Clinical Relevance of Streptococcal Pyrogenic Exotoxins in Streptococcal Toxic Shock-Like Syndrome and Other Severe Invasive Infections

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The reemergence of Streptococcus pyogenes (group A Streptococcus) as a cause of serious infections in the 1980s has been a striking reminder that medical science knows little about the forces, molecular or otherwise, driving temporal variation in bacterial disease frequency and severity. The rapidity with which S. pyogenes has moved from an "endangered species" to an organism that we once again seek to push to extinction has affected virtually all medical specialties, including pediatrics, gerontology, and surgery. The death of the puppeteer Jim Henson in May 1990 highlighted that no one is isolated from the apparent randomness of severe S. pyogenes infection and illustrated several important features of the bacteriologic epidemiology in contemporary invasive streptococcal disease. First, most patients had been previously healthy, with no known underlying immunologic dysfunction. Second, the disease course can be fulmi-

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gence of Acute Rheumatic Fever in the United States, in this issue (pp 816-820). Those readers who desire more in-depth information about contemporary severe streptococcal infections should consult several recent reviews.1,6,11

IDENTIFICATION OF THE PROBLEM AND DEFINITIONS

Substantial morbidity and mortality were caused by invasive S pyogenes infections in the first half of this century in the United States, Europe, and elsewhere.19 However, since the late 1940s, the frequency of occurrence of these infections decreased, a trend presumed to be due in part to the introduction and widespread use of penicillin.20,21 In 1987, Gaworowsk and Colman1 noted that the frequency of recovery of type 1 and type 28 streptococci from invasive infections increased substantially in the United Kingdom in the early to mid-1980s. Their observation was rapidly followed by several case reports from European and American investigators, who described additional patients with severe, often fulminant and frequently fatal S pyogenes septic episodes.22-26 The report by Stevens et al27 in 1989 of 20 patients with severe invasive disease living in the Rocky Mountain region brought resurgent invasive streptococcal disease to the widespread attention of the medical community.

It is important to realize that unlike staphylococcal toxic shock syndrome,27 to date, no formal case definition of the disease referred to as "toxic shock-like syndrome," "toxic strep syndrome," and other names23,24 has been formulated by the Centers for Disease Control (CDC). Several investigators have summarized signs and symptoms characteristic of groups of patients in the United States and Europe, including children.23,11,20-35 As a working definition of toxic shock-like syndrome used mainly for purposes of patient classification, we routinely employ the CDC's definition for staphylococcal toxic shock syndrome,27 with the modification that the infecting strain of S pyogenes must be recovered from a normally sterile site.13 We use the term severe invasive disease to define a clinical entity characterized by recovery of the organism from a normally sterile site in a patient who fails to satisfy the toxic shock-like syndrome case definition.13 We accept that there are several limitations to these definitions. Although the requirement for bacteria recovery from a sterile source will encom-

pass virtually all patients, it is important to realize that toxic shock-like syndrome has been reported in individuals who apparently were only pharyngeal carriers.36,37 In addition, the disease has been recorded in association with use of catenial products.38

ROLE OF TOXINS: BACKGROUND

It is well known that isolates of S pyogenes synthesize many extracellular molecules.5,39 Many of these products are thought to be causally involved in pathogenesis and are therefore called "virulence factors." M protein, a fibrillar molecular displayed on the outer cell surface, and hyaluronic acid, the group-specific capsular material, are the two virulence factors remembered by most clinicians because both are antipagocytic.40,41 M protein is highly variable among group A streptococci and is the antigen that serves as the basis for a serotyping scheme commonly employed to categorize isolates in epidemiologic studies. There are apparently more than 80 serologic variants circulating in natural populations.40 Additional putative virulence factors include streptolysin O, DNase, streptokinase, opacity factor, C5a peptidase, and several other proteins that share structural similarity to M protein.42 Streptococcus pyogenes strains also synthesize three extracellular protein toxins that have the ability to induce fever in humans and experimental animals and are therefore called pyrogenic or erythrogenic exotoxins.43,44 One or more of these three toxins is undoubtedly a major virulence factor in many contemporary episodes of severe invasive disease and toxic shock-like syndrome.

STREPTOCOCCAL PYROGENIC EXOTOXINS

Streptococcal pyrogenic exotoxin A (SPE A) is also called erythrogenic exotoxin A, blastogen, a, exotoxin A, or scarlet fever toxin—all are apparently the same molecule.43,44 Streptococcal pyrogenic exotoxin A is the toxin initially characterized by Dick and Dick in their landmark studies of scarlet fever conducted in the 1920s.45,47 The molecule is synthesized as a 251 amino acid precursor, and cleavage of a 30-amino acid "signal peptide" from the amino terminus results in a mature extracellular form of 221 amino acids.43 Like several bacterial toxins, the structural gene is associated with a virus that infects bacterial cells. The gene has been cloned and sequenced and shown to be present only in certain strains of S pyogenes.13,46 Most strains that have the gene express the toxin in relatively small amounts.

Streptococcal pyrogenic exotoxin C (SPE C) was first characterized in the 1970s. The precursor and mature toxin are similar in size to SPE A, and the structural gene also is associated with a bacterial virus. Like speA, the gene encoding SPE C (speC) is variably present among S pyogenes strains.13,49

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The disease course of S pyogenes infection can be fulminant and is frequently characterized by tissue destruction (eg, cellulitis, myositis, and necrotizing fasciitis) that can be massive.

regard. Finally, in two separate mouse models of serious streptococcal disease, organisms expressing SPE A were more virulent than isolates of the same clone expressing SPE B, SPE C, or no exotoxin. Taken together, the data strongly indicate that SPE A is causally involved in some episodes of severe invasive disease or toxic shock-like syndrome.

There is also evidence that SPE B is involved in the pathogenesis of severe invasive disease or toxic shock-like syndrome. First, purified streptococcal cysteine proteinase has the potential to cause several pathologic changes. Elliott showed that in addition to cleaving streptococcal M protein, the proteinase can inhibit fibrin clot formation. Moreover, purified proteinase injected into experimental animals produces myocardial necrosis and death. Second, as noted above, all isolates of S pyogenes have the speB gene. Third, Holm et al have recently demonstrated that among patients with recent invasive infections in Sweden, there was a statistical association between lack of antibody to SPE B and more severe disease course.

POSTULATED MECHANISM OF EXOTOXIN INVOLVEMENT

If, as the cumulative evidence indicates, SPE A, SPE B, or SPE C are causally involved in many toxic shock-like syndrome cases, it is important to understand the relative contributions of these toxins to each phase of pathogenesis, from colonization to invasion to death. The observation that a genetically heterogeneous array of more than 30 distinct streptococcal strains (clones) expressing many different combinations of pyrogenic exotoxins has been recovered from contemporary invasive disease episodes strongly suggests that multiple pathogenic mechanisms are involved in toxic shock-like syndrome. This situation contrasts dramatically with Bordetella pertussis, in which virtually all pertussis cases on a global scale are caused by a single bacterial clone that probably had relatively recent evolutionary origin.

It is possible that SPE A and SPE C contribute to pathogenesis in a manner that is fundamentally different than SPE B. As noted above, SPE A and SPE C are members of a class of molecules called...
Strains recovered from patients with severe invasive disease or suspected toxic shock-like syndrome should be analyzed for toxin genes.

Superantigens that have the ability to powerfully stimulate T-cell mitogenesis. It is thought that superantigens trigger production of the cytokines tumor necrosis factor-alpha (TNF-α) and interleukin-B (IL-1B), a process which in turn results in shock. Evidence has been presented that is consistent with aspects of this hypothesis. The exact role of SPE B in severe invasive disease and toxic shock-like syndrome is less clear. Initially it was thought that SPE B, like SPE A and SPE C, is a superantigen, and it was therefore presumed that SPE B also acted through a TNF-α/IL-1B pathway. However, it has been suggested that SPE B is not a superantigen. On the presumption that SPE B produced by some or all S pyogenes strains has protease activity, it does not seem unreasonable to suggest that the molecule exerts direct toxicity to the host; several observations are consistent with this idea. First, the extensive tissue destruction (cellulitis, fasciitis, and myositis) observed in many patients with severe invasive disease and toxic shock-like syndrome could be due in part to a bacterial protease. Second, certain autopsy findings, especially well-documented cardiac lesions, are consistent with the pathology observed in experimental animals injected with purified SPE B. Clearly, additional insight is needed regarding the exact molecular role of the pyrogenic exotoxins in toxic shock-like syndrome pathogenesis. Many such studies are underway.

TEMPORAL VARIATION IN DISEASE FREQUENCY

The significant increase in frequency of occurrence of severe streptococcal disease has presented an opportunity to study the bacterial forces driving cyclic variation in infections. What role, if any, have pyrogenic exotoxins played in this process? To address this question, the general approach has been to conduct large-scale comparative toxin gene sequencing studies comparing strains causing contemporary episodes with those recovered earlier in this century. The hypothesis underlying this strategy is that changes (mutations) in bacterial virulence genes may contribute to the creation of new, unusually virulent strains. Thus far, studies have focused on genes coding for important streptococcal virulence factors such as SPE A, SPE B, SPE C, and streptokinase (Kapur V, Kanjilal S, Musser JM. Unpublished data. 1992). The major discovery generated by this approach is that compared with "old" strains (1920s to 1950s), the two common streptococcal clones causing most contemporary toxic shock-like syndrome episodes have mutant genes for SPE A.

Interestingly, the two mutant toxin genes are each different at only a single basepair, and these changes result in production of two toxins, each of which differs from the "old" form by only a single amino acid. The two mutations are clustered in a region of the gene that codes for part of the toxin that is apparently involved in causing the powerful T-cell mitogenic thought to trigger the pathway that ultimately results in shock and other signs and symptoms of toxic shock-like syndrome. Studies are underway to delineate the full clinical relevance of these mutations.

CONCLUSION

Much remains to be learned regarding the host and bacterial factors mediating invasive streptococcal disease, especially in children. As a consequence, we recommend that strains recovered from patients with severe invasive disease or suspected toxic shock-like syndrome be analyzed for toxigenic strains. The causative strain, and acute and convalescent sera should be obtained.

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REFERENCES

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47. Dick GE, Dick GH. A skin test for susceptibility to scarlet fever. JAMA. 1924;82:265-266.


