Streptococcus suis: An Emerging Human Threat

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(See the article by Ye et al., on pages 97–107.)

THE HISTORY OF STREPTOCOCCUS SUIS INFECTION IN HUMANS

In the world of Streptococcus, S. suis has been somewhat neglected. Indeed, at this year’s Lancefield International Symposium on Streptococci and Streptococcal Diseases, only one oral presentation was devoted to this pathogen. However, this perception should change, because S. suis is emerging as an important threat to human health.

S. suis is an encapsulated Gram-positive coccus possessing cell-wall antigens related to Lancefield group D. There are 35 serotypes that have been described on the basis of the composition of the polysaccharide capsule [1]. S. suis infections are considered to be a major problem worldwide in the swine industry. The pathogen’s natural habitat is the upper respiratory tract of pigs, as well as the genital and alimentary tracts [1]. The pig carrier rate is near 100%, and, in the absence of treatment, mortality reaches 20% [2]. The most important clinical feature associated with S. suis infection in pigs is meningitis. In severe cases, pigs are found dead with no premonitory signs. Other manifestations are arthritis, endocarditis, pneumonia, rhinitis, abortion, and vaginitis [1].

Until recently, S. suis disease in humans has been rare [3, 4]. Since the first human case in Denmark in 1968 [5] and before 2005, only 250 S. suis infections were reported in Europe and Asia. However, S. suis recently was identified as the third most common cause of community-acquired bacterial meningitis in Hong Kong, behind S. pneumoniae and Mycobacterium tuberculosis [6], and as the leading cause of adult meningitis in Vietnam [7]. Mysteriously, only 2 cases of S. suis meningitis have been reported in Canada [8, 9], and only 1, very recently, in the United States [10].

Although the epidemiology of S. suis infections in humans remains largely undefined, nearly all cases can be ascribed to either handling or consumption of unprocessed pork meat or to close contact with pigs. Therefore, most infected people are pig farmers, abattoir workers, meat inspectors, butchers, and veterinarian practitioners [4]. In humans, S. suis usually produces a purulent or nonpurulent meningitis. Additionally, endocarditis, cellulitis, peritonitis, rhabdomyolysis, arthritis, spondylodiscitis, pneumonia, uveitis, and endophthalmitis may occur [4, 11, 12]. Both severe infections with shock and a high mortality also have been described [13, 14]. One striking feature of S. suis–related meningitis is the complication of deafness and/or vestibular dysfunction, which occurs at a rate consistently higher than that reported for other meningitis-causing bacteria and which reaches 50% and 65% in Europe and Asia, respectively [11, 12]. Most cases of S. suis infection have been attributed to serotype 2 strains; however, cases due to serotypes 4, 14, and 16 also have been reported [4]. Strains isolated from humans are phenotypically and genotypically similar to those recovered from swine within the same geographical region [15].

IMPORTANT EMERGENCE OF THE PATHOGEN: THE 2005 CHINESE OUTBREAK

In 2005, an outbreak of acute disease in humans that was caused by S. suis serotype 2 was reported in Sichuan, China [16]. Notably, the outbreak in humans followed a local outbreak in swine, which killed >600 backyard pigs. Although several reports of this outbreak in humans are available [17, 18], the official count from Sichuan and the Beijing Centers for Disease Control and Prevention indicated a total of 215 cases, with 39 deaths [19]. The most important feature of this outbreak was the high incidence of systemic
The unusual clinical presentation and epidemiology of the Sichuan outbreak also suggested the possible involvement of superantigens. However, no superantigens have been identified in the ST7 strain [18]. The Chinese ST7 strain is reportedly more toxic to peripheral-blood mononuclear cells in vitro than is a well-characterized European virulent ST1 strain [21], although this observation requires further research. Moreover, the Chinese clone is pathogenic in experimentally infected pigs [18, 24], although only 4 pigs were evaluated and no reference S. suis strains were included for comparative analysis. It is also reasonable to propose that this new, more virulent strain acquired genetic material from other microorganisms. Yet, Xiong et al., using whole-genome polymerase chain reaction (PCR) scanning, failed to demonstrate new genetic changes in the genome structure of isolates from either humans or animals in the Sichuan and Jiangsu outbreaks [25]. These findings might be limited by the PCR/primer design and the fact that no comparisons with strains from other ST complexes were made. Thus far, it is unclear why the ST7 clone emerged and induced such a serious outbreak of STSLS in humans.

In this issue of the Journal, Ye et al. provide new insights into the epidemiology of S. suis infection. They show that the ST7 strain responsible for the Sichuan epidemic evolved recently from a highly pathogenic ST1 type, which, in turn, evolved from the intermediate virulent ST25 type. Two major findings of their work should be emphasized. First, comparative analysis of S. suis genomes revealed both that the ST1 strain acquired 132 genomic islands, including 5 pathogenicity islands, when it evolved from the ST25 strain, and that the epidemic ST7 strain acquired 5 additional genomic islands when it evolved from the ST1 strain. Second, patients with STSLS had higher levels of proinflammatory cytokines than did patients with meningitis only. Notably, this is the first study that has analyzed cytokines during the acute phase of S. suis infection in humans. These findings are in agreement with the higher cytokine levels observed in mice infected with the ST7 strain versus those infected with either the ST1 strain or the ST25 strain. Previous in vitro [4, 23] and in vivo [26] studies have suggested that the inflammatory cascade plays a role in the pathogenesis of S. suis infection. Ye et al. show that the inflammatory response differs depending on the S. suis type and the onset of STSLS versus meningitis. Therefore, ST7 stimulates the production of massive amounts of proinflammatory cytokines, leading to STSLS and death. The underlying mechanism remains unknown, because no superantigens or homologous genes have been identified in S. suis isolates from the Sichuan outbreak.

**WHAT QUESTIONS STILL NEED TO BE ADDRESSED?**

The 2005 Sichuan outbreak has provoked strong interest and extensive research. However, many questions remain: Why did the outbreak suddenly appear and then disappear? Because S. suis remains in the tonsils of clinically healthy animals for a long time, is the strain still in circulation at some farms? What are the selective pressures acting to increase the virulence of this strain in humans? Should we expect more cases of STSLS elsewhere?

Furthermore, both the distinct evolution of ST7 within the ST1 complex and the potential emergence of more-virulent types within the ST27 complex, as well as their respective geographical localizations, are important issues to elucidate. To date, only North American isolates from humans have been assigned to the ST25 type within the ST27 complex. A recent study in Thailand has shown that 80% of human clinical isolates belong to the ST27 complex [27]. Although previous studies have suggested that ST27-complex members may have lower potential to cause invasive diseases in swine, all isolates considered in those studies have been from the blood or cerebrospinal fluid of infected patients, suggesting a...
high degree of invasiveness. Thus, the ST27 complex is another clonal group that can cause serious human infection. Because MRP, EF, and suilysin are not appropriate virulence markers for the ST27 complex, novel virulence markers are necessary for efficient discrimination of \textit{S. suis} strains that are virulent in humans [27]. The geographical distribution of ST1 and ST27 complexes should be subjected to continuous surveillance. Future \textit{S. suis} research, accelerated by the power of genomics, will help to advance our understanding of the complex evolution of this emerging human threat. Meanwhile, physicians and microbiologists, especially in North America, should be aware of this infection and give more attention to streptococcal meningitis or STSLS cases in people working with pigs or pork products. Because \textit{S. suis} is very often misidentified, diagnosis might be improved if emergency units obtained a better occupational history of patients presenting with this infection [14].

References