adults have

Table 10-1 Comparison of characteristics of *S. aureus* and *S. pyogenes* and diseases they cause.

Characteristic	*S. aureus*	*S. pyogenes*
Staining reaction	Gram positive, grow in clusters	Gram positive, grow in chains
Colony morphology	Large, often yellow, colonies; β-hemolytic	Small white colonies; β-hemolytic
Biochemical differentiation	Catalase positive	Catalase negative
Growth requirements	Hardy, not fastidious	Nutritionally fastidious
Source	Resident microflora of nose, vagina, colon	Carriers, upper respiratory tract
Diseases	Food-borne disease	Pharyngitis (rheumatic fever, kidney failure)
	Soft tissue infections	Boils, skin abscesses
	Impetigo	Impetigo
	TSS	Scarlet fever
	Septicemia	Septicemia
	Pneumonia	
	Osteomyelitis	

become immune as a result of exposure earlier in life. Scarlet fever is spread by aerosols from infected people or asymptomatic carriers. Humans are the only known reservoir. Scarlet fever had been a common disease for many years, but during the 1800s outbreaks of a particularly virulent form of scarlet fever occurred in England and Europe. The death rate was unusually high, and whole families were decimated. One particularly memorable case involved a well-to-do family with six children. One by one the children died of scarlet fever until only one child was left. In desperation, the parents abandoned their home and sent the child to live elsewhere in an attempt to save it. At that time, antisepsis with carbolic acid was just coming into vogue, and the parents had their house "sterilized" with carbolic acid in the hope that this would prevent further infection. Shortly after they and the child returned to the house, the child developed scarlet fever and died. Probably one of the servants, or perhaps even one of the parents, was an asymptomatic carrier of the strain responsible for the disease. From the early 1900s to around 1950, a much milder form of scarlet fever predominated, and the virulent form was not seen again. Scarlet fever soon came to be considered a normal childhood disease, like chickenpox, which was unpleasant but not particularly dangerous. Then, in the 1950s, scarlet fever virtually disappeared. This abrupt disappearance may have resulted from widespread use of penicillin to treat sore throats in children (another disease caused by *S. pyogenes*). On the whole, the virulent form of scarlet fever seemed to have run its course and to have sunk into a well-deserved obscurity.

In 1978, a new disease called TSS made its debut. TSS was caused by certain strains of *S. aureus* that produced an exotoxin called **toxic shock syndrome toxin (TSST-1)**. TSS was a serious disease that could cause a condition resembling septic shock. Some of the symptoms of TSS (fever, diffuse rash, and exfoliation of skin from the palms and soles of the feet) bore a superficial resemblance to those of scarlet fever, but there was no apparent reason to connect the two diseases at first. Unlike scarlet fever, which occurred in children of both sexes and rarely in adults, TSS was seen almost exclusively in women aged 20 to 40 years. Eventually the cause of TSS was traced to the use of certain types of super-absorbent tampons that did not have to be removed and discarded as often as standard tampons. Normally *S. aureus* is only a minor component of the vaginal microflora because it cannot compete with the major populations of vaginal bacteria such as lactobacilli for colonization sites. The super-absorbent tampons created a new niche that *S. aureus* was able to colonize. Production of TSST-1 occurs maximally under aerobic conditions. The vaginal tract is relatively anaerobic, but a tampon containing many pockets of trapped air would provide some oxygen and would thus allow toxin production to occur. TSST-1 produced by bacteria growing in the tampon entered the bloodstream and caused the symptoms of TSS (Figure 10-1).

The TSS problem appeared to have been solved when the offending tampons were removed from the market. An immediate decline in cases ensued, but the disease did not disappear altogether. Some cases of TSS continued to occur in people with wound infections caused by *S. aureus*, although such cases were uncommon, and the disease seemed to be disappearing. Interestingly, some of these later cases of TSS occurred in people having nasal surgery. One of the preferred colonization sites for *S. aureus* is the nose, and infections arising from contamination of surgical wounds by *S. aureus* produced a nidus of infection where toxin production could occur. Once again, human activities created an opportunity for disease-causing bacteria to exploit.

Just as TSS was fading into oblivion, outbreaks of a disease with symptoms remarkably similar to TSS began to be reported. Yet these cases did not involve tam-

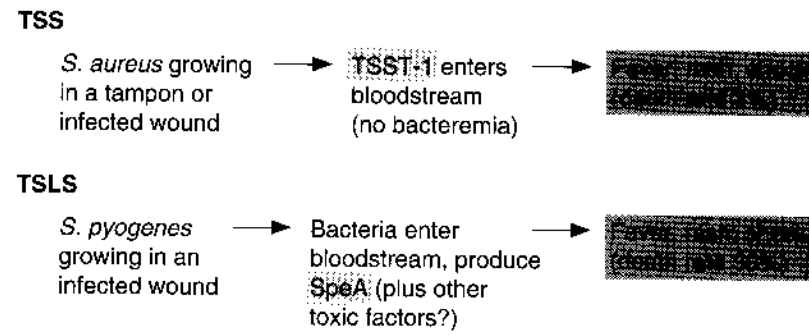

Figure 10-1 Comparison of TSS caused by *S. aureus* and TSLS caused by *S. pyogenes*.

pon use, nor were they caused by *S. aureus*. Rather, they were usually associated with *S. pyogenes* infections, which frequently began as a skin or wound infection and developed into bloodstream infections (see Figure 10-1). Because of the resemblance of the symptoms to those of staphylococcal TSS, the disease caused by *S. pyogenes* strains was called **toxic shock–like syndrome (TSLS)**. The death rate in cases of TSLS was over 30% in some hospitals, about tenfold higher than that for TSS. Part of the reason for the higher mortality was that the disease was frequently seen in people with underlying conditions that weakened the immune system (e.g., alcoholism and diabetes), but many victims of the disease were otherwise healthy adults. At the same time, there was an increase in cases of invasive *S. pyogenes* infections other than the ones that resembled TSS. These cases, too, had a high fatality rate because of rapid development of shock and multiple organ system failure that accompanied the infections (see box). Although this new form of *S. pyogenes* disease is probably not the same disease as the virulent form of scarlet fever seen in the 1800s, the two diseases have features in common. They can occur in otherwise healthy people, and both were associated with a high fatality rate. There is another connection between the new invasive *S. pyogenes* strains and scarlet fever strains: They produce essentially the same exotoxin, a toxin called **streptococcal pyrogenic exotoxin (Spe)**. Spe has also proved to be similar in mechanism to TSST-1.

Virulence Factors

Studying Virulence of *S. aureus* and *S. pyogenes*

Until recently, the study of virulence mechanisms of gram-positive cocci relied primarily on biochemical and immunological analysis because genetic tools were not available. The recent development of methods for making directed insertional mutations, constructing transcriptional fusions, mapping by phage transduction, and transposon mutagenesis has opened up the field to modern genetic analysis. This means that putative virulence factors can now be tested for their importance in infection by constructing mutant strains that no longer produce them and testing the effect of the mutation in an animal model. Previously all that could be done was to demonstrate that a particular trait was associated with most virulent strains, to show that antibodies against a bacterial component were protective, or to characterize spontaneous mutants that could have more than one genetic alteration. These approaches led to the mistaken hypothesis that an *S. pyogenes* surface protein (**M protein**) and lipoteichoic acid formed an adhesin that allowed the bacteria to adhere to fibronectin. The new genetic tools have now allowed this long-standing hypothesis to be rejected and have also led to the discovery and characterization of some important new virulence factors. Research on virulence properties of gram-positive cocci has become one of the hottest new areas in the study of molecular pathogenesis.

Rabbits are used as an animal model for the study of TSS. Bacteria are injected into a plastic chamber implanted in the back of the rabbit. Rabbits develop a disease that is similar to human TSS. Toxin can also be injected into the animal's bloodstream or tissue. Mice are used to study soft tissue and systemic infections caused by *S. aureus* and *S. pyogenes*. Cultured cells and organ cultures are beginning to be used to study adherence of the bacteria to host cells, but this type of study is not nearly so far advanced as in the case of some other bacterial pathogens (see Chapters 12 to 19).

Exotoxins: TSST-1 and Streptococcal Pyrogenic Exotoxin A

Except for the rash that usually accompanies TSS and TSLS, the main symptoms of TSS and TSLS (fever, shock, and multiple organ failure) are virtually indistinguishable from those of septic shock caused by

The New Invasive Form of *S. pyogenes* Disease: An Outbreak in Ontario, Canada, 1987 to 1991*

The first case of severe invasive *S. pyogenes* infection in Ontario was seen in early 1987. Then a few sporadic cases occurred in 1988 and 1989, followed by a sizeable increase in the number of cases in 1990 to 1991. A total of 50 cases occurred during the 1987 to 1991 period. In part, the increase in identified cases could have resulted from an increased awareness of the disease, but there seems to have been a real increase in incidence of the disease in 1990 to 1991 compared with previous years. The 50 cases were evenly divided between men and women. The median age was 40 to 50 years, although patients ranged in age from 4 to 100 years. In all cases, *S. pyogenes* was isolated from blood or body fluids, and symptoms of shock were evident. *S. pyogenes* is an occasional cause of hospital-acquired infections, but only a fraction of the patients appeared to have acquired the infection in the hospital. Nor were most patients severely immune compromised. Half of them had no known underlying conditions that would compromise host defenses, and only a few had severe underlying conditions such as AIDS. The disease thus appears capable of striking otherwise healthy adults and can be community acquired. Most of the patients (38) had some visible focus of infection when admitted to the hospital, usually a soft tissue infection, but 12 had no sign of prior infection, and only one third of the patients recalled an injury (scratch, wound, fall) that could have precipitated the infection. Of the people who recalled an injury, only one thought the injury serious enough to seek immediate medical attention. Thus, for most of the patients, there were no early warning signs of the disease. In cases where the injury was recalled, the time from injury to development of hypotension was less than 1 week. In patients who had an identifiable focus of initial infection, such as a soft tissue infection, an unusual degree of pain at the site of infection was the most frequent symptom that distinguished these infections from ordinary wound infections. Some patients complained of an influenza-like illness several days prior to hospitalization. Nearly half of the patients died, some within 1 day of admission to the hospital. The high fatality rate may have been due to the fact that the lack of clear early symptoms allowed the disease to be identified only after it had progressed to the point where shock had already begun. Outbreaks of a similar invasive, often fatal, form of *S. pyogenes* infection have also been reported during the past several years in the United States and Europe.

*Adapted from B. Demers, A. E. Simor, H. Vellend, P. M. Schlievert, S. Byrne, F. Jamieson, S. Walmsley, and D. E. Low. 1993. Severe invasive group A streptococcal infections in Ontario, Canada: 1987–1991. Clin. Infect. Dis. 16:792–800.

gram-negative bacteria. In gram-negative septic shock, LPS circulating in blood is responsible for the fever, circulatory collapse, and multiple organ system failure (see Chapter 4). In TSS and TSLS, the symptoms appear to be caused by protein exotoxins. TSST-1, the toxin associated with TSS, proved to be a superantigen (see Chapter 4 for characteristics of superantigens). Subsequently, the type of toxin produced by the *S. pyogenes* strains responsible for TSLS and other forms of severe invasive *S. pyogenes* disease also proved to be a superantigen. Although the two toxins have the same mechanism of action, they have only limited similarity at the amino acid sequence level. Instead, the toxin thought to be responsible for TSLS is most closely related to the toxin previously associated with scarlet fever, a toxin originally called **erythrogenic toxin** but now designated **Spe**. Three serotypes of Spe have been described: SpeA, SpeB, and SpeC. In many of the outbreaks of TSLS or other invasive *S. pyogenes* disease, virtually all of the strains produced SpeA, whereas *S. pyogenes* strains producing less serious diseases did not. This led to the suggestion that SpeA was responsible for the unusual virulence of the TSLS strains. However, some studies have found that SpeA is not

produced by all isolates associated with the most serious form of disease, so the possibility remains that either SpeA is not the main virulence factor in this disease or that SpeB and SpeC can also contribute.

How do TSST-1 and Spe cause shock and multiple organ system failure? There are three hypotheses, which are not mutually exclusive. The first is that TSST-1 and Spe cause shock the same way LPS does, by triggering release of cytokines such as IL-1 and TNFα. Superantigens act by forcing an association between macrophages and helper T cells that results in proliferation of the T cells and production of high levels of IL-2. A secondary effect appears to be increased production of IL-1 and TNFα. Injection of TSST-1 into animals causes elevated levels of TNFα and IL-1. A second hypothesis is that TSST-1, and possibly Spe as well, exerts its effects by increasing the body's sensitivity to LPS. TSST-1 acts synergistically with LPS to amplify the toxic effects of LPS, both in in vitro assays and in animal experiments. It is conceivable that low levels of LPS are constantly leaching into the bloodstream because of lysis of members of the resident microflora or antigen sampling by the MALT. Normally these low levels of circulating LPS have no observable effect, but in the presence of Spe or TSST-1, low levels of LPS could exert toxic effects. In the case of TSLS, the circulating gram-positive cell wall fragments could also contribute to shock because the streptococcal form of the disease generally arises in connection with *S. pyogenes* bacteremia. Nothing is known about whether TSST-1 or Spe acts synergistically with gram-positive cell wall components to cause shock.

There is some evidence to support a role for LPS in TSS and TSLS. Injection of TSST-1 or Spe was lethal for rabbits, but injection of **exfoliatin** (another exotoxin of *S. aureus*) or concanavalin A was not. Both exfoliatin and concanavalin A elicit T cell proliferation, as do TSST-1 and Spe, but they do not share the ability of these superantigens to enhance sensitivity of animals to LPS. Also, TSST-1 was not lethal in gnotobiotic piglets or specific pathogen–free rabbits, animals in which leakage of LPS into the bloodstream would be minimized but the T cell proliferation response to TSST-1 would still occur. Although these experimental results suggest that T cell proliferation caused by TSST-1 and Spe may not be as important as synergy with LPS, they are not conclusive because it is difficult to be sure that exactly the same level of T cell stimulation and proliferation occurred in all cases. Thus, the question of whether the symptoms of TSS and TSLS are caused entirely by TSST-1 and Spe, respectively, or by some synergistic action of these toxins with other toxic bacterial components remains to be resolved.

A third hypothesis about toxic effects of TSST-1 and Spe is suggested by a report that TSST-1 can act directly on endothelial cells. Damage to endothelial cells would contribute to malfunction of the circulatory system and to the development of hypotension. Swelling associated with massive leakage of fluid from capillaries is a marked symptom of both TSS and TSLS, although this could equally be the result of action on blood vessels by cytokines, coagulation, or complement cascade components.

S. pyogenes Versus the Host's Defenses

The mortality rate of TSLS is much higher than that of TSS. One explanation for this difference is that *S. pyogenes* strains associated with TSLS enter the bloodstream, whereas in TSS only the toxin circulates in blood. *S. pyogenes* is well known for its ability to cause invasive, systemic disease, a property that is due primarily to its extraordinary skill in evading the host's immune system. *S. pyogenes* is readily killed by macrophages and PMNs if it is ingested. Virulent strains survive in blood because they have developed a number of strategies for evading phagocytosis. Perhaps the most important of these is an antiphagocytic bacterial surface protein, M protein. M protein is anchored in the bacterial cell wall by its carboxy terminus, and its amino terminus extends outward from the bacterial cell. M protein and some similar cell surface proteins are probably responsible for the fuzz of fibrillar structures that covers virulent *S. pyogenes* strains (Figure 10-2). M protein is antiphagocytic because it binds factor H more avidly than factor B, leading to degradation of C3b. Thus, it prevents opsonization of the bacteria by C3b and formation of C3 convertase. Mutants lacking M protein have been shown to be more susceptible to phagocytosis and less virulent than wild type. Antibody to M protein is protective against *S. pyogenes* infections. There are about 80 serotypes of M protein. This raises the possibility that the bacteria could escape the opsonizing effect of host antibodies against M protein by changing the serotype of M protein produced, but this possibility remains speculative.

S. pyogenes produces an unusual protease that cleaves C5a. C5a is the activated complement component that attracts phagocytes to an area where bacteria have invaded and stimulates their oxidative burst response (see Chapter 2). Some activation of complement could occur in spite of the protective effects of M protein because bacterial lysis releases teichoic acid or other bacterial surface components that can activate complement. Streptococci could protect themselves from complement activation by using **C5a peptidase** to reduce the amount of C5a leaving the area. C5a protease, like M protein, appears to be important for survival of *S. pyogenes* in tissue and blood because mu-

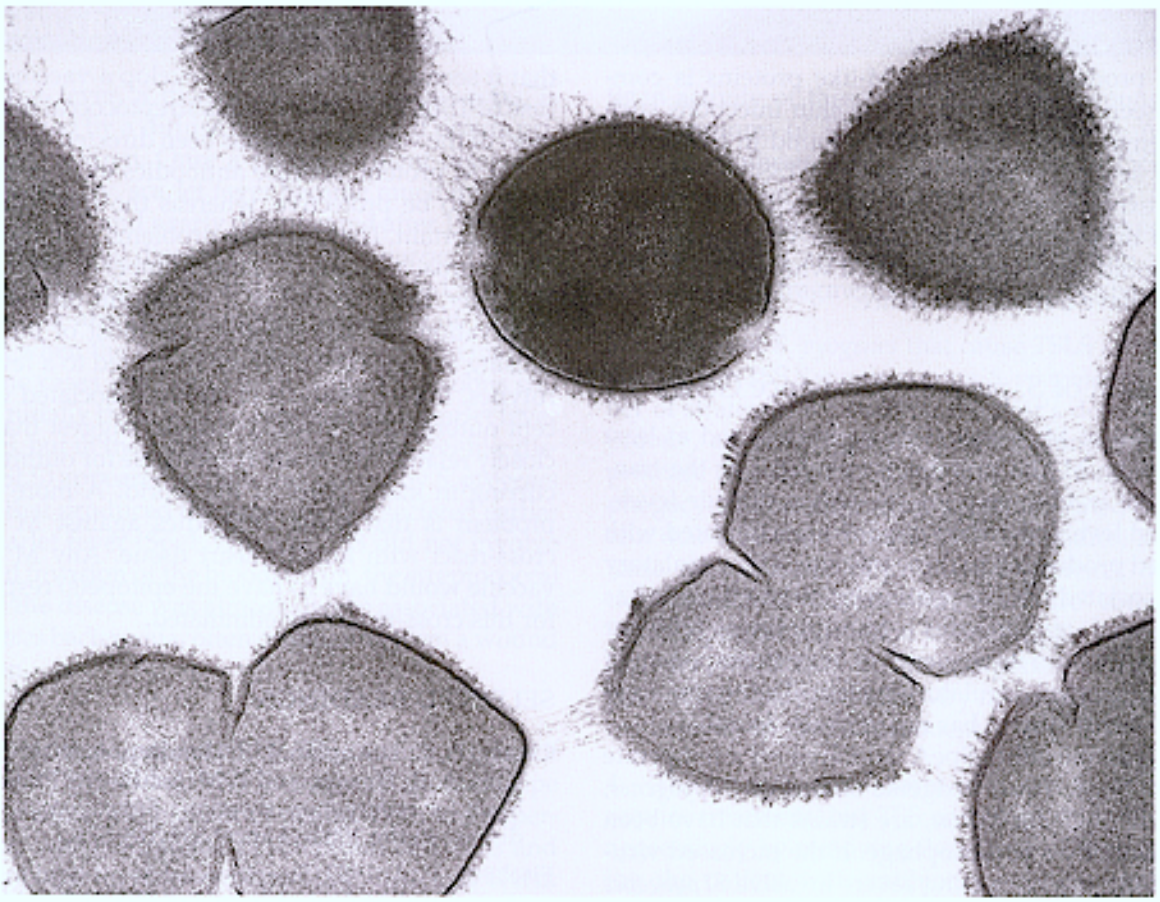

Figure 10-2 Electron micrograph of ultrathin sections of group A streptococci exhibiting M protein fibrils on the cell surface. Junctions between streptococci reveal M protein fibers from one coccus interacting with those from the adjoining organism. Magnification, × 56,000. (Reprinted from V. A. Fischetti. 1989. Streptococcal M protein: molecular design and biological behavior. Clin. Microbiol. Rev. 2:285–314.)

tants that do not produce C5a protease are less virulent than the wild type in animals.

S. pyogenes strains produce a number of surface proteins, called **M-like proteins**, that have some sequence and structural similarity to M protein. As in the case of M protein itself, the M-like proteins are embedded in the bacterial cell wall via their carboxy termini, with their amino terminal ends exposed on the bacterial surface. The M-like proteins are most similar to each other and to M protein in their carboxy terminal ends. Whereas M protein binds factor H, these other proteins bind the Fc portions of IgG and IgA. That is, the streptococcal proteins attach nonspecifically to antibodies not directed against their own surfaces (Table 10-2). One role of this activity could be to coat the bacteria with a layer of host proteins and thus make them less likely to be recognized as an invader by complement and the immune system. Another possible role of these proteins is adherence to body cells that contain antibody molecules on their surfaces. An interesting property of some M-like proteins is their ability to bind host protease inhibitors, such as α_2-macroglobulin. The host uses these protease inhibitors to protect tissues from proteases, such as those released by phagocytes. The protease inhibitors may also protect the bacterial surface from host proteases. A surface protein called **F** binds fibronectin, a common host cell protein. This activity could contribute both to adherence of bacteria to host tissues and to evasion of the immune system. So

Table 10-2 Examples of M-like surface proteins of *S. pyogenes*.

Surface protein	Size (kDa)	Binds to
Arp4	43.8	Fc portion of IgG, IgA
SpH	42.5	Fc portion of IgG; α_2-macroglobulin
FcRA76	44.3	Fc portion of IgG; fibrinogen

far, there is little direct evidence that M-like proteins make a significant contribution to virulence. Also, although production of these M-like proteins is commonly seen in strains that cause skin infections such as impetigo, they are not always found in the strains causing severe invasive disease and TSS-like disease. Future experiments in which mutants lacking one or more of these proteins are tested for virulence in animals should settle the question of whether the M-like proteins have a role in virulence.

Regulation of *S. pyogenes* Virulence Genes

Expression of M protein, C5a peptidase, and at least some of the M-like proteins is regulated at the transcriptional level in response to carbon dioxide levels. Increased levels of carbon dioxide are associated with increased production of these proteins. One regulatory gene associated with regulation by carbon dioxide has been located. *mry* encodes a transcriptional activator that appears from its sequence to be one component of a two-component regulatory system. The sensor component of this system has not yet been found.

The gene encoding SpeA is located on a temperate bacteriophage. Thus, toxigenic strains of *S. pyogenes*, like those of *C. diphtheriae*, are strains that have been lysogenized by a bacteriophage. If the increased virulence of the strains causing severe invasive *S. pyogenes* disease is due to a special form of SpeA, the possibility exists that the gene could be transmitted to less virulent strains. There is some evidence from sequence analysis of different SpeA-producing strains of *S. pyogenes* that such horizontal transfer of *speA* between strains of *S. pyogenes* has occurred.

Treatment and Prevention

The milder, modern form of scarlet fever is self-limiting and usually does not require treatment. By contrast, TSS, TSLS, and other severe invasive *S. pyogenes* infections are medical emergencies that must be treated very aggressively. The focus of bacterial infection must be removed immediately if it can be found (e.g., surgical debridement of infected wounds) to prevent further production of toxin. Antibiotic therapy is also important, particularly in the case of *S. pyogenes* infections where the bacteria are in the bloodstream. Fortunately, *S. pyogenes* remains susceptible to penicillin and a number of other antibiotics. In cases of TSS, antibiotics help to clear the bacterial colonization of the vagina or infected wound. The toxic effects of TSST-1 are countered by providing supportive therapy (e.g., intravenous rehydration to counter the effects of hypotension). If TSST-1 and Spe are, in fact, responsible for the symptoms of TSS and TSLS, it should be possible to design an effective vaccine. TSS is now so rare that it seems unnecessary to develop a vaccine. In the case of TSLS and other serious streptococcal infections, most of the vaccine effort has been directed not at SpeA but at M protein, because antibodies to M protein are known to be protective, whereas the role of SpeA is still uncertain. There are two problems with the M protein approach. One is the large number of M serotypes. However, this may not be a significant problem since observations to date suggest that most of the strains causing serious infections are restricted to a few M serotypes. In fact, analysis of strains associated with recent outbreaks of invasive disease suggest that a few closely related strains are responsible for outbreaks occurring in many parts of the world. A more serious problem is that some antibodies against M protein cross-react with human heart tissue. Any M protein vaccine would have to have the epitope(s) responsible for this cross-reactivity eliminated.

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SUMMARY

1. Scarlet fever, a disease caused by *S. pyogenes*, is characterized by a diffuse rash and fever. It occurs primarily in children. Once a highly virulent disease in the 19th century, scarlet fever became much milder in the early 1900s and nearly disappeared after 1960. TSS, a potentially fatal disease caused by *S. aureus*, first appeared in the late 1970s and was associated with the use of super-absorbent tampons. Incidence of TSS decreased when the tampons were taken off the market, but some cases associated with wound infections still occur. Initially there was no reason to link scarlet fever and TSS, but in the 1980s a high-mortality TSS-like disease (TSLS) appeared, which was caused by *S. pyogenes* strains that produced the same toxin associated earlier with scarlet fever (Spe). Whereas TSS did not involve bacterial invasion of the bloodstream, the streptococcal form of the disease was almost always associated with *S. pyogenes* bacteremia, often originating from a wound infection.

2. The exotoxin produced by TSS-causing strains of *S. aureus* (TSST-1) and the *S. pyogenes* exotoxin Spe have the same mechanism of action. Both are superantigens, which stimulate proliferation of T cells and release of high levels of cytokines IL-2, IL-1, and TNFα. There is some controversy as to whether the superantigen activity of these toxins is solely responsible for the symptoms of TSS and TSS-like disease. An alternative hypothesis arises from the ability of TSST-1 and Spe to enhance the activities of LPS. TSST-1 and Spe could be exerting their toxic effects by enhancing the ability of small amounts of circulating LPS or other toxic cell wall fragments to trigger septic shock.

3. Strains of *S. pyogenes* that cause TSLS are more invasive than TSS *S. aureus* strains. *S. pyogenes* has a number of strategies for evading the host's defenses: (i) M protein, an antiphagocytic surface component; (ii) a protease that cleaves C5a so that it no longer attracts phagocytes; and (iii) surface proteins related to M protein that bind the Fc portions of antibodies, host protease inhibitors, or other plasma proteins. Many of these virulence factors and SpeA are coregulated. Transcriptional regulation is due in part to an activator, Mry, which may be one component of a two-component regulatory system. Mry responds to carbon dioxide levels in the environment.

4. The modern (mild) form of scarlet fever does not require treatment, but TSS and TSLS must be treated aggressively by removing the source of bacteria, treating the patient with antibiotics, and providing supportive therapy.

QUESTIONS

1. Compare and contrast diphtheria, TSS, and TSLS.

2. Provide three possible explanations for the fact that some *S. pyogenes* strains that produce SpeA cause a mild form of scarlet fever, whereas other SpeA-producing *S. pyogenes* strains cause serious disease such as TSLS.

3. The tampons that were associated with the TSS cases of the 1980s have been taken off the market. Why are there still cases of TSS?

4. What is the evidence that TSST-1 or Spe alone is not responsible for the symptoms of TSS and TSLS? What is the alternative hypothesis? Could both be correct?

5. What are the difficulties involved in demonstrating that synergistic action of TSST-1 and LPS are responsible for the symptoms, not the superantigen activity of TSST-1?

6. If there is synergism between TSST-1 and LPS, would this create difficulties for an attempt to demonstrate the molecular version of Koch's postulates for TSST-1?

7. The sequences of TSST-1 and Spe are not similar to each other, yet they apparently cause the same type of disease. Assuming that Spe is the actual cause of the symptoms of TSLS, how do you explain this?

8. Explain how *S. pyogenes* evades the host defenses of tissue and blood.

9. How would you prove (or disprove) the importance of M-like proteins for virulence of *S. pyogenes*?